Blood 2024

ABSTRACT BOOK

2024 Annual Scientific Meeting

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Brisbane Convention and Exhibition Centre

www.blood2024.com

The combined Annual Scientific Meeting of the:

HSANZ
Haematology Society of Australia and New Zealand

ANZSBT
Australian & New Zealand Society of Blood Transfusion Ltd

THANZ
Thrombosis & Haemostasis society of Australia and New Zealand

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Barry Firkin Oration: Morbus maculosus haemorrhagicus – where are we now?

Bird R

Barry Firkin's book, "the platelet and iats disorders", published in 1984 and was intended as a guide to role of, and disease states, relating to platelets. Immune thrombocytopenia (ITP) is just one of many platelet disorders, but it is the most common, aside from drug induced platelet dysfunction.

Unlike many haematological disorders, we have had access to reasonably effective treatment for ITP for over 100 years, albeit, relying on the skills of our surgical colleagues. Steroids have been used for 70 years and remain the generally used initial treatment, despite failing to prevent progression to chronic ITP (cITP) in more than 50% of adults with newly diagnosed ITP (nITP).

There have been considerable advances in the treatment of cITP, particularly over the past 20 years, and it has been my privilege to have been onboard for the journey. There are now very few patients with "relapsed/refractory ITP" who cannot be managed with currently available treatments, used in combination, if necessary. As a consequence of better availability to better treatments, recruitment to cITP trials in resource rich countries has become difficult. A much needed refocus on improving outcomes in nITP has recently occurred.

Patient reported outcomes, leading to attention to a broader range of challenges faced by ITP patients, are now part of ITP management. Guidelines and advocacy have contributed to a better standard of care. I think Barry would have been happy with the progress made in the 40th anniversary year of his book.

Ruth Sanger Oration: History redux: Humanity, harm and healing

Street A

Understanding history is important to humankind in learning from the past, valuing the present and guiding the future. Blood Transfusion in Australia and New Zealand has a rich history based on principles of the Red Cross Society and Blood Transfusion Services which embody humanity

ANZSBT was founded as ASBT in 1964 and in celebration of our sixtieth anniversary this year, a group of Life Members, at Council's request, has collated and reviewed our society's journey. This oration is based on global and local events that have shaped our history

Throughout this period there has been increased recognition and understanding of the inadvertent harms of transfusion (and non-transfusion) In response there have been many changes to procedures for donor collection, product preparation, recipient selection and transfusion practice oversight. Patient Blood Management and Haemovigilance programs are now widely employed in NZ and in Australia.

Harms of transfusion transmitted infection (TTI) with HBV, HIV and HCV were present until the early 1990's. The UK experience from this era has recently been reported by the Infected Blood Inquiry. Recommendations from that report have important, contemporary relevance for patients, clinicians, institutions and governments in Australia and New Zealand. The acknowledgement of inadvertent harm and action to further reduce occurrence and recurrence of adverse events will promote healing from this dark chapter.

Opening Symposiums

Cell and immunotherapies; paradigm shifting and curative potential

Jacobson C

This talk with explore the data related to chimeric antigen receptor (CAR) T-cell therapy and bispecific antibody therapy in B-cell non-Hodgkin lymphoma, with a particular focus on large B-cell lymphoma (LBCL). It will review the transformative value of these therapies for patients who previously would not have had effective treatment options, opportunities in earlier lines to limit disease relapse, issues related to treatment sequencing, and finally persistent unmet needs and how they can be addressed.

Survivorship

Kenyon M

In an era of rapidly evolving therapies, the prospect of cure and all its promises; remains a moving target for many. However survivorship, not merely living past an arbitrary milestone, but an expectation of the return to physical (and mental) well-being and continuation of the pursuit of a meaningful life, can be difficult for many.

This lecture will provide an overview of survivorship and present some of the challenges of delivering survivorship care and survivorship care planning in the HCT setting.

Haemophilia gene therapy and gene editing

Young G

The era of gene therapy in haemophilia is upon us with the approval in various regions of up to three different gene therapy products, and commercial use has begun. Nevertheless, the current iteration of gene therapy have many limitations. Several novel approaches including gene editing and non-viral gene transfer are entering clinical trials. This lecture will provide a brief overview of the currently available products, discuss their limitations, and explore novel approaches aimed at overcoming those limitations.

Combined Symposiums

Haematologic malignancies in pregnancy

Haematological malignancies (HM) affect 12.5 per 100,000 pregnancies, with an increasing frequency of diagnosis over the last two decades. Life-threatening HM in pregnancy, such as acute leukaemia and high-grade lymphoma, pose a unique therapeutic challenge, whereby clinicians must consider both maternal and fetal wellbeing, aiming to deliver optimal curative therapy for the patient and a successful pregnancy outcome. A multidisciplinary approach to management is paramount, and clinical practice guidelines are lacking. A summary of the recommendations for diagnosis and staging, imaging safety in pregnancy, therapy in pregnancy incorporating a multidisciplinary approach, supportive care, oncofertility and pregnancy and birth management will be presented.

Overcoming transfusion challenges for patients with sickle cell disease

Messig I

In recent years Australia has seen a growing number of patients with sickle cell disease requiring transfusion support. This group of patients have increased exposure to antigens they lack due to their transfusion burden with up to 50% of patients being alloimmunised and developing red cell antibodies over their lifetime[1]. To avoid alloimmunisation in this population, provision of phenotype matched blood is usually requested. This can be limited to ABO, Rh and K or extended to include Fy^a, Fy^b, Jk^a, Jk^b, S and s and is based on local policy and/or availability. With the increase in requests for phenotype matched blood, provision can be challenging due to availability. In addition to this, there is increased incidence of RHD and RHCE variants - as well as negativity for high frequency antigens in other systems - in this population[2,3]. Should patients make antibodies to high frequency antigens, this dramatically reduces the likelihood of having compatible blood available for transfusion support.

I aim to discuss the increase in phenotype order requests received by the Australian Red Cross Lifeblood (Lifeblood) from 2016 up to and including numbers to date for 2024 and the steps being taken by Lifeblood to increase our phenotyped inventory as well as our rare donor pool.

1. Red blood cell alloimmunization and sickle cell disease: a narrative review on antibody induction; Jeanne E. Hendrickson; Annals of Blood 2020;5:33
2. RH genotypes and red cell alloimmunization rates in chronically transfused patients with sickle cell disease: A multisite study in the USA; Narek Israelyan et al; Transfusion. 2024;64:526–535.
3. Transfusion Support of Minority Patients: Extended Antigen Donor Typing and Recruitment of Minority Blood Donors; Jenna Khan; Meghan Delaney; Transfusion Med Hemotherapy (2018) 45 (4): 271–276.

Sickle cell disease care for adults

Yue M

Sickle cell disease (SCD) is a hereditary haemoglobin disorder which alters red cell shape, leading to vaso-occlusive events and haemolysis.

SCD adults have reduced life expectancy compared to the general population. Challenges in adult SCD care include engaging with the adolescent/young adult group transitioning from paediatric to adult services, optimal pregnancy management, acute and chronic pain, and progressive end organ damage.

The SCD working group is a network of Australian clinicians involved in the care of SCD patients. The group has been developing national guidelines for the management of various aspects of SCD care in the Australian context.

Next generation GVHD prevention

Zeiser R

Acute graft-versus-host disease (aGVHD) is a major cause of morbidity and mortality in patients undergoing allogeneic hematopoietic cell transplantation (allo-HCT). Classical standard prophylaxis for aGVHD included a calcineurin inhibitor plus an antimetabolite. In the past decade, this basic structure has been reshaped by approval of antithymocyte globulin products, the rise of posttransplant cyclophosphamide, and recent clinical trials studying abatacept and vedolizumab for GVHD prophylaxis. Vedolizumab is a gut-selective anti-α4β7 integrin monoclonal antibody that reduces gut inflammation by inhibiting migration of GI-homing T lymphocytes. The efficacy and safety of vedolizumab added to standard GVHD prophylaxis (calcineurin inhibitor plus methotrexate/mycophenolate mofetil) was evaluated for prevention of lower-GI aGVHD after unrelated donor allo-HSCT in a randomized, double-blind, placebo-controlled phase 3 trial. The primary end point of the study was met; Kaplan-Meier (95% confidence interval) estimated rates of lower-GI aGVHD-free survival by day +180 after allo-HSCT were 85.5% with vedolizumab versus 70.9% with placebo. In my talk I will review recent developments in aGVHD prevention outlining what future goals should be.

Closing Symposiums

Engineering red cells

Griffiths R

Red blood cells (RBCs) are used therapeutically in the treatment of clinically significant anaemia. For patients with rare blood groups or who are multi-transfused, it can be challenging or impossible to provide matched blood components.

Fully functional cultured RBCs (cRBCs) can be grown in the laboratory from haematopoietic stem cells (HSCs) isolated from adult peripheral blood, cord blood or bone marrow.
There are numerous advantages of cRBCs over donated RBCs including greater transfusion efficacy due to increased lifespan in comparison to donor RBCs, reduced immunisation risk for those who have rare blood group antigens or are multi-transfused and constant availability due to stem cell banks.

However, primary HSCs have a finite proliferative capability and are technically challenging to genetically manipulate. Alternative stem cell sources for RBC production which are both sustainable and genetically malleable such as induced pluripotent stem cells and immortalised erythroid cell lines have been developed and continue to be explored but have failed to recapitulate erythropoiesis as well as primary derived HSC stem cells sources.

HSANZ Invited Speakers

What to target in myelodysplasia - shotgun or bulls eye?

Enjeti A

Myelodysplasia is a heterogenous clonal bone marrow disorder. It characterised by a mutation and microenvironment profile which is different to acute myeloid leukaemia. This session will provide an overview of targets, both mutation and non-mutational that can direct therapeutic advances for MDS.

Masterclass: The treatment of monoclonal gammopathies in Spain under a universal healthcare system: Advantages and limitations

Fernández de Larrea C

Spain ranked among the longest life expectancy in the world. The country offers (almost) universal healthcare throughout the whole country in a decentralized model. This healthcare system is mostly paid for by taxpayers through social security system. Treatments approved by the European Medicines Agency (EMA) for multiple myeloma and other hematological malignancies are not immediately available in Spain. The reimbursement price has to be agreed between the pharmaceutical companies and the government. Even then, local decisions in each region can limit further the access. Academic strategies are trying to bring expensive therapies, such as CAR-T cells, to a wider population. Moreover, the inclusion of patients in clinical trials is extremely high in multiple myeloma, allowing the treatment with the newest alternatives many years before a reimbursement is available. However this limitation, a comprenhensive algorithm for the treatment of multiple myeloma, AL amyloidosis and macroglobulinemia, among other malignant monoclonal gammopathies, has been developed with real-life clinical impact. These protocols can be compared to those existing in other countries, such as Australia.

CAR-T cells in multiple myeloma

Fernández de Larrea C

Despite recent therapeutic advances, the prognosis of patients with relapsed/refractory multiple myeloma (MM) remains poor. Thus, new strategies to improve outcomes are imperative. Chimeric antigen receptor (CAR) T-cell therapy has changed the treatment landscape of B-cell malignancies, providing a potentially curative option for patients who are refractory to standard treatment. Long-term remissions achieved in patients in advanced phases encouraged its further development in MM. B-cell maturation antigen (BCMA)-targeted CAR T-cells have established outstanding results in heavily pre-treated patients. However, several other antigens such as GPRC5D are currently under advanced investigation with promising results. Ide-cel and cilta-cel are approved in several countries; however, the worldwide access is limited, being one of several challenges of CAR T-cell therapy in the future. Academic strategies in some regions are trying to bring these therapies to a wider population. Unfortunately, relapses after CAR T-cell infusion is reported in the majority of patients. Understanding the underlying mechanisms of resistance with clinical and pre-clinical data is essential to promote prevention strategies and to enhance CAR T-cell efficacy.

Glofitamab plus gemcitabine and oxaliplatin (Glofit-GemOx) for relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): results of a global randomized phase III trial (STARGLO, NCT04408638)

Gregory G[1], Ku M[2], Hertzberg M[3], Fox C[4], Herbaux C, de la Cruz-Vicente F[6], Huang H[7], Yoon D[8], Kim W[9], Zhang H[10], Zaucha J[11], Abdulhaq H[12], Townsend W[13], Simko S[14], Orellana-Noia V[14], Ta R[14], Xie Y[15], Kallemeijn M[16], Lundberg L[16], Abramson J[17]

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Aim: We present efficacy and safety results of Glofit-GemOx versus R-GemOx in R/R DLBCL patients from STARGLO.

Method: ASCT-ineligible patients were randomized 2:1 to receive either Glofit-GemOx (8 cycles, plus 4 cycles glofitamab monotherapy) or R-GemOx (8 cycles). Following obinutuzumab pretreatment, glofitamab was administered during C1 as weekly step-up doses (2.5/10mg), then 30mg every 21 days from C2D1.

Results: 274 patients were enrolled (Glofit-GemOx, n=183; R-GemOx, n=91), including 172 (62.8%) after only 1 prior therapy. 153 (55.8%) had primary refractory disease, and 166 (60.6%) were refractory to last therapy.

At primary analysis (Mar 2023), significant OS benefit was observed for Glofit-GemOx versus R-GemOx (HR 0.59, 95% CI: 0.40–0.89; p=0.011). Significant benefit of Glofit-GemOx was observed in IRC-assessed PFS (HR 0.37, 95% CI: 0.25–0.55; p<0.0001) and CR rate (p<0.0001).

A follow-up analysis was conducted once all pts had completed therapy (cut-off date Feb 16, 2024; median follow-up of 20.7 months) and showed Glofit-GemOx continued to demonstrate superior mOS (25.5 vs 12.9 months; HR 0.62, 95% CI: 0.43–0.88), mPFS (13.8 vs 3.6 months; HR 0.40, 95% CI: 0.28–0.57), and CR rate (58.5 vs 25.3%) versus R-GemOx, respectively.

Although AE rates were higher with Glofit-GemOx versus R-GemOx, including Grade (Gr) 3–4 AEs (69.4 vs 36.4%), Gr 5 AEs (8.3 vs 4.5), and serious AEs (54.4 vs 17.0%; primarily CRS), AE rates were similar between arms when adjusting for exposure differences. In patients exposed to glofitamab, CRS was the most frequently reported AE (Gr 1: 31.4%, Gr 2: 10.5%, and Gr 3: 2.3%), and ICANS were reported in four patients (2.3%) and were concurrent with CRS.

Conclusion:
Glofit-GemOx demonstrated statistically significant and clinically meaningful benefit in OS, PFS, and CR rate over R-GemOx in patients with ASCT-ineligible R/R DLBCL, and was well tolerated.

Masterclass: CAR T-cells in lymphoma: Real world cases

Jacobson C

This talk will use real world cases to explore issues related to chimeric antigen receptor (CAR) T-cell therapy patient selection, toxicity recognition and mitigation, and patterns of response and resistance in B-cell non-Hodgkin lymphoma.

The great debate: CAR vs bispecifics in DLBCL and FL

Jacobson C

This talk will compare and contrast the results of clinical trials and real-world series of anti-CD19 chimeric antigen receptor (CAR) T-cells and CD20 bispecifics in diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) and draw conclusions about how to best position each therapy in the treatment paradigm for these diseases.

Update on digital and machine learning in haematology morphology

Juneja S

Increasing use of artificial intelligence (AI) and machine learning (ML) is advancing the diagnostic haematology field resulting in potentially improved assessment of blood/bone marrow morphology, providing more objective results, improved TAT, better screening of and diagnoses of various haematologic diseases & enhanced monitoring of novel therapies like CAR-T cell therapy.

Furthermore, it is leading to better education & training of laboratory staff as well as better access to quality results particularly in remote, smaller laboratories.

Obviously, this progress is dependent upon concurrent IT developments & has implications for resource allocations.

Inevitably the role of AI & ML will increase in future diagnostic haematology. All these aspects will be presented & discussed in this session.

Treating acute myeloid leukaemia in older persons – through the lens of frailty

Ling V

Acute myeloid leukaemia is an aggressive blood disorder and is primarily a disease of older persons. The mainstay of treatment is urgent intensive chemotherapy (IC) for sufficiently fit patients. Unfortunately, most older patients are ineligible for intensive therapy due to comorbidities, poor performance status and an increased risk of treatment-related morbidity and mortality. Older patients with AML thus have dismal survival rates. Whilst adverse disease attributes occur more frequently in AML of older patients, increasing frailty is also prevalent and independently associated with poor outcomes in the setting of IC. Since 2020, lower intensity regimens incorporating targeted pro-apoptosis agent, venetoclax, combined with either hypomethylating agent (HMA), azacitidine (aza) or low dose cytarabine have demonstrated overall survival improvements and tolerability in patients unfit for IC in Phase 3 clinical trials, re-defining standard of care in 'IC unfit' patients. The availability of an effective lower intensity, but ultimately non-curative treatment heightens the imperative to select patients inappropriate for highly toxic but potentially curative IC.

Frailty is an important component of assessment for fitness for chemotherapy. Frailty is the sum of the complex interplay of age, functional abilities, comorbidities and social factors and age or performance status alone is considered an insufficient surrogate for frailty. Frailty is dynamic and is influenced over time by factors leading up to disease presentation (age-related senescence and comorbidities) and following cancer diagnosis (cancer factors and treatment complications). Studies have highlighted the value of comprehensive, objective assessments of frailty in the treatment of AML.

This talk will cover treatment approaches and prognostication in older patients with AML, the concept of frailty as it applies to AML treatment, utility of objective frailty assessments and a guideline to implementing frailty assessments in clinical practice.

The disparity of rural/remote Australians with haematological malignancies

Peters L

Haematological malignancies combined are the third most frequently diagnosed cancer in Australia, with an incidence of ~20,000 people/year, and are the second leading cause of mortality.[1, 2] Well established access barriers to cancer care exist including geographical, socioeconomic and cultural determinants of health, which result in health outcome disparity. These are prevalent within Australia given the vast land mass, unique population density and cultural diversity. Although only 28% of Australians live outside the metropolitan region, in 2022 they accounted for 41% of the people diagnosed with a haematological malignancy.[1, 3] Furthermore, those living in regional/remote locations have worse survival outcomes than their metropolitan counterpart. Modelling of the State Cancer Registry and Australian Institute of Health and Welfare data indicates that if the metropolitan-regional divide was addressed survival disparity could be reduced by 5%.[1] Moreover, there is an overrepresentation of marginalized people, such as First Nations Australians, living in regional/remote locations. The intersectionality of these minority populations contributes to compounding health outcome disparities and inequity.[4] This talk will focus on the outcomes of rural/remote Australians with haematological malignancies with reference to geographical location, access barriers, determinants of health and intersectionality and will include real world data.

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Unlocking the Mind's defence: Exploring the brain behind the CAR-T service.

Simpson T

Aim: This abstract aims to provide commentary on the distinctive approach of our Chimeric Antigen Receptor T Cell Therapy (CAR-T) program, emphasising the integral role played by our Neuroimmunology team which consists of Neurologists, a CAR-T Neurology Fellow and Neuropsychologists.

Neurological toxicities represent a significant concern following CAR-T manifesting in diverse presentations ranging from mild cognitive impairment to severe Immune effector Cell Associated Neurotoxicity Syndrome (ICANS). We will discuss the involvement of the Neuroimmunology team in providing a comprehensive understanding of the neurocognitive aspects of CAR-T, ultimately enhancing patient care and outcomes.

Baseline Assessment (Pre CAR-T): Prior to all CAR-T infusions, patients are referred to our Neuroimmunology team for a comprehensive neurocognitive baseline assessment and baseline MRI brain. Neuropsychologists assess the patient's attention and processing speed, language, visuospatial function, memory and executive function. Neuroimmunologists conduct a full neurological examination including baseline ICE assessment and clock drawing test (CDT). These assessments help to provide information on baseline neurocognitive function and help identify pre-existing conditions or risk factors that may increase the risk of ICANS prompting decision for prophylactic steroids or anti-seizure medication

Inpatient monitoring: Patients are reviewed daily including weekends following the CAR-T infusion by the Neuroimmunology team. Assessments consist of comprehensive neurological examination, ICE assessment, CDT and bedside cognitive testing. Neuroimmunology provide guidance on the frequency of ICE and CDT, particularly in patients with subtle ICANS when ICE and CDT are normal. In the setting of ICANS, investigations such as MRI and EEG are performed promptly and therapeutic interventions are recommended.

Long-term follow-up: Long-term neurocognitive sequalae from CAR-T occasionally occurs and can manifest weeks to months after treatment. Patients have regular neuroimmunology follow-up on discharge (for 24 months) with detailed assessments for early detection of neurological symptoms that may arise.

Conclusion: Early involvement of Neuroimmunology in our CAR-T program is essential for enhancing patient care outcomes. This involvement facilitates early identification and intervention of ICANS, tailoring treatment plans to individual needs, provides comprehensive care and drives forward research and innovation initiatives.

ANZSBT Invited Speakers

Masterclass: Implementing patient blood management

McKeown D

Implementing effective patient blood management (PBM) programs is essential to optimising transfusion practices, which has far-reaching implications for both patient outcomes and healthcare efficiency. PBM initiatives focus on minimising the need for allogeneic blood transfusions through strategies like preoperative anaemia management, blood conservation, and patient-centred approaches. Drawing from my experiences in London and Northern Ireland, I have witnessed how these programs lead to reduced transfusion dependency, decreased healthcare costs, and better clinical outcomes. This masterclass will explore practical strategies and challenges faced during PBM implementation, showcasing examples that highlight the transformative role these programmes can play in modern healthcare systems

Insights into the diversity of blood donation practice across Asia

Fung L

Over 59% of the world's population live in Asia. However, much of the published scientific literature on blood donations originates from Europe, North America or Australia. In 2020, we developed a collaboration of Asian blood collection agencies (BCAs) to improve our understanding of current blood donation practices in Asia. Our first study investigated the contribution and potential of older blood donors and involved five BCAs (1). In our second study, we looked into the donors and donation practices in 10 BCAs (2). This study included six national BCAs and four regional BCAs with each providing details on their donation criteria and 12 months of blood donation data. The study revealed that eligibility criteria and donation practices varied between the 10 BCAs. Differences in donor demographics and donation criteria were observed. The data showed how each BCA has tailored their donation practices based on their donor population and blood supply needs. And we are beginning to understand the Asian blood donor phenotype. Because 30.7% of Australian people were born overseas and about 10% are from Asia, this understanding is needed to help us secure our blood supply into the future (3).

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Laboratory investigation of severe adverse transfusion reactions

Fitch K

Blood transfusion can be associated with various adverse effects. Some of these reactions are acute and arise during or shortly after the transfusion. The clinical effects of others are delayed, usually occurring 24 hours to 28 days post transfusion. Severity of symptoms also range widely dependant on the underlying aetiology.

Any adverse symptom or physical sign occurring during a blood or blood component transfusion should be considered as potentially life-threatening.

Action must be taken as soon as possible. The transfusion should be stopped immediately and necessary steps taken to investigate the transfusion reaction.

The pathology laboratory has a significant role in determining whether the patient's reaction is related to the transfusion, and differentiating the cause with the aim to guide patient treatment and implement appropriate modification to future transfusion.

A review of how a large laboratory network investigates reports of transfusion reactions will be presented including a case study of a rare acute isolated hypotensive transfusion reaction (AHyTR).

Supplying blood in emergencies

Lennard S

Pathology Queensland provides diagnostic pathology services to public Hospital and Health Services in Queensland, Australia. There are currently 106 public hospitals in Queensland, with 35 of these serviced by on-site laboratories. 34 of 35 laboratories include transfusion testing in their scope.

Red cells for emergency use (referred locally as Medevac units) are routinely provided throughout the state to 74 hospitals and 16 retrieval medicine sites. Prior to 2020, O RhD negative units were routinely provided to all sites. Recognition of the increasing burden on the RhD negative supply, exacerbated by projected shortages due to the COVID outbreak, lead to a rationalisation and review of this service. Selection of RhD type for Medevac issue is now determined by the age and sex of the patient as communicated at the time of request. For hospitals without onsite pathology, local patient demographics were reviewed and a mixed inventory of RhD positive and RhD negative units are provided where appropriate.

The change to a ‘mixed’ inventory of Medevac units has demonstrated a reduction in O RhD negative red cell usage. However, beyond this anticipated reduction, the change in practice has impacted overall inventory management. The impacts on inventory and red cell usage will be illustrated with case studies of several Pathology Queensland laboratories ranging from large metropolitan, to small regional, and remote.

Subcutaneous immunoglobulin: When and why?

Crispin P

Subcutaneous immunoglobulin administration has greater flexibility but is less commonly prescribed than intravenous immunoglobulin. Subcutaneous immunoglobulin also has a favourable safety profile. Indications include immune replacement therapy or immune modulation in chronic inflammatory demyelinating polyneuropathy. The benefits and barriers associated with subcutaneous immunoglobulin will be explored to consider how to tailor immunoglobulin therapy to individual patient needs.

Disaster preparedness

Gore C

Effective planning, management, and coordination of responses to blood supply failures and/or demand surges are crucial for optimal patient outcomes. In 2022, Blood, Organ, and Tissue Programs, Department for Health and Wellbeing (the Department), developed a State-wide Blood Supply Contingency Plan (State Plan) to ensure South Australia is prepared for blood supply emergencies and disruptions.

In addition to the State Plan, each health network had its own existing Emergency Blood Management Plan (EBMP), detailing roles, responsibilities, and communication pathways in a blood supply crisis. The EBMPs were evaluated for currency and alignment with the National Blood Supply Contingency Plan and the State Plan. Extensive stakeholder consultation involved a discussion-style workshop that gathered key contributors from across organisations. This provided an opportunity to examine and discuss the management of blood and blood products during supply disruptions or demand surges, based on what was documented in their EBMPs. To test the State Plan and revised EBMPs, representatives from the public health networks, public pathology, the Department and Australian Red Cross Lifeblood participated in a functional exercise based on a mass casualty scenario, which helped identify gaps and areas for improvement. Since the exercise, all plans have been refined, and the introduction of a Mass Casualty Incident response will ensure coordinated efforts during substantial demand surges and significant restrictions on blood and blood product availability.

By facilitating and enabling collaboration across organisations to define and document EBMPs, South Australia has achieved an advanced state of preparedness for any potential supply failures or disruptions.

Navigating major incidents

McKeown D

Major incidents demand an efficient, well-coordinated response to ensure patient safety, particularly within transfusion services where timely provision of blood component support can be critical. Through my experiences in London, I've learned that preparedness is key to successfully navigating such crises. Ensuring adequate blood stock levels, having rapid communication protocols, and maintaining flexibility in operations are just some of the strategies that have proven effective. In this presentation, I will share best practices and lessons learned, focusing on how hospitals can enhance their preparedness, response, and recovery efforts when facing major incidents. The goal is to foster resilience, ensuring that patient care remains uncompromised even in the most challenging situations.

Emerging platelet therapies

Marks D

Platelets have a short shelf life, which can lead to shortages and wastage. Frozen or cold storage of platelets can extend platelet component shelf-life to weeks or even years, as well as reducing the risk of bacterial contamination. Other approaches, such as lyophilisation and depletion of HLA antigens are also being explored.

Pre-clinical *in vitro* studies have evaluated the impact of cold storage and cryopreservation on platelet quality and function, with comparisons to platelets stored at room temperature. Both cold storage and cryopreservation increase the procoagulant activity of platelets, due to increased phosphatidylserine externalisation, generation of more procoagulant microparticles and increased thrombin generation. These features suggest that they may be more haemostatically effective than conventional room temperature stored platelets, and therefore particularly useful for the treatment of haemorrhage and traumatic resuscitation. Similarly, lyophilised platelets, also known as thrombosomes, have high levels of externalised phosphatidylserine that facilitates thrombin generation, and they can adhere to collagen under flow. Acid-treatment of platelets to deplete HLA antigens may provide a means of providing platelets to refractory patients when no other platelets are available.

In order to achieve regulatory approval and more widespread availability of these products, clinical trials of cold-stored and cryopreserved platelets are currently in progress. Pilot studies have shown that frozen and cold-stored platelets are effective in reducing bleeding in a number of settings, including cardiac surgery and chemotherapy-induced thrombocytopenia. Similarly, phase I trials of lyophilised platelets suggest they may be safe and effective.

In this presentation, the advantages and disadvantages of these novel platelet products, together with findings from *in vitro* and clinical studies will be reviewed.

PBM in ICU? Impact of small volume blood sampling

Keogh S

The use of small volume blood sampling tubes in Intensive Care Units (ICUs) represents an essential strategy within the broader framework of Patient Blood Management (PBM). National and global guidelines strongly advocate for minimising phlebotomy-related blood loss, especially in vulnerable populations such as critically ill patients. Despite these recommendations, the adoption of small volume sampling tubes remains limited and inconsistent across healthcare settings. A systematic review highlighted the scarcity of high-quality trials in this area, underscoring the need for robust research. Notably, a recent multi-site trial demonstrated that implementing small volume blood sampling tubes led to a decrease in ICU-related haemoglobin reductions and a reduced risk of red blood cell (RBC) transfusion. However, the observed effect size was modest, indicating that the full potential of this intervention is yet to be realised. To optimise the impact of such interventions, it is crucial to incorporate the principles of implementation science in future research. This approach will ensure that promising strategies, like small volume blood sampling, are effectively translated into sustained improvements in patient care. This talk will explore the current evidence, barriers to adoption, and the critical role of implementation science in enhancing the uptake and effectiveness of responsible blood sampling practices in ICUs.

Transfusion technology

McKeown D

The implementation of advanced transfusion technologies can significantly improve the safety and efficiency of blood transfusion processes. Over the course of a 4-year program in Northern Ireland, we will be introducing a single

- Laboratory IT system,
- Electronic Health Record (EHR)
- Blood Tracking system.

These technologies will revolutionise how blood components are managed, ensuring accurate identification, real-time tracking, and seamless communication between laboratories and the blood transfusion service. The aim of integrating these systems, is to minimise the risk of transfusion errors, optimise the blood supply chain, and enhance patient safety. This presentation will outline the key phases of this transformative project, from planning to execution, and discuss the operational benefits it will deliver to the Northern Ireland healthcare system.

THANZ Invited Speakers

Masterclass: How I treat paediatric venous thromboembolism

Young G

The treatment for paediatric venous thromboembolism has evolved significantly in the past 5 years with the approval of direct oral anticoagulants and the large amounts of data they have offered from the various clinical trials. As such, treatment approaches have changed given the advantages of these oral agents over the much less well studied parenteral medications we relied upon for decades. The discussion will revolved around the modern approach for managing paediatric venous thromboembolism across the spectrum of paediatric age groups.

Thrombin generation assays in haemophilia

Young G

During this session, a review of what thrombin generation assays are and how they are conducted will be discussed. Following this, the use of thrombin generation in clinical research as well as it use in several clinical scenarios where clinical decisions were made using this assay will be described.

Liver patients in sticky situations

Ng S

Advanced liver disease is generally accompanied with cirrhosis-associated coagulopathy and an increased risk for bleeding events. Standard laboratory markers do not truly reflect the complexity of changes that take place in the coagulation system in patients with advanced liver disease. The parallel decrease of procoagulant and anticoagulant factors has resulted in the concept of “rebalanced coagulation” with an increased risk of risk of bleeding episodes and thrombotic events, depending on the patients’ clinical context and underlying risk factors. The safe administration of anticoagulation can be beneficial in patients with liver disease if the indication is present and bleeding prophylaxis has been established.

Remember bleeds? The importance of maintaining vigilance in era of excellent prophylaxis

Young G

The newer treatments for haemophilia including emicizumab, efanesoctocog alfa, and gene therapy have driven bleed rates to very low levels. This has resulted in situations where both patients, caregivers, and even physicians fail to recognize when serious bleeds occur resulting in delayed treatment. While bleed rates have decreased, a re-emphasis on the recognition of bleeding as well as the acknowledgement of subclinical is important for the clinician.

Ischemic endothelial necroptosis induces red blood cell hemolysis and COVID-19 microangiopathy

Yuan Y

Microangiopathy is a major complication of SARS-CoV-2 infection and contributes to the acute (multi-organ dysfunction) and chronic (Long COVID) complications of the disease. Endotheliopathy and dysregulated blood coagulation are prominent in COVID-19 and are considered a major cause of microvascular obstruction. Here, we demonstrate extensive endothelial cell (EC) death in the microvasculature of COVID-19 organs. Surprisingly, EC death was not associated with extensive fibrin formation or platelet deposition but was linked to widespread microvascular red blood cell (RBC) hemolysis. This RBC microangiopathy was associated with ischemia-reperfusion (IR) injury and was prominent in the microvasculature of humans with myocardial infarction, gut ischemia and stroke. Mechanistically, IR injury induced MLKL-dependent EC necroptosis and complement C9-dependent RBC hemolysis. Deposition of hemolyzed RBC membranes at sites of EC death resulted in the development of a previously unrecognized hemostatic mechanism that prevented microvascular bleeding. Exaggeration of this RBC hemolytic response promoted RBC aggregation and microvascular obstruction. Genetic deletion of *Mlkl* from ECs reduced RBC hemolysis and microvascular obstruction, leading to reduced ischemic tissue injury. Our studies demonstrate the existence of a RBC hemostatic mechanism that is induced by dying ECs and functions independently of platelets and fibrin. Therapeutic targeting of this RBC hemolytic process may reduce microvascular obstruction in COVID-19 and other major cardiovascular diseases.

Nursing Invited Speakers

Leukodepletions: The last 10 years at the Royal Brisbane and Women's Hospital (RBWH)

Scarffe M

Introduction: Leukodepletion or Leukapheresis is used to rapidly and effectively reduce excessive numbers of circulating white blood cells in patients at risk of or with symptoms of leukostasis due to hyperleukocytosis. This retrospective includes 27 patients who received a total of 37 leukapheresis procedures due to with either newly diagnosed haematological malignancies or new hyperleukocytosis from July 2014 to June 2024 at the RBWH.

Aim: This retrospective examines the 27 patients who presented to the RBWH over a ten-year period with symptoms of leukostasis due to hyperleukocytosis, in the setting of either new or existing haematological cancer diagnosis. Each patient received at least one leukapheresis apheresis procedure and all patients had already or shortly post procedure commenced adjuvant therapy. Patient outcomes and the role of leukapheresis will be discussed.

Method: Between July 2014 to June 2024, a total of 37 leukapheresis procedures were performed on 27 patients at the RBWH. Included were 14 new diagnosis AML patients, 5 new diagnosis ALL patients, 7 CML patients with only 1 with existing diagnosis at time of leukapheresis and 1 new diagnosis non-Hodgkin lymphoma patient. Each patient was assessed by a haematology consultant and deemed in clinical need of leukapheresis to either reverse or prevent leukostasis.

Results: Response to leukapheresis was varied and difficult to assess as the majority of patients who had leukapheresis presented with leukostasis, a clinical condition which often results in high mortality rates. Of 27 patients who underwent leukapheresis in the last 10 years at the RBWH 10 patients have survived, 14 died (8 within the first 28 days, 6 within 5 years of leukapheresis). 3 patients have unknown outcome.

Conclusion: Haematology patients who present requiring leukapheresis are associated with high early mortality and morbidity rate. Leukapheresis is generally well tolerated by patients despite their clinical condition and current research suggests the use of leukapheresis is favoured by clinicians for symptom management and comfort.

Sickle cell disease (SCD): A 21-year old patient's journey from Zambia to red cell exchange and everything in between

Scullion A

Aim: To describe, using a case study, the challenges that red cell exchange (RCE) presents to the patient and the health care professional focussing on vascular access.

Method: This case study examines the transition of a 21 year old female patient with sickle cell disease (SCD) from paediatric to adult medical care. The monitoring and treatment of her sickle cell disease episodes and sickle cell crisis resulting in admissions to ED, the ward and ICU resulting in RCE will be discussed. Treatment, both manual and automated, in the acute and chronic setting and the need for credentialing for sickle cell disease (ASFA categories I – III and grades 1A – 2C) will be further explored.

Results: Vascular access assessment and device selection is vitally important in apheresis and sickle cell patients possess unique challenges due to endothelial dysfunction caused by their condition and their preferences of device for a chronic red cell exchange program. This patient experienced a subarachnoid haemorrhage and subsequent ICU admission requiring emergency RCE. This admission involved multiple attempts at vascular access, resulting in vascular injury and a reluctance from the patient to pursue further red cell exchange which is considered gold standard for the treatment of and prevention of stroke in SCD patients. Therefore a robust plan for vascular access was essential for this patient to minimise the risks posed by sickle cell disease.

Conclusion: As apheresis operators we will see more SCD patients due to increasing immigration and displacement of people from regions where sickle cell disease is more prevalent. Developing a deeper understanding and effective strategies to manage acute and chronic disease states such as this described will be of increasing importance. Credentialing of apheresis staff using internationally recognised standards in a tertiary hospital centre ensures best practice and continuity of care.

The management of adult congenital Thrombotic Thrombocytopenic Purpura with recombinant ADAMTS13: An advanced practice nurse perspective

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Background: Thrombotic thrombocytopenic purpura (TTP) is a rare microangiopathy, with clinical presentations characterised by haemolytic anaemia, thrombocytopenia, fever, and neurological and renal dysfunction. Deficiency of the von Willebrand factor-cleaving protease ADAMTS13 leads to microthrombi formation within organs causing ischaemia and end organ damage. Most TTP is immune mediated, however congenital TTP (cTTP) represents a minority of presentations. cTTP is an autosomal recessive disorder where events such as pregnancy precipitate the microangiopathic haemolytic anaemia (MAHA).

Clinical Case: A 24-year-old indigenous female from regional Victoria presented at 23 weeks gestation with her first pregnancy. She had fragmentation of red cells on her film, thrombocytopenia, and biochemical features of haemolysis consistent with MAHA. Therapy for TTP was commenced including plasma exchange (PLEX). Subsequently ADAMTS13 activity of 5.5% was reported in the absence of an inhibitor which raised suspicion of cTTP. Despite markers for haemolysis improving greatly, severe intrauterine *growth restriction* with fetal compromise was identified. After induction of labour, she delivered a non-viable baby boy. She improved with TTP therapy and was discharged home. cTTP was confirmed with genetic testing which demonstrated two compelling *ADAMTS13* variants: Arg1060Trp and Cys242Tyr. The Arg1060Trp is a known pathogenic variant in the setting of cTTP, it is associated with later disease onset and often with first presentation during pregnancy. The Cys242Tyr was a novel mutation not previously described. Since discharge persistent manifestations of cTTP have been troublesome despite normal haemolytic markers. These include neurological symptoms, pain, headaches, and mental fog. Severe allergic reactions to fortnightly fresh frozen plasma required pursuing other options for treatment. Compassionate access to a recombinant ADAMTS13 product (ADZYNMA) has been instrumental in managing symptoms and restoring ADAMTS13 levels.

Conclusion: cTTP is rare and therapy is often complicated. ADZYNMA has been instrumental in improving the quality of life of this patient.

HCT late effects prevention and screening

Kenyon M

Survivors of HCT and cellular therapy experience significant medical issues and psychosocial difficulties that can contribute to morbidity and mortality, and negatively impact quality of life. Prevention and detection of late effects, followed by appropriate intervention, are crucial to improving long-term outcomes in survivors.

This lecture will provide an overview of late effects, an outline of the recently published International Recommendations for Screening and Preventative Practices for Long-Term Survivors of Transplantation and Cellular Therapy and present a late effects clinic model.

Nursing-led model of care for cytopenias post CAR T-cell therapy in R/R large b-cell lymphoma. A single centre experience

Van Der Linde S[1], O'Leary N[1], Scott H[1], Dowling M[1], Kuzich J[1], Minson A[1], Thompson P[1], Anderson M[1], Dickinson M[1], Seymour J[1], Harrison S[1]
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Aim: To describe the incidence of cytopenias following chimeric antigen receptor T-cell (CAR-T) therapy and to suggest an advanced practice nursing framework for monitoring and managing cytopenias at the Peter MacCallum Cancer Centre (PMCC)

Method: Retrospective data analysis of patients with R/R Large B-Cell Lymphoma (LBCL) infused with axicabtagene ciloleucel or tisagenlecleucel CAR-T-cell products at PMCC between 2020-2024. The Common Terminology Criteria for Adverse Events (CTCAE) V5[1] was used to grade cytopenias. A narrative report was used to provide nursing framework for post CAR-T.

Results: A total of 154 patients with LBCL underwent CAR-T between years 2020-2024 (101 axicabtagene , 53 tisagenlecleucel). Table 1 details patient baseline characteristics. Incidence of cytopenias is detailed in Table 2. Table 3 details transfusion requirements and growth factor support (filgrastim and eltrombopag). The advanced practice nurse role included monitoring post CAR-T patients in the nurse-led outpatient clinic at least twice weekly which included review of pathology for cytopenias, identification for intervention indications, and a comprehensive patient physical assessment. Transfusion indications were hemoglobin <80g/L or symptomatic anemia, platelets <20x10^9/L or bleeding, special cases outside these parameters included, cardiovascular comorbidities, gastrointestinal bleed, and neurological toxicities including seizure risk. Filgrastim was considered in patients with neutrophils <1.0 x10^9/L, in consultation with medical team. Further considerations for neutropenia included infection prevention, early detection of infection, indication for prophylactic antimicrobials and vaccinations.

Table 1. Baseline patient characteristics

Characteristic	Percentage of patients
≥3 prior therapies	29%
Prior autologous transplant	32%
History of primary refractory disease or relapsed within 12 months of completion of upfront therapy	66%
Bone marrow involvement at apheresis	22%

Table 2. Incidence of cytopenia pre and post CAR T-cell therapy

	Pre-lymphodepletion n, (%)		Day 0 - Day +30 n, (%)		Day +90 n, (%)		Max n, (%)	
	All grades	G≥3	All grades	G≥3	All grades	G≥3	All grades	G≥3
Anemia	110, (71%)	3, (2%)	121, (79%)	4, (3%)	62, (62%)	1, (1%)	149, (97%)	55, (36%)
Thrombocytopenia	79, (51%)	8, (5%)	133, (86%)	55, (36%)	64, (64%)	14, (14%)	145, (94%)	78, (50%)
Neutropenia	39, (25%)	6, (4%)	105, (68%)	58, (48%)	49, (49%)	18, (18%)	144, (94%)	138, (89%)

Table 3. Transfusions and growth factor support

	Pre-lymphodepletion n, (%)	Day 0 - Day +30 n, (%)	Day +90 n, (%)
Red cells within 30days of timepoint	11, (7%)	44, (31%)	10, (13%)
Platelets within 7 days of timepoint	4, (3%)	28, (19%)	5, (6%)
Eltrombopag	2, (1%)	1, (0.7%)	0, (0%)
GCSF within 7 days of timepoint	2, (1%)	56, (50%)	17, (25%)

Conclusion: This single site retrospective descriptive analysis demonstrates that cytopenias post CAR-T are frequent, and the acuity of patients being managed post CAR-T. The advanced practice nurse role post CAR-T is a beneficial resource for monitoring and managing cytopenias in this complex patient group. Future research will identify risk factors for cytopenias to aid nurse-led management framework.

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Navigating the challenges in delivering bi-specific antibodies at an outer metropolitan hospital

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Background: Rockingham General Hospital (RGH) is a 229-bed outer metropolitan public hospital. The haematology department conducts outpatient clinics with the support of a 10-bed chemotherapy unit, with inpatient support from the medical team.
Bi-specific antibodies, including epcoritamab, are a new treatment option for patients with relapsed/refractory lymphoma. They can cause potentially severe yet manageable toxicities, particularly cytokine release syndrome (CRS) and immune effector cell-associated neurologic syndrome (ICANS).

Aim: This case series details the experience at RGH in overcoming the challenges for safe administration of epcoritamab in an outer metropolitan centre.

Methods: The following has been put in place for safe delivery of epcoritamab:

- Multidisciplinary team (MDT) formation: Members include haematologists, intensivists, inpatient medical team, clinicians, emergency physicians, pharmacists and nursing staffs.
- Education: focusing on anticipating, identifying and managing adverse events, especially CRS and ICANS.
- Development of local protocols: formulating site-specific materials for the recognition, grading, treatment and escalation pathways of CRS and ICANS.
- Hospital administration involvement: stakeholder involvement to ensure appropriate inpatient bed availability.
- Development of patient education program: to enhance patient understanding and education regarding early recognition of toxicities.
-

Results: To date, four patients with relapsed/refractory lymphoma have received Epcoritamab on the pre-approval access program at RGH. Treatment was delivered in the outpatient unit, with mandatory inpatient admission for the first full dose of epcoritamab under general medicine and ICU. This allowed 48-hour inpatient monitoring given the recognised risks of CRS and ICANS.

Adverse events including tumour flare, grade 2 CRS and grade 3 ICANS have been successfully managed and resolved with timely identification and intervention.
Conclusion: Our program has successfully navigated the challenges and safely delivered novel bispecific antibodies for patients with relapsed/refractory lymphoma. Allowing patients to have bispecific treatment closer to home has revolutionised therapy for patients in the regional/outer metropolitan areas.

Nurse-led change: The development of an outpatient Venetoclax ramp up pathway

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Aim: To move the delivery of Venetoclax ramp up dosing from the inpatient setting to an outpatient pathway (for patient's that meet the eligibility criteria).

Method: Using the existing Eastern Health Leukaemia Database, a comprehensive data analysis was performed with the aim of establishing a new pathway for delivering Venetoclax in the outpatient setting.

Results: Key findings highlighted the need for an Outpatient Venetoclax Ramp Up Pathway. These findings include that it will:

- Reduce inpatient bed days
- Improve patient experience of care
- Improve level of symptom support offered to patients
- Improve patient self-management and self-care strategies
- Reduce Emergency Department presentations.

Conclusion: An Outpatient Venetoclax Ramp Up Pathway is currently in development.

Developing evidence-based nursing guidelines: Advancing knowledge of glofitamab and epcoritamab bispecific antibody treatment for non-Hodgkin's lymphoma

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[1]Peter Maccallum Cancer Centre, Melbourne , Australia, [2]Barwon Health, Geelong, Australia

Aim: To develop an educational resource package for nurses aimed at improving their knowledge and understanding of glofitamab and epcoritamab, two novel bispecific antibodies used in the treatment of B-cell non-Hodgkin Lymphoma (B-NHL).

Method: While there have been recommendations recently published discussing assessment and management of bispecific antibodies[1], it has been demonstrated that there are currently no nursing resources available for glofitamab and epcoritamab. Therefore, guidelines and education packages are required to support safe delivery of these treatments to patients with B-NHL.

These guidelines will be developed by utilizing the Reporting Items for Practice Guidelines in HealThcare (RIGHT) checklist[2]. This tool will assist us to create guidelines that promote quality practice and are comprehensive, to be effectively adopted by nurses.

Once the guidelines are drafted, we will employ the Delphi model[3] to obtain a consensus among a panel of anonymous, diverse, and advanced experts from metropolitan and regional centres. The Delphi method uses a series of survey rounds to obtain recommendations or improvements until a consensus is widely accepted by the expert panel.

The finalised guidelines will be implemented into the educational resource package. This package will include detailed information on glofitamab and epcoritamab, their mechanism of action, administration protocols, side effects and nursing considerations. We propose this to be available via eVIQ, as a user-friendly resource which is accessible to nurses worldwide.

Results: This project is currently underway, and results will be available to be presented at the meeting.

Conclusion: By using the RIGHT checklist and Delphi model, we propose that our guidelines will be evidence based and comprehensive, while also being endorsed by leading experts. This methodology also ensures a rigorous and collaborative approach to developing educational resources for nurses and to support safe delivery of glofitamab and epcoritamab to patients with B-NHL.

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EBMT

Kenyon M

In 2024, the European Society of Blood and Marrow Transplantation (EBMT) marked their 50th year, while the EBMT Nurses group celebrated their 40th. This longstanding collaboration between nurses and physicians and more recently encompassing the whole transplant community is a hallmark of EBMT. In this session, attendees will learn more about the EBMT Nurses Group, its structure and programme of education and research alongside global collaborations to benefit the transplant community and patient care.

Myeloma Australia and Myeloma Research Laboratory: Insights from laboratory tours by the myeloma community

Gardiner J

Since 2009 Myeloma Australia (MA) and the Myeloma Research Laboratory (MRL, University of Adelaide) have conducted annual laboratory tours for people and their families affected by myeloma, aiming to increase understanding of local myeloma research, through a personalised experience.

Over 15 years, the MA support nurse worked with MRL staff, coordinating groups of 10-20 participants to tour facilities at the South Australian Health & Medical Research Institute (SAHMRI), hosted by PhD students and postdoctoral researchers.

Tours aim to provide an immersive experience, with participants viewing laboratory techniques, engaging with scientists, and gaining insights into ongoing local cancer research projects. Tours include interactive presentations, hands-on demonstrations, Q&A sessions and informal discussions over morning tea between researchers and participants. To understand the tours' effectiveness, participants and researchers were each invited to complete a short qualitative survey using Survey Monkey, before and after a tour held in February 2024.

100% of participants rated the tour as very good or excellent, meeting their expectations. They reported an increased understanding of cancer research and treatment development, and it provided hope for improved treatments. Meeting the disease under the microscope was reported as a powerful experience.

Researchers reported the tours were very valuable in advancing their research (71%), increased their understanding of the patient experience (100%) and enhanced their communication skills from explaining complex science in simpler terms (88%). Postdoctoral researchers highlighted potential opportunities for consumer involvement in grant applications and clinical studies (83%) and has resulted in a high response from the MA SA myeloma community to study recruitment. PhD students reported positive impacts on their training and development (100%).

Clearly the tours are valued by everyone involved. They are an important link between this myeloma specific support organisation, scientists working in the myeloma field and the people living with this chronic blood cancer.

Self-administration of subcutaneous Bortezomib in the home setting in regional NSW: A feasibility study

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Aim: Bortezomib-based regimens for patients with multiple myeloma (MM) are generally administered in cancer day units (CDU). Patients and carers in regional New South Wales, reported anxiety provoked by frequency of hospital visits, waiting times, travel and parking. This study examined the feasibility, safety and acceptability of a new model of care (MOC) enabling myeloma patients or their caregiver to self-administer subcutaneous bortezomib at home, supported by guidelines, educational resources, competency tools, telehealth tools, and safety protocols.

Method: Twenty-three MM patients participated in the prospective mixed-methods study. Patients or caregiver underwent an education cycle and competency assessment before approval for home administration. Day one of subsequent cycles was delivered in the CDU, remaining injections of the cycle were self-administered at home with telehealth monitoring. Patient experiences were explored through patient reported experience measures, appointment and MOC survey and semi-structured interviews with a sub-set of patients. Pre- and post- Self-Injection Assessment Questionnaires (SIAQ) was administered at baseline, week 1 and week 4. Safety and efficacy were evaluated using pathology results, self-injection adverse event (AE), PRO-CTCAE neuropathy items and FACT-NTX-13. Cost was measured for bortezomib manufacture, chair time and staffing.

Results: Patients ranged from 50 – 87 years, with 81% male and 57% having first line therapy. Twenty-one patients completed the study. SIAQ satisfaction scores showed significant improvement over time (baseline vs T1, $p = 0.0046$; vs T4, $p = 0.0139$). One self-injection AE was recorded. The self-administration model required 30 minutes of the patient's time weekly compared to 1-3 hours for CDU administration. Interviews revealed self-administration significantly improved patients' daily lives, with time savings the most frequently reported benefit. Cost analysis indicated higher expenses for CDU-administered bortezomib ($308 per cycle) compared to self-administration ($216 per cycle).

Conclusion: Self-administration of bortezomib is a safe and feasible option for patients with myeloma in a regional setting. There is a high level of satisfaction from patients and carers, reducing the time toxicity and treatment burden. The comprehensive design of the MOC is potentially transferable and adaptable to other drugs and tumour streams.

BMTSAA Symposium

Young matched unrelated donors improve disease free survival compared to other donor sources: A CIBMTR analysis

Nath K

Background: Post-transplant cyclophosphamide-based (PTCy) graft-vs-host-disease (GvHD) prophylaxis results in favorable outcomes after HLA-matched and mismatched allogeneic hematopoietic stem cell transplantation (allo-HCT). Whether younger alternative donors are superior when an older-aged, matched sibling donor (MSD) is available remains unclear. We hypothesized that use of younger alternative donors, including HLA-matched unrelated donors (MUD, HLA-8/8), HLA-mismatched unrelated donors (MMUD, HLA-≤7/8), or related/haploidentical donors (haplo), would result in improved outcomes compared to older-aged, MSDs using PTCy.

Methods: This retrospective analysis accessed data from the CIBMTR database from allo-HCT recipients aged ≥50-years with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) or myelodysplastic syndromes (MDS) who underwent their first allo-HCT between 2014-2021 using an older-aged MSD (donor age: ≥50-years) or young (donor age: ≤35-years) MUD, haplo, or MMUD. All recipients of allo-HCT received PTCy-based GvHD prophylaxis. The primary endpoint was overall survival (OS). Secondary endpoints were disease-free survival (DFS), relapse, non-relapse mortality (NRM), acute and chronic GvHD, and platelet/neutrophil engraftment. A Bonferroni stepdown model was used for multiple comparison adjustment.

Results: Amongst 3,746 allo-HCT recipients (61% male; mean age, 63-years; 57% AML, 31% MDS, 12% ALL), 540 underwent allo-HCT with older-aged MSDs (mean donor age, 60-years), 1,221 with young MUDs (26-years), 1,518 with young haplo (28-years) and 467 with young MMUDs (26-years). Patient baseline characteristics were similar between donor groups. The estimated 5-year OS was 44% (95% CI 38-49%) with older-aged MSDs versus 52% with younger MUD (48-56%; p=0.07), 45% with haplo (41-48%; p=1.0) and 46% with MMUD (39-52%; p=1.0). On multivariable analysis, there was no significant difference in OS with older-aged MSDs versus haplo (HR 1.02, 95% CI 0.88-1.18, p=1.0) or MMUDs (HR 1.00, 0.83-1.21, p=1.0), and the 8% difference in OS with young MUDs did not reach statistical significance (HR 1.20, 1.03-1.41, p=0.09). Compared to older-aged MSD recipients, DFS was improved after young MUD allo-HCT (HR 1.21, 1.05-1.40, p=0.048), and similar to haplo donor (HR 1.04, 0.90–1.19, p=1.0) and MMUD allo-HCT (HR 1.07, 0.90-1.28, p=1.0) – Figure 1B. Allo-HCT with older-aged MSDs also associated with a significantly higher relapse compared to recipients of both MUDs (HR 1.29, 1.08-1.53, p=0.02) and haplo donors (HR 1.30, 1.10-1.54, p=0.02). NRM was significantly lower with older-aged MSDs versus haplo donors (HR 0.68, 0.53–0.88, p=0.01), but there was no significant difference with MUDs (HR 1.00, 0.77-1.30, p=1.0) – Figure 1D. Regarding young MMUDs versus older-aged MSDs, there was no significant difference in DFS, relapse or NRM. All groups had similar rates of acute and chronic GvHD, and platelet and neutrophil engraftment. Within the younger donors, haplo donors had a significantly lower OS compared to MUDs (HR 1.18, 1.05-1.33, p=0.04), which was driven by NRM. HLA-DPB1 matching status did not impact the primary or secondary outcomes.

Conclusion: In allo-HCT recipients aged ≥ 50-years receiving PTCy-based GvHD prophylaxis, use of a young MUD resulted in superior DFS, lower relapse and similar OS compared to an older-aged MSD, and improved OS compared to young haplo donors, suggesting a benefit of young MUDs in this setting.

An optimised approach to achieving and maintaining compliance with multiple codes

Rodwell R

The regulatory oversight for cellular therapy products is linked to the risks posed by product manufacture to its critical quality attributes (CQAs) of purity, identity, efficacy, and safety, and ultimately to patient safety. The level of risk varies with the cell source, their intended use, the type of manipulation, and whether processing occurs off-site, or international product exchange occurs. The regulatory infrastructure encompasses country-specific applicable laws and codes, the FACT and AABB voluntary accreditation standards, and the requirements of commercial manufacturers and trial sponsors for emerging therapies. Although quality management system (QMS) elements are shared between codes, minor differences exist. Therefore, an incremental approach to an existing QMS when transitioning to a new code may lead to QMS gaps and citations during regulatory inspections. Gap audits, however, effectively identify missing components in existing systems. A quality plan that follows the order of the most prescriptive standards provides a guide to procedures. Strategies to achieve compliance include the application of quality risk management principles, change management linked to risk analysis and validation, a quality-by-design life-cycle process for validation activities, and establishing a quality culture. Implementing lean thinking principles for documentation, such as template forms or electronic document record systems can improve efficiency. Master validation and inventory management plans can ensure the product consistently meets its CQAs. A risk management plan details risks and control measures, and a contingency plan guides responses to service interruptions or significant disasters. Audit plans designed to assess critical issues and code compliance support the maintenance of inspection readiness. The results of a site-specific panel of quality metrics can form the basis of quarterly and annual QMS and outcome data reviews. The benefits of this approach include a robust QMS, continuous improvement, and the ability to maintain inspection readiness and compliance with multiple codes.

HSANZ Oral Presentations

HO001

Practices and outcomes during a watch and wait approach for follicular lymphoma: a study from the Australasian Lymphoma Alliance.

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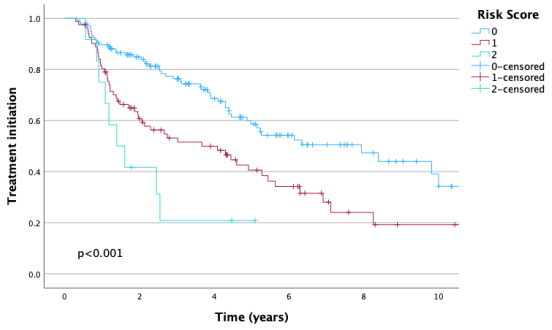
Background: Watchful waiting (WW) in follicular lymphoma (FL) defers treatment and has been considered safe. An assessment of the risks and real-world practices during WW has not been undertaken.

Aim: We examined the risks and outcomes for patients with FL managed with a WW approach in the rituximab era.

Method: We conducted a retrospective analysis of patients with newly diagnosed grade 1-3A FL managed with a WW approach across eight academic centres within the Australasia Lymphoma Alliance.

Results: 267 patients were included with a median follow-up of 5.5 years. The median age was 64 years, 55% were male, 78.7% had advanced stage disease. 28 patients (10.5%) met ≥1 GELF criteria at diagnosis. Median time to treatment (TTT) was 4.88 years (95% confidence interval [CI] 4.1-5.6yrs), with 29.6% continuing WW at 10 years. Treatment was commenced in 138 patients. Complications during the WW period occurred in 75 (28.1%) patients with the most common being transformation (n=34, 12.7%), pain/discomfort (12.4%) and B symptoms (5%). There was no mortality associated with WW. Imaging prior to treatment was surveillance imaging in 19.9% and prompted by clinical findings in 80.1%. Excluding patients with transformation, 68% (71/104) fulfilled GELF criteria at the time of treatment. GELF criteria at diagnosis was not associated with treatment initiation, complications or transformation during WW. OS was similar for patients treated vs ongoing WW (p=0.61). For GELF negative patients (n=230), >4 nodal stations and elevated LDH were independent prognostic factors for TTT that identified three groups (low score 0, intermediate score 1, high score 2).

Conclusion: Current practices for patient selection and management are safe with few major complications during WW. LDH and number of nodal stations at diagnosis identified a low-risk group with prolonged TTT and a high-risk group predicted for early progression who may be candidates for immediate treatment.



Risk score	No patients	Median time to Rx (95% CI)	HR (95% CI)
0	136	7.94 (4.78-11.10)	1.0
1	82	3.67 (1.54-5.79)	1.92 (1.31-2.83)
2	12	1.38 (0.67-2.11)	3.66 (1.79-7.49)

HO002

Myocarditis complicating early acute myeloid leukaemia: a case series.

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We present five cases of myocarditis complicating the diagnosis and initial treatment of acute myeloid leukaemia (AML). Patient ages ranged from 26 to 68 years and four were male. Leukaemia diagnoses are listed in Table 1. Infective screening tests including COVID-19 PCR were negative in all patients.

Cardiac findings are listed in Table 1. In all cases myocarditis was confirmed on cardiac MRI except in case 4, who died prior to MRI. Evidence of pericardial involvement was seen in cases 1 to 4. Case 1 and 5 presented to hospital with severe cardiac chest pain and AML was incidentally diagnosed. The remaining three patients experienced minor chest pain, leading to myocarditis diagnosis, during early hospitalisation for AML. Other frequent clinical features included high fevers and markedly elevated C-reactive protein, the subsequent development of significant fluid overload and cardiac rhythm disturbances.

Four patients received corticosteroids and two received colchicine. Case 4 suffered a rapid deterioration with hypotension and multi-organ failure, dying three days into the hospital admission. The remaining four cases received standard first-line AML treatment including an anthracycline (idarubicin dose reduced in one patient due to hepatic dysfunction). Follow-up echocardiography showed resolution of changes in the four surviving cases, and overall cardiac status remained stable.

Potential mechanisms of myocarditis in AML include paraneoplastic, leukaemic infiltration and infection. Although myocardial pathology was common in historical leukaemia autopsy studies, myocarditis complicating early AML is today considered a rare diagnosis; only a small number of single case reports exist in the current literature. Our case series is therefore significant and highlights and importance of this diagnosis, given the cardio-toxicity risk of AML therapies. Fortunately, of the four surviving patients, all tolerated first-line AML therapy and maintained normal cardiac function.

Case	AML diagnosis	Morphology	Peak Troponin (ng/L)	ECG	Ejection fraction (EF) nadir	Arrhythmia	Outcome
1	APML	Promyelocytic	23 484	ST elevation (global, concave)	55%	Ventricular tachycardia	Stable EF
2	AML with mutated NPM1	Myeloblastic	11 951	ST elevation (inferior, lateral)	10%	No	Recovered EF
3	AML with mutated TP53	Myeloblastic/ monoblastic	4 978	ST elevation (global, concave)	58%	Atrial fibrillation	Stable EF
4	MDS/AML with mutated TP53 post cytotoxic therapy	Myeloblastic	69 898	ST elevation (lead II)	35%	Atrial fibrillation	Death
5	AML, not otherwise specified	Monoblastic	5 777	No ST changes	50%	No	Recovered EF

HO003

A window study of acalabrutinib & rituximab, followed by chemotherapy & autograft (ASCT) for treatment naïve mantle cell lymphoma (MCL) patients: Results from the investigator-initiated ALLG NHL33 'Wamm' trial.

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Aim: Here we report the primary endpoint (EP) from the phase 2 'WAMM' trial exploring a 'sandwich' model of an acalabrutinib-rituximab (AR) 'window' before RDHAOx +/- ASCT, followed by fixed-duration AR-maintenance to improve therapy response and minimise additional toxicity.

Method: WAMM is a multicentre single-arm phase 2 trial. Key eligibility: age 18-70 years, untreated stage II-IV MCL, ECOG<2; no contraindications to ASCT or BTKi. Pts received 2 cycles of AR, followed by RDHAOx x 4. Those with a response underwent a ASCT then AR maintenance (A; 1yr continuous & R; 3-monthly x 8 cycles). Co-primary EPs were safety; defined by lack of prohibitive toxicity causing treatment cessation AND PET-determined CR rate after AR+RDHAOx. Secondary EP: ORR, toxicity, OS & PFS and MRD negativity rates. Baseline whole exome sequencing was performed. MRD analysis was done by LymphoTrack® Dx *IGH* Assay platform (Invivoscribe, Inc). This study was the first Australian blood cancer trial to use telehealth transplant model.

Results: 44 pts were enrolled from Sept 2020 to Apr 2022 (43 evaluable for 1° EP). Baseline characteristics: median age 59 years, 77% male, ECOG 0-1 in 98%, 84% stage IV, Ki-67 >30% in 66%, blastoid/pleomorphic histology in 9% and 11% were *TP53* mutated. CR rate post AR+RDHAOx induction was 88% with no prohibitive toxicity. AR window ORR was 93% (CR 57%). MRD negativity was achieved in 18% post AR window, and 94% post RDHAOx. 35 pts (81%) experienced ≥1 G3+ adverse events, with no treatment related deaths. After a median follow up of 22 months, the 2-year OS was 89%.

Conclusion: AR delivered in a sandwich approach is active and safe. An AR window yields a high ORR and compared to historical studies, improves post-chemo induction CR rates and MRD negativity. A telehealth model allowed rapid recruitment in a rare cancer.

HO004

Should large cell transformation of mycosis fungoides be recognised as a separate entity? Patterns of care and patient outcomes from Australia's only quaternary service for cutaneous lymphomas.

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Aim: Large cell transformation of mycosis fungoides (LCTMF) is rare, and frequently associated with more aggressive clinical course and inferior survival than classical MF. Yet, LCTMF is not recognised as an independent entity in the World Health Organisation Classification, nor staging systems for MF.[1,2] Reflecting the paucity of published data to guide management, LCTMF is frequently omitted from clinical guidelines. Herein, we describe patient characteristics, management and outcomes of LCTMF, from Australia's only quaternary service for the management of cutaneous lymphomas.

Method: Eligibility for this retrospective study required clinico-pathological diagnosis of LCTMF from 1/1/1990-01/10/2021 and treatment at Peter MacCallum Cancer Centre.

Results: 83 patients with biopsy-proven LCTMF were eligible. Median age was 67 years; 53 (64%) were male, 28% early-stage MF (IA-IIA). 63 (76%) had cutaneous-only LCTMF, of these 49% were uni-lesional. CD30 expression was positive (defined as >10% atypical lymphocytes) in 47 (57%) patients. Median time from diagnosis of MF to LCTMF was 2.1 (range, 0-27.2) years, median follow-up thereafter was 8 years.

Treatment for LCTMF was delivered concurrent to MF management. For LCTMF, 8 different therapeutic groups were used first-line: skin-directed therapies (radiotherapy (48%), phototherapy (2%)), systemic therapies (multi-agent chemotherapy (23%), single-agent chemotherapy (10%), interferon (8%), monoclonal antibody-based monotherapies (4%), histone deacetylase inhibitors (2%)) and best supportive care (2%). Median number of treatment lines for LCTMF was 3 (range, 0-11).

Median overall survival (OS) was 3.5 years (95%CI: 2.23-8.20), with 5- and 10-year OS of 41% (95%CI: 32-54) and 31% (95%CI: 21-46), respectively.

In multivariate analyses, age (>55 years) and extracutaneous LCTMF were both independent adverse prognostic factors.

Conclusion: Differences in pathology, behaviour, management and outcomes between LCTMF and MF, favour recognition of LCTMF as a distinct entity. Further research is required to identify patients at highest risk of LCTMF, and for development of risk-based treatment protocols.

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HO005

Developing precision CRISPR-Cas13-based RNA therapeutics for haematological malignancies

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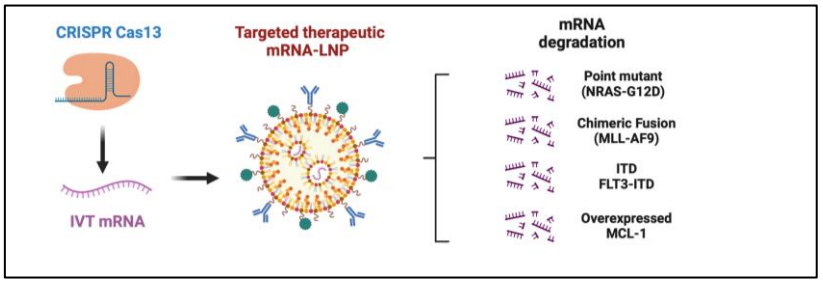
Background: AML remains a clinical challenge due to the lack of targeted therapies for many driver mutations. CRISPR-Cas13 offers a novel approach by enabling precise RNA degradation without impacting genomic DNA. Accordingly, as a potential therapeutic, Cas13 is safer and more adaptable than DNA-targeting CRISPR-Cas9.

Aim: 1. Pioneer a modular platform targeting various **classes** of AML mutations using CRISPR-Cas13, including over-expressed transcripts (MCL-1), point-mutated oncogenes (NRAS-G12D), internal tandem duplications (FLT3-ITD), and chromosomal fusions (MLL-AF9). **2.**To develop CRISPR-Cas13 tools as in vitro-transcribed (IVT) mRNA therapeutics that can be delivered to AML cells by lipid nanoparticles (LNPs).

Method: We designed guide RNAs (crRNAs) targeting clinically relevant genes and assessed mRNA silencing using an in-house fluorescence reporter assay. A panel of AML cell lines (THP-1, MV4-11, MOLM-13) were transduced with CRISPR effectors and top-performing crRNAs, and downstream phenotypic consequences of Cas13-mediated silencing were assessed. LNP candidates encapsulating CRISPR-Cas13 IVT-mRNA were synthesised and screened in leukaemia cells for effective delivery. Anti-CD33 monoclonal antibodies were conjugated to LNPs using maleimide click chemistry.

Results: CRISPR-Cas13 consistently silenced AML target transcripts with >90% efficiency, including MCL-1 and FLT3, but also undruggable targets such as MLL:AF9 transcripts, wild-type NRAS and $NRAS^{G12D}$. crRNA engineering achieved mutant-selective silencing, even for single nucleotide variants. Target silencing generated concordant phenotypes in AML cells including cell death and impaired proliferation. Iterative LNP design yielded a previously unreported formulation capable of delivering CRISPR-Cas13 IVT-mRNA to 'untransfectable' leukaemia cells with >90% efficiency (THP-1, MOLM-13). Conjugated anti-CD33 monoclonal antibodies enhanced LNP targeting specificity and efficiency in THP-1 cells.

Conclusion: These data provide proof-of-concept justifying further development of LNP-delivered, mRNA-based RNA-targeting with Cas13. CRISPR-Cas13 massively expands the range of druggable targets, achieving exquisite specificity in AML and conceivably any malignancy. This platform represents a potential paradigm shift and novel approach to personalised cancer medicine.



HO006

Mosunetuzumab demonstrates clinically meaningful outcomes in high-risk patients with heavily pre-treated relapsed/refractory (R/R) follicular lymphoma (FL) after ≥3 years of follow-up: subgroup analysis of a pivotal phase II study

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Aim: To present a subgroup analysis of a Phase II study in high-risk R/R FL patients treated with mosunetuzumab, after ≥3 years of follow-up.

Method: Eligible patients had R/R FL Grade (Gr) 1–3a and ≥2 prior therapies.Efficacy and safety were assessed in patients with a history of progression of disease within 24 months (POD24) from start of first-line therapy, patients receiving mosunetuzumab in 3L vs 4L+, and patients aged ≥65 years.

Results: As of May 2023, 90 patients received mosunetuzumab; 52% had POD24, 61% had 4L+ therapy, 33% aged ≥65 years. CR rates in patients with POD24 (60%), patients ≥65 years (67%) and 4L+ patients (55%) consistent with the overall population (60%). Numerically lower 30-month DOCR rate observed in 4L+ (66%) vs 3L (77%) pts. 3-year PFS rate: 44% in patients with POD24, 47% in patients ≥65 years, consistent with overall population (43%). 3-year PFS rate was lower in 4L+ (36%) vs 3L (54%) patients.

Safety across subgroups was consistent with the overall safety cohort (OSC). Incidence of CRS events: 51% in patients with POD24, 47% in 4L+ patients, 30% in patients ≥65 years, and 44% in the OSC. In the OSC, any-grade infections occurred in 51% of patients; after C8, 8 events were reported in 8 patients. Gr≥3 infections observed in 17% of patients. Most common Gr ≥3 infections: pneumonia (3%), upper respiratory tract infection (2%), septic shock (2%) and COVID-19 (2%). Most serious infections (14/19 [74%]) occurred in the first 4 cycles; after C8, 3 events reported in 3 pts. Serious infections concurrent with neutropenia were rare (1%). Hypogammaglobulinemia reported in 2% of pts.

Conclusion:

Fixed-duration mosunetuzumab monotherapy showed durable remissions and clinically meaningful survival outcomes in high-risk patients with heavily pre-treated R/R FL. Safety was manageable and consistent across subgroups supporting outpatient administration.

HO007

Antibiotic-induced ablation of gut microbiota in murine models of acute lymphoblastic leukaemia results in variable patterns of leukaemic cell engraftment.

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Aim: Dysbiosis of the gastrointestinal microbiome has been associated with disease pathophysiology in several contexts including; cancer, allergies and metabolic conditions. Emerging evidence postulates a role for gut microbiota dysbiosis in the development and treatment response of blood cancers. Here, we investigated the role of dysbiotic microbiota on the engraftment of ALL cells in a murine model.

Method: Six-week-old Nod Scid Gamma mice were provided with drinking water with or without ampicillin and neomycin (n=20 in each group) to deplete the gut microbiota. Mice were injected with B-ALL patient cells via tail-vein from one of the following subtypes; *NUP214::ABL1, DUX4::IGH, KMT2A::AFF1,* or *P2RY8::CRLF2*. Faecal samples were collected weekly, and gut microbiota changes were assessed by 16s rRNA bacterial load qPCR. Bone marrow, extramedullary organs, ileum and caecum were harvested for histological analysis. Immunophenotyping of tissues was conducted via flow cytometry and statistical significance was analysed via unpaired t-test and 2-Way ANOVA.

Results: A significant increase in leukaemic engraftment was observed at day 42-43 post-injection in antibiotic-treated mice compared to controls in *NUP214::ABL1* and *P2RY8::CRLF2* groups (p=0.0113 and p=0.0222 respectively; Fig.1). There was also an increase in the spleen size (p=0.0087 and p=0.0087 respectively).

Interestingly, antibiotic-treated mice harbouring *KMT2A::AFF1* had significantly smaller spleens than controls (p=0.0003), an inverse observation to *NUP214::ABL1* and *P2RY8::CRLF2* cohorts. No significant changes were observed between organ weights, phenotypic profiles or survival (72 days) in the *IGH::DUX4* cohort.

Conclusion: A dysbiotic microbiota appears to provide an environment supporting leukaemic engraftment in mice harbouring blasts from patient cells harbouring *NUP214::ABL1* and *P2RY8::CRLF2* subtypes, with differences most pronounced in the spleen. Our observations require further exploration of the interaction using ALL cells from additional patients with the same and differing lesions. These preliminary results suggest gut microbiome dysbiosis may have an influence on certain ALL subtypes.

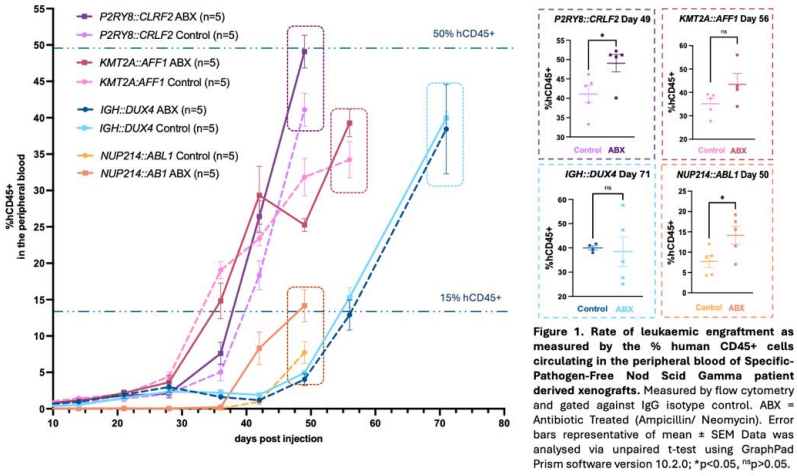

Figure 1. Rate of leukaemic engraftment as measured by the % human CD45+ cells circulating in the peripheral blood of Specific-Pathogen-Free Nod Scid Gamma patient derived xenografts. Measured by flow cytometry and gated against IgG isotype control. ABX = Antibiotic Treated (Ampicillin/ Neomycin). Error bars representative of mean ± SEM Data was analysed via unpaired t-test using GraphPad Prism software version 10.2.0; *p<0.05, nsp>0.05.

HO008

Megakaryocyte emperipolesis in MPN: Neutrophils Friend or Foe?

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Aim: Emperipolesis is a biological process in which a cell penetrates and exists as a viable intact cell within another. Megakaryocyte emperipolesis, primarily involving neutrophils, is a recognised morphological feature of myeloproliferative neoplasms (MPN). It is thought to be a passive process with the emperipolesed cells remaining intact. Our aim was to determine whether there has been any interchange of neutrophil protein or RNA within the megakaryocyte.

Method: Blood and bone marrow samples were obtained from 222 consenting MPN patients and 45 controls (three tertiary public hospitals in WA). Marrow biopsies were assessed morphologically and following immunohistochemical staining (H&E, CD15, CD61, myeloperoxidase, lactoferrin). Platelets isolated from blood were assessed for protein expression using SWATH-MS (Sequential windowed acquisition of all theoretical fragment ion-mass spectra) and subjected to an independent t-test. Platelet mRNA was examined using transcriptomic NGS and assessed using a Wald test, followed by a Benjamin-Hochberg p-value adjustment.

Results: 84% of MPN patients had megakaryocyte emperipolesis, confirmed as neutrophils by CD15 positivity. Megakaryocytes in MPN, but not controls, showed positivity for azurophilic neutrophil granule protein myeloperoxidase (<1-30%) and specific granule protein lactoferrin (<1%-59%). Platelet protein analysis showed increased expression of neutrophil azurophilic, specific and gelatinase granules and secretory vesicle proteins. Examples include cathepsin-G (azurophilic) and lactoferrin (specific) with 1.8-fold and 1.4-fold protein increases, and *CTSG* 5.1-fold and *LTF* 4.6-fold increase in mRNA, respectively.

Conclusion: Megakaryocyte emperipolesis is common in MPN. The protein and mRNA data show evidence of neutrophil-unique granule proteins and mRNA within megakaryocytes and platelets. The mechanism by which this exchange occurs is unclear. It could be due to active release of neutrophilic constituents into megakaryocytes (and then to platelets) during emperipolesis. Alternatively, megakaryocytes could lead toxic damage to neutrophils resulting in loss of cellular material into the megakaryocyte.

HO009

Cord blood-derived microtissues as a preclinical testing platform for pediatric vascular inflammation

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Aim: There is a substantial absence of clinical trial data for drugs prescribed to children whereby data is mostly extrapolated from adults (1). Difficulty in recruiting pediatric volunteers due to ethical and safety issues (2) prompts us to reconsider how to ensure the safety of children during testing who have more complex physiological and developmental characteristics from adults (3). We have engineered a three-dimensional culture platform mimicking the body's inflammatory response using cells derived from cord blood (CB) to represent pediatric haematopoietic-endothelial crosstalk. This novel system is the first to combine endothelial colony forming cells (ECFCs) and mononuclear cells (MNCs) in a 3D cell culture. This 3D model does not aim to replace clinical trials but presents a translatable, economical, and physiologically relevant alternative to pre-clinical drug screening for pediatric populations.

Method: ECFCs and MNCs were isolated from human CB units and cocultured in a fibrin hydrogel. Vascular-like networks self-assembled in culture and were characterized phenotypically by immunocytochemistry. Cultures were exposed to TNF-α (10ng/ mL) to induce inflammation. Detection of inflammatory cytokines and staining with ICAM-1 were evaluated thereafter. Coculture with adipose-derived mesenchymal cells (AD-MSCs) was conducted as control.

Results: CB-MNCs can support vascular network formation of ECFCs (Figure 1A) with MNCs populating ECFC microvessel surfaces. Inducing inflammation by TNF-α exposure in ECFC:MNC cultures showed positivity for ICAM-1 that was not observed in ECFC:AD-MSCs (Figure 1B). Inflammatory markers (TNF-α, IFN-γ, IL-6) were also upregulated in ECFC:MNC cocultures more than ECFC:AD-MSCs.

Conclusion: This novel 3D coculture platform highlights the capability of MNCs to support perivascular growth. As a preclinical testing model, coculturing with MNCs allowed for more sensitive detection of inflammatory cytokines compared with commercial cell lines.

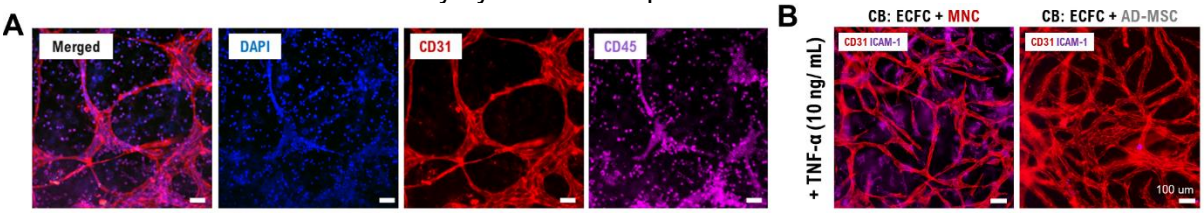

Figure 1. ECFC (CD31) and MNC (CD45) cocultures in 3D fibrin hydrogel (A). Positive ICAM-1 staining in ECFC: MNC cultures after TNF-α stimulation (B).

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HO011

Impact of socioeconomic status on utilisation of ASCT and overall survival in multiple myeloma: a report from the Australian and New Zealand (ANZ) Myeloma and Related Diseases Registry (ANZ MRDR)

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Aim: There has been a dramatic improvement in survival outcomes in multiple myeloma (MM) over the last 20 years. However, these benefits have not been recognised equally among patient populations[1]. We aimed to assess the impact of non-biologic factors on treatment and survival outcomes.

Method: We conducted a retrospective review of 3392 MRDR patients with MM from 44 sites across ANZ between June 2012-April 2024. Deciles of area-level socioeconomic status (SES) were generated by linking individual postcodes to data from the Australian Bureau of Statistics utilising the composite Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD). Low SES was defined as IRSAD deciles 1-5 (n=1281) and high SES as deciles 6-10 (n=2111). Baseline characteristics were compared between high and low SES as well as between ASCT recipients and non-recipients. Kaplan-Meier methods were used to estimate overall survival from the date of diagnosis (OS). Multivariate analysis was undertaken for OS using cox regression.

Results: The low SES group had a higher BMI (median 28.32 vs 26.64, p<0.001), increased rates of diabetes (14.6% vs 10.5%, p<0.001) and pulmonary disease (6.7% vs 4.4%, p=0.007%). There was no statistical difference between groups for age, gender, disease stage (ISS-3), ECOG ≥2, liver disease or peripheral neuropathy. Compared to the low SES group, those in the high SES group were more likely to have an ASCT (55% vs 48.2%, p<0.001) and had an improved median OS (89.3 vs 74.4 months, p=0.001). These findings retained statistical significance after adjustment for BMI, diabetes and pulmonary disease.

Conclusion: These data demonstrate a disparity in OS and utilisation of ASCT favouring higher SES independent of biological factors in a universal healthcare model. Given ASCT has proven survival benefit[2] and is recommended as upfront treatment for eligible patients[3], this disparity warrants further research to address barriers and enhance equitable outcomes.

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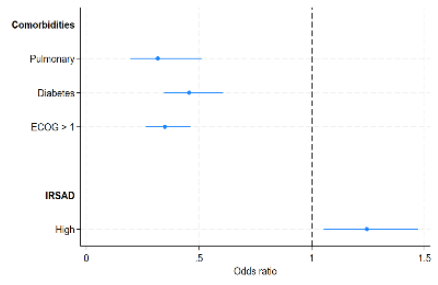

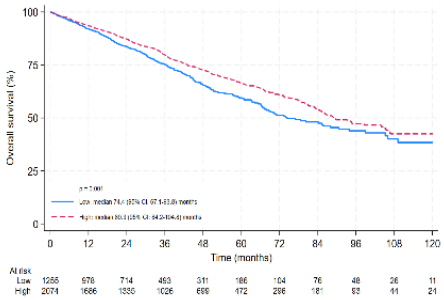

HO012

Treatment of First Relapse of Multiple Myeloma in Australia and New Zealand (ANZ): Treatment Patterns and Outcomes: An ANZ Myeloma and Related Diseases Registry (ANZ MRDR) Analysis

Gration B[1], Wellard C[2], Moore E[2], Tan M[3], Rowland J[4], Murphy M[5], Lim K[6], Hamad N[1], Rajagopal R[3], Mollee P[4], Spencer A[5], Quach H[6], McCaughan G[1]
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Aim: There remains lack of consensus regarding whether relapsed multiple myeloma should be treated at clinical or biochemical progression (CP/BP), and the ensuing clinical outcome. We described practices in ANZ and the outcomes in these cohorts.

Method: We conducted a retrospective review of MRDR patients across 5 sites in ANZ that had progressed following first line therapy. Additional information was sought regarding timing of treatment at myeloma relapse (BP or CP) and presence of end organ damage (EOD) at 3-6 months. We determined PFS and OS in these cohorts.

Results: Among 284 patients, 53% were treated at BP and 47% at CP. There was no difference in age, gender, ECOG, ISS-3 or high-risk cytogenetics at diagnosis between groups. There was no difference in time to first progression (CP=21.1 months vs BP=21 months) or time between progression and initiation of therapy (CP=1.6 vs. BP=1.7 months). Patients treated at CP had a higher rate of persistent opioid requirement at 6 months (CP=33% vs BP=15.2%, $p<0.001$) and need for a mobility aid at 6 months (CP=14.4% vs. BP=6.6%, $p=0.044$), but there was no difference in fracture rates between the groups at 6 months. 68% of patients with renal EOD had no renal response as per IMWG at 3 months. There was no difference in PFS between the two groups (CP=10.3 months vs. BP=12.2 months, $p=0.203$). Those treated at BP had improved OS from initiation of second line therapy compared to treatment at CP (CP=23.5 months vs. BP=34.4 months, $p=0.046$).

Conclusion: Initial disease characteristics, time to first progression and from progression to initiation of second line therapy did not differ between groups. Treatment at BP was associated with less persistent EOD and those treated at BP had significantly improved OS, but not PFS, compared to treatment at CP. This inferior OS may be related to persistent EOD or more aggressive disease biology, and warrants further investigation.

HO013

Pembrolizumab plus the anti–LAG-3 antibody favezelimab in patients with anti–PD-1–naive relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL): updated analysis of a phase 1/2 study

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Aim: Pembrolizumab plus favezelimab demonstrated acceptable safety and sustained antitumor activity in patients with anti–PD-1–naïve R/R cHL (cohort 1) in a phase 1/2 study (NCT03598608). We present updated results from cohort 1.

Method: Patients were ≥18 years, had anti–PD-1–naïve R/R cHL, and were ineligible for ASCT, failed to respond to or progressed after ASCT, or did not respond to salvage chemotherapy. A safety lead-in to determine RP2D was followed by efficacy expansion. Patients in the safety lead-in received pembrolizumab 200 mg plus favezelimab 200 mg escalating to 800 mg IV Q3W. In efficacy expansion, patients received pembrolizumab 200 mg plus favezelimab 800 mg (RP2D) IV Q3W for ≤35 cycles. Safety was the primary end point. ORR per IWG 2007 criteria by investigator review was secondary. DOR, PFS, and OS were exploratory.

Results: Cohort 1 included 30 patients. Median follow-up at data cutoff (February 22, 2024) was 43.2 months (range, 35.7-54.9). Any-grade treatment-related AEs occurred in 27 patients (90%) with grade 3 or 4 events in 7 (23%). Five patients (17%) discontinued treatment and no patients died because of treatment-related AEs. AEs of clinical interest occurred in 20 patients (67%); 3 (10%) had grade 3 events (colitis, pneumonitis, severe skin reaction) and 1 (3%) had a grade 4 event (hepatitis). ORR was 83% (95% CI, 65-94; CR 11/PR 14). Median DOR was 17.0 months (range, 2.6 to 33.3+). Median PFS was 19.4 months (95% CI, 9.5-28.5). Median OS was not reached (95% CI, 46.9 months-NR).

Conclusion: In this updated analysis, pembrolizumab plus favezelimab continued to demonstrate manageable safety and sustained antitumor activity in patients with anti–PD-1–naive R/R cHL.

HO014

Immunotherapy plus escalating radiotherapy dose and field in relapsed lymphoma. The phase I RaDD study.

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Aim: Relapsed/refractory (RR) Diffuse Large B-Cell (DLBCL) and Follicular Lymphoma (FL) are exquisitely radiosensitive, with limited effective therapies and poor outcomes. Our study examined the safety of escalating doses of radiotherapy (RT) plus durvalumab, (PD-L1 inhibitor) in RRDLBCL and RRFL and the role of immune-cell subsets on response and survival.

Method: RaDD (NCT03610061) was a multisite phase I study in adult transplant-ineligible RRDLBCL & FL. Patients (pts) received external-beam RT (2.5–30Gy, 5 or 10 fractions) to 1-3 target sites, plus Durvalumab 1500mg IV Q4W starting Day 2 RT until PD (RT+D). Primary endpoint was RT recommended phase two dose (RP2D). Secondary endpoints: response rate, toxicity, progression-free- and overall survival (PFS & OS). Tissue markers were analysed (NanoString pan cancer immune and OLINK immune response panels). Novel immunePET was performed in a subset of patients examining biodistribution of 89Zr-Durvalumab & CD8 minibody 89Zr -Df-cremirlimab.

Results: 34 pts were enrolled; 5 FL, 29 DLBCL. Median age was 74y. Median prior lines was 2 (range 1–3). No DLTs occurred. RT RP2D was 20 Gy/5# to 3 sites in FL & 30 Gy/10# to 3 sites in DLBCL. Most common G3-4 adverse events were anaemia (9%, n=3), neutropenia (11%, *n*=4), LFT derangement (5%, *n*=2). In evaluable pts, 66% achieved reduction in target lesions, in 33% shrinkage was >50%. ORR was 60% in FL (CMR 40%); 14% in DLBCL (CMR 10%). Median PFS & OS were 1.9m and 7m respectively. Evidence of T-cell activation in tumour at baseline by PET was correlated with ORR ($p<0.05$).

Conclusion: RT+D with RT doses up to 30Gy/10# to 3 disease sites is safe with minimal toxicity and offers promising responses in FL. Baseline T-cell activity on CD8-PET and tissue correlates with response to RT+D.

HO015

The EpiMAP Myeloma model: A new tool for predicting the impact of changes to the Multiple Myeloma treatment pathway

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Aim: The Pharmaceutical Benefits Advisory Committee makes reimbursement decisions for new therapies based on economic models and clinical trial results submitted by sponsors. It is difficult to determine the downstream impact of listing a new therapy from such evidence. The aim of this study was to estimate the impact of listing bortezomib, lenalidomide and dexamethasone (VRd) for first-line stem cell transplant (SCT)-ineligible multiple myeloma (MM) using the novel EpiMAP Myeloma model developed using the Australia & New Zealand Myeloma and Related Diseases Registry.

Methods: We assessed the impact of listing VRd in August 2019 using 5 years of published estimates of the incidence of MM in Australia. Results from the pivotal VRd clinical trial were used to estimate the distribution of responses to VRd that would be observed in routine clinical practice. Outcomes were median overall survival (OS), total lines of chemotherapy received, and total time on chemotherapy.

Results: From 2020 to 2024 there were an estimated 12,314 new MM diagnoses in Australia. The EpiMAP Myeloma model estimated that the introduction of VRd improved the median OS for SCT-ineligible patients from 4.6 to 5.3 years. Based on an estimated 35% uptake, there were no significant changes in the total number of chemotherapy lines (No VRd 70,883, VRd 70,672) or total time on chemotherapy (No VRd 2,574 days, VRd 2,589 days).

Conclusion: By improving the best clinical response to induction therapy, the model predicted that the introduction to VRd would marginally improve OS without a downstream impact in terms of subsequent chemotherapy lines or time on chemotherapy. These results demonstrate how the EpiMAP Myeloma model could inform future budget-impact analyses.

HO016

Virtual Chemotherapy Day Unit (VCDU): functionality, safety and experience

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Aim: The VCDU aims to optimise the current self-delivery model of care for people with Myeloma at St Vincent's Public Hospital Melbourne, specifically:
Reduce gaps between nurse-administration and self-administration.
Facilitate benefits of self-administration, without loss of expert nursing support.
Decrease time and financial toxicity of eligible treatments.
Improve assessment and safety with telehealth supervision.
Recruit new patients though creation of a sustainable business model.
Improve the capacity of the chemotherapy day unit (CDU).

Method: The myeloma nurse team reviewed current model of care, specifically sustainability barriers and workflow differences, then benchmarked against other similar models of care. A quality improvement project was proposed and supported by haematology and nursing leadership. A Western and Central Melbourne Integrated Cancer Service grant and a successful business case funded the project lead and VCDU clinical nurse.

Multidisciplinary steering committee and expert nursing group oversaw pre-pilot setup of model of care, inclusive of all patient facing material and organisational deliverables, the physical clinic, and full integration of hospital systems.

Result: Results: Running each Friday since 16/2/24, the VCDU has transitioned 15 patients out of CDU with no adverse or clinical incidents noted over 3 months. 29 VCDU attendances created 44 hours of treatment capacity in the CDU.

Eligible treatments include Bortezomib and subcutaneous immunoglobulin. Whilst initially myeloma focused, eligibility expanded as immunoglobulin therapy crosses haematology streams.

Conclusion: The Virtual CDU uses a nurse-led clinic backbone to facilitate real time pre-treatment assessment, positive identification, supervision of administration and disposal, as well as expert follow up education and support. Informal consumer feedback has been positive, with formal survey results planned for 6 and 9 months post implementation.

Integration with hospital systems has created a sustainable and accessible model which facilitates smooth patient flow into and out of CDU.

Early success of model of care has facilitated exploration of Daratumumab self-administration, an exciting future development in patient centred care for people with Myeloma.

HO017

Engineering a human model of TET2-mutated pre-leukemic monocyte to understand the biology of chronic myelomonocytic leukemia

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Aim: Mutations in epigenetic regulator gene, ten eleven translocation 2 (TET2), are observed in age related clonal haematopoiesis, and prevalent in chronic myelomonocytic leukemia (CMML) [1], which is characterized by inflammatory monocytosis [2]. We aim to model and investigate the effect of TET2-mutations on differentiated human monocytes to develop personalized targeted strategies.

Method: TET2 was knocked out (KO) in three different cord blood hematopoietic stem progenitor cells (CB HSPCs) using CRISPR. TET2-KO HSPCs and wild type (WT) were differentiated into monocytes over 21 days using human cytokines cocktail. The effect of TET2-KO in monocytes was investigated by immunophenotyping using flow cytometry, gene expression of inflammatory cytokine and inflammatory protein production after lipopolysaccharide (LPS) and ATP stimulation. The secretome of monocytes was also analysed before and after stimulation. Data was analysed using one-way ANOVA after normalization.

Results: Using TIDE analysis, at least 89% of HSPCs had TET2-KO. Functional differentiated Mono/Mac were confirmed by the expression of CD14, CD11b, CD206, CD68, and CD80. Increased inflammasome NLRP3 protein was observed in TET2-KO monocytes, that also showed higher IL-1β gene expression and active IL-1β protein excretion after stimulation. Evaluation of secretome had shown differential protein expression between TET2-KO monocytes and WT with upregulation of pro-inflammatory cytokines in TET2-KO monocytes.

Conclusion: We successfully engineered a human functional model of TET2-mutated monocytes differentiated from CB HSPCs to understand the biology of CMML. CMML is a disorder of profound innate immune activation, where TET2 mutations could contribute to more inflammatory features in monocytes. Our model phenocopies several features of TET2- mutated clonal hematopoiesis where TET2 mutations constitutively activate innate immune response in monocytes. Our model characterized differential protein secretion that would be investigated as novel targets.

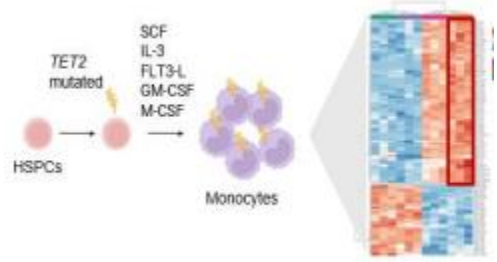

Figure 1: TET2- KO CB HSPCs were differentiated to monocytes. Heatmap shows differential protein expression between groups.

References:

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HO018

A Prospective Assessment of Quality of Life in People with Multiple Sclerosis following Autologous Haematopoietic Stem Cell Transplant

Karki N[1,2,3], Moore J[1,2,3], Massey J[1,2,3,4], Milliken S[1,2,3], Ma D[1,2,3], Withers B[1,2,3], Sutton I[4]
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Aim: Autologous Haematopoietic Stem Cell Transplant (AHSCT) has demonstrated significant clinical benefits in people with Multiple Sclerosis (PwMS). To understand its outcome from patient's perspective, a quality of life (QOL) instrument has been employed but the MS-specific QOL tool is lacking. This study aims to assess longitudinal QOL data in mental composite (MC) and physical composite (PC) using the validated and MS-specific 54-itemed QOL (MSQOL-54) instrument and assess changes between pre- and post-HSCT over the long-term in a large cohort.

Method: This prospective longitudinal study, conducted at St. Vincent's Hospital, Sydney (HREC/10/SVH/135) focuses on PwMS transplanted since 2010 using the BEAM-ATG (Carmustine, Etoposide, Cytarabine, Melphalan with Anti-thymocyte globulin-Horse) regimen. QOL was assessed with MSQOL-54 scores pre-HSCT and at intervals of 3, 6, 12 months, then yearly up to 10 years. MSQOL-54 data available up to December 2023 was included. Statistical analysis was conducted using the linear mixed model and Šídák's multiple comparison test to control error rate and validate results.

Results: 62 PwMS (22 males, 40 females) with median age 37 (22-55) had median follow-up of 5.9 years (range 1.9-11.7 years). 18% had a family history of MS, 21% had a family history of autoimmune disease and median time from the diagnosis to HSCT was 79 months (9-256). Overall, compared to baseline, there was improvement in PC by a minimum of 10 points up to 5 years with greatest peak at 36 months post HSCT (*p<0.0001, 95%CI 11-28*). Similarly, improvement in MC occured at different time points excluding 24 months and 60 months with the highest improvement at 36 months (*p<0.0001, 95%CI 7-27)* – (Figure 1).

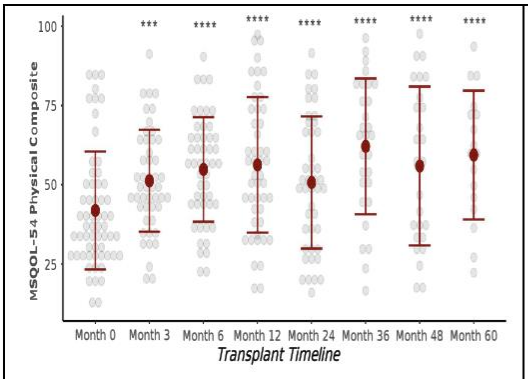
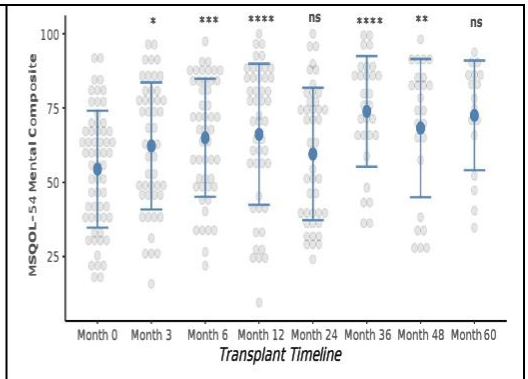


Figure 1: Change in Physical Composite



Change in Mental Composite

Conclusion: The results highlight a significant improvement in both physical and mental QOL in PwMS after HSCT. These results will help multidisciplinary team caring for PwMS with interventions that can be implemented to sustain QOL improvement post HSCT.

HO019

Clinical utility of a computerised cognitive test in identifying immune effector cell associated neurotoxicity syndrome following chimeric antigen receptor T-cell therapy

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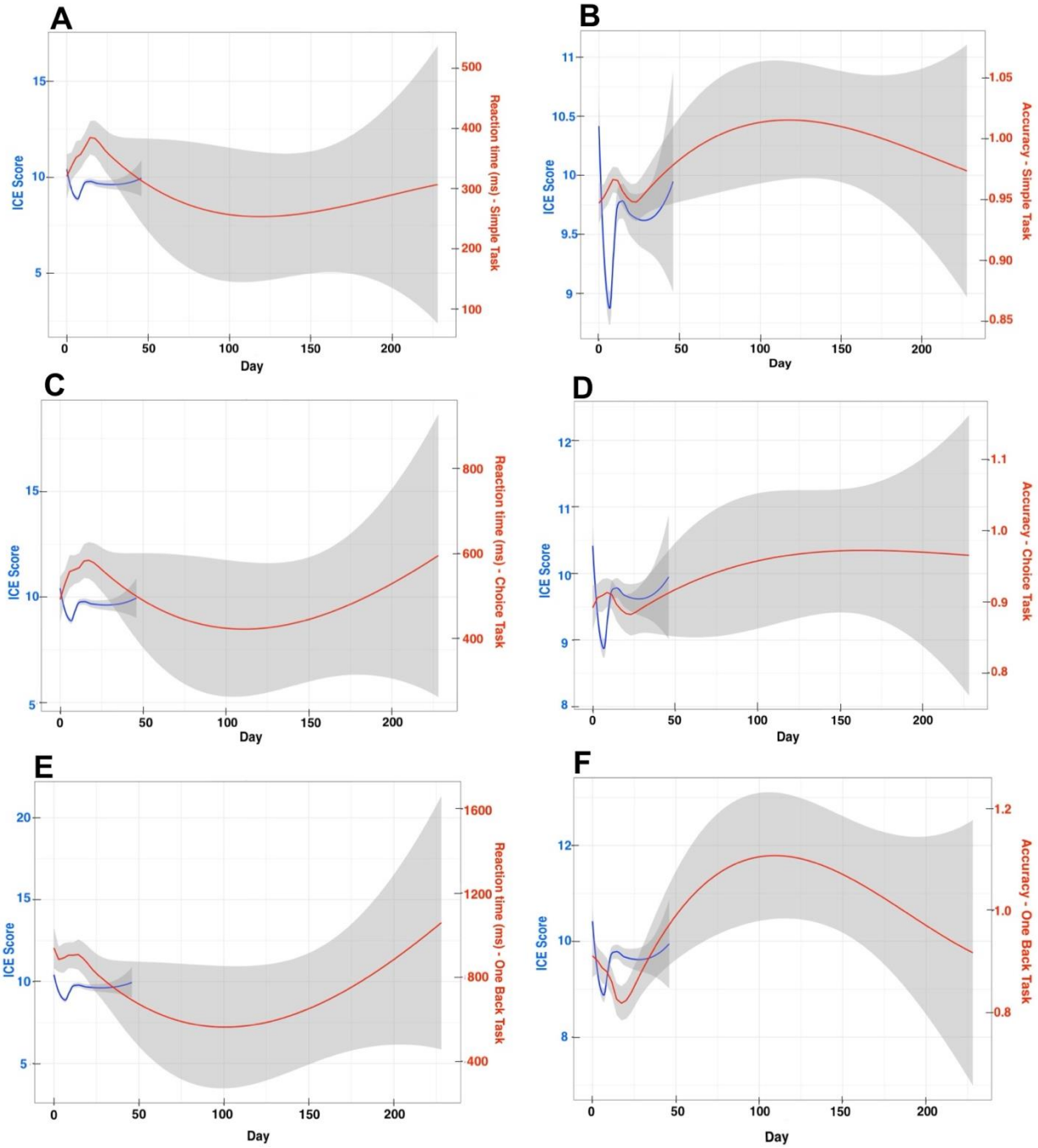
Aim: Change in cognition is characteristic of immune effector cell-associated neurotoxicity syndrome (ICANS), which is a potentially life-threatening complication of chimeric antigen receptor T-cell therapy (CAR-T). This study investigated the clinical utility of a computerised test of processing speed, visual attention, and working memory (CARTcog) in identifying ICANS.

Method: Thirty-one patients underwent CAR-T at the Alfred Hospital in Melbourne between 28 August 2023 and 23 April 2024. 28 patients consented to the study. Participants completed serial CARTcog assessments and immune effector cell-associated encephalopathy (ICE) scores at baseline, daily during inpatient admission, and 1-, 3-, and 6-month time points. Trajectory plots of ICE scores and CARTcog scores across time were fitted with loess smoothing functions. Linear mixed-effect modelling was constructed to investigate the association between ICANS status (predictor) and CARTcog response measures (outcome). Receiver operator characteristic curves were constructed to investigate the discriminative ability of CARTcog measures in predicting ICE scores.

Results: Twenty-eight participants (78% male, 64.07±12.49 years old at infusion) completed 345 CARTcog assessments. Eight (29%) patients developed ICANS. Trajectory plots illustrated a temporal relationship between ICE scores and CARTcog scores; in general, CARTcog scores worsen with decreases in ICE scores and recover with the improvement of ICE scores (See Figure 1). Linear mixed-effects models revealed a significant interaction between time and ICANS groups ($p<0.05$), such that the patients who developed ICANS performed worse over time compared to those who did not develop ICANS. CARTcog scores were found to distinguish between patients with ICANS (i.e., ICE score<10) and those without ICANS (i.e., ICE score=10) (AUC>0.95 across different scores).

Conclusion: CARTcog has the potential to be used in conjunction with ICE scores to improve the detection of ICANS in patients who receive CAR-T. Earlier detection of ICANS, and hence, earlier treatment and management, can lead to improved patient outcomes.

Figure 1. Trajectory plots with loess smoothing functions of ICE scores and CARTcog scores: (A) Task 1 simple task reaction time; (B) Task 1 simple task accuracy score; (C) Task 2 choice reaction time; (D) Task 2 choice task accuracy score; (E) Task 3 one back task reaction time; (F) Task 3 one back task reaction time.
Note. Loess plots do not respect variable limits (i.e., ICE maximum score is 10, and CARTcog accuracy maximum score is 1.0).


A
ICE Score
Reaction time (ms) - Simple Task
Day
B
ICE Score
Accuracy - Simple Task
Day
C
ICE Score
Reaction time (ms) - Choice Task
Day
D
ICE Score
Accuracy - Choice Task
Day
E
ICE Score
Reaction time (ms) - One Back Task
Day
F
ICE Score
Accuracy - One Back Task
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HO020

Pembrolizumab plus the anti–LAG-3 antibody favezelimab for patients with heavily pretreated anti–PD-1–refractory classical Hodgkin lymphoma (cHL): updated analysis of a phase 1/2 study

Timmerman J[1], Lavie D[2], Johnson N[3], Avigdor A[4], Borchmann P[5], Andreadis C[6], Bazargan A[7,8], Gregory G[9], Keane C[10], Tzoran I[11], Vucinic V[12], Zinzani P[13,14], Marceau West R[15], Pillai P[15], Yusuf R[15], Herrera A[16]
[1]UCLA Medical Center, [2]Hadassah Medical Center, [3]Jewish General Hospital, [4]Sheba Medical Center, Ramat Gan and School of Medicine, Tel Aviv University, [5]University Hospital Cologne, [6]UCSF, [7]University of Melbourne, [8]St Vincent's Hospital, [9]School of Clinical Sciences at Monash Health, Monash University, [10]Princess Alexandra Hospital, [11]Rambam Health Care Campus, [12]Leipzig University Medical Center, Clinic and Polyclinic for Hematology, Cell Therapy and Hemostaseology, [13]IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli", [14]Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, [15]Merck & Co., Inc., [16]City of Hope

Aim: Pembrolizumab plus favezelimab demonstrated manageable safety and promising antitumor activity in patients with heavily pretreated anti–PD-1–refractory cHL (cohort 2) in a phase 1/2 study (NCT03598608). We present updated results from cohort 2.

Method: Patients were ≥18 years, had anti–PD-1–refractory R/R cHL, and had no response to or progressed after ASCT, were ineligible for ASCT, or had no response to salvage chemotherapy. Safety lead-in was followed by efficacy expansion. In safety lead-in, patients received pembrolizumab 200 mg plus favezelimab 200 mg escalating to 800 mg IV Q3W. In efficacy expansion, patients received pembrolizumab 200 mg plus favezelimab 800 mg (RP2D) IV Q3W for ≤35 cycles. Primary end point was safety. ORR per IWG 2007 criteria by investigator review was secondary. DOR, PFS, and OS were exploratory.

Results: Cohort 2 included 34 pts. Median follow-up at data cutoff (February 22, 2024) was 47.0 months (range, 26.7-61.1). Treatment-related AEs occurred in 28 pts (82%); grade 3 or 4 in 6 (18%). Six patients (18%) discontinued treatment and no patients died because of treatment-related AEs. AEs of clinical interest occurred in 17 patients (50%); 2 (6%) grade 3 events (encephalitis, hepatitis) and 1 (3%) grade 4 event (type 1 diabetes mellitus) occurred. ORR was 29% (95% CI, 15-48; CR 3/PR 7). Median DOR was 21.9 months (range, 0.0+ to 26.1+). Median PFS was 9.7 months (95% CI, 5.1-14.7). Median OS was not reached (95% CI, 27.9 months-NR).

Conclusion: In this updated analysis, pembrolizumab plus favezelimab continued to demonstrate manageable safety and sustained antitumor activity in patients with heavily pretreated anti–PD-1–refractory R/R cHL. Coformulated favezelimab and pembrolizumab is being evaluated (KEYFORM-008; NCT05508867).

HO021

Atezolizumab + obinutuzumab (A+O) with PET-directed radiotherapy (RT) for treatment-naïve follicular lymphoma (FL): The phase II FLUORO study.

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Aim: PD1 or PDL1i plus antiCD20 antibodies offer responses of 90% in 1L FL with significantly less toxicity than immunochemotherapy (Hawkes et al. ICML 2021). Our study assessed the efficacy of A+O +/- RT in 1L FL patients with the aim of minimizing toxicity but maintaining efficacy.

Method: FLUORO (NCT03245021) is a multi-centre, phase 2, study of A+O+/-RT (N = 15, stage II-IV grade 1-3A FL, ECOG ≤2; adequate organ function). All patients received 6 cycles (C) of A 1200mg + O 1000mg IV 3-weekly (plus O on C1,days 8 & 15) followed by 12 cycles of maintenance O. Patients with PET-assessed <Complete Response (CR) post-C2 underwent RT (4Gy) to residual PET-avid disease. Primary endpoint was CR rate. Secondary endpoints: Objective Response Rate (ORR), Progression-free survival, overall survival , and toxicities. Exploratory endpoints included biomarker studies and PET radiomics.

Results: 16 patients were enrolled between 08/2021-10/2022, 1 patient was replaced due to Grade(G) 4 infusion reaction to O requiring cessation. Baseline characteristics included median age 53 years, stage IV disease in 81%, B symptoms in 12.5%, 44% had FLIPI >2. CR rate was 87% (95% CI: 60%, 98%; ORR 100% [95% CI:75%, 100%]), with 80% receiving RT (median number of irradiated sites = 3 (95% CI: 2, 4)). 13% discontinued due to PD.

Most frequent Adverse Events (AE): G1-2- fatigue 44%, constipation 31%, nausea 25%, fever 25%, abdominal pain 18.6%. Serious AEs were reported in 7/16 (44%) patients, including grade 3 infections: COVID19 12%, upper respiratory tract 12%, urinary 6.2%. Median follow-up is 27m (range 20-32) and ongoing, 20m PFS is 80% (95% CI: 52%, 96%) & OS 100%. 6 patients have completed all study treatment; survival follow up and biomarker analysis is ongoing.

Conclusion: A+O +/- PET-adapted RT yielded high CR rate and low toxicity in treatment-naïve FL.

HO022

High burden of Healthcare utilisation in older AML treated with First line Venetoclax-based Therapies: a real-world analysis based on the SA-MN registry.

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Aim: Venetoclax with azacitidine (VEN/AZA) or low dose cytarabine (VEN/LDAC) is the standard of care for AML patients unfit for intensive chemotherapy. However, there is limited insight into the associated healthcare burden. We evaluated the outcome, treatment schedules and healthcare utilisation in older AML patients treated with first line venetoclax-based therapy.

Method: Hospitalisation and transfusion data of older AML patients treated with first line VEN/AZA or VEN/LDAC between January 2021 to September 2023 was assessed.

Results: 48 AML cases received first line VEN/AZA (n=42; 87.5%) or VEN/LDAC (n=6; 12.5%). Median age at diagnosis was 74.3 years (interquartile range, IQR 67.8, 79.3). Intermediate risk cytogenetics was most prevalent (n=29, 60.4%), followed by adverse risk (n=16, 33.3%).

The median number of cycles completed was 5 (IQR 1,10) and ~60% patients experienced delay in starting subsequent cycles (**Figure 1A**). After the first cycle, 61.8% of the evaluable patients achieved CR/CRi (n=21), while 23.5% (n=8) and 14.7% (n=5) achieved partial remission or had refractory disease, respectively.

At the time of last follow-up, 81.3% (n=39) patients discontinued therapy and 69.2% (n=27) died. The median OS of the whole cohort was 12.9 months (**Figure 1B**), with significantly longer OS in patients achieving CR/CRi (**Figure 1C**).

All patients required RBC transfusions with mean 29.8 ± 30.2 units/patient. 81.3% and 58.3% of patients required RBCs during cycle 1 and 2 compared to 30-40% during subsequent cycles. 37.5% (n=3) of the 16 evaluable patients who received ≥1 phenotype-mismatched RBC unit developed RBC alloantibodies *(anti-D, C, Jkb, Fya).* 81.3% (n=39) patients required platelet units with mean 23.3 ± 30.7 units/patient. All patients required hospitalisation with total 283 admissions for 2757 days and hospitalisation was higher during the first cycle.

Conclusion: Venetoclax-based therapy was associated with high healthcare resource utilisation and only 41.4% of treatment cycles could be delivered on schedule.

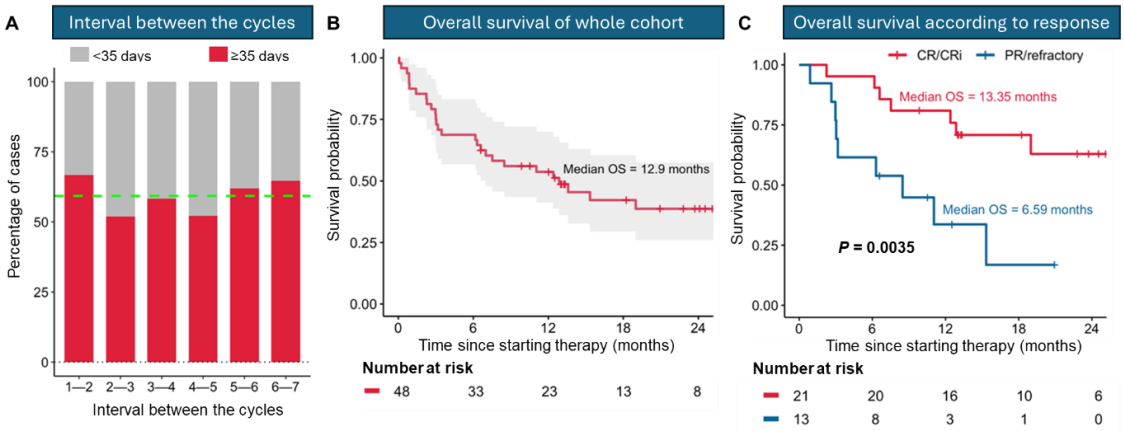

Figure 1. Majority of older AML treated with venetoclax based therapy experience treatment delay. (A) In 50-60% of cases, interval between the cycles was ≥35 days. (B) The median overall survival (OS) of older AML patients treated with first line venetoclax based therapy was 12.9 months. (C) Significantly longer median OS in patients achieving CR/CRi (complete remission/ complete remission with incomplete haematologic recovery) than PR (partial remission)/refractory.

HO023

Implementation of Frailty Screening and Comprehensive Geriatric Assessment (CGA) service in older people with haematological cancer in an acute care hospital- Opportunities and challenges

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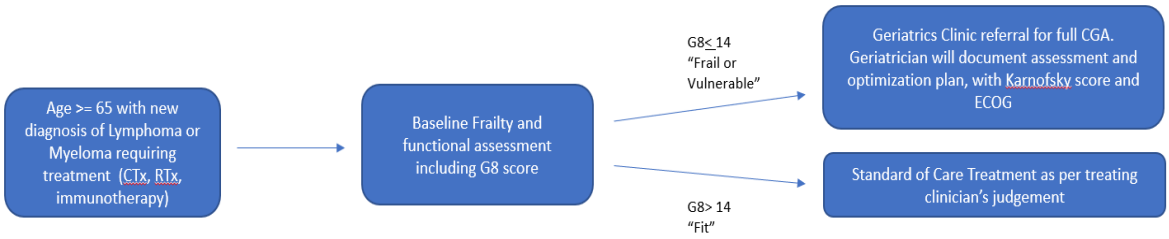
Aim: Comprehensive Geriatric Assessment (CGA) can be beneficial in geriatric populations with haematological malignancies. Since 2021, our health service established a streamlined pathway involving frailty screening-CGA referral. This audit aims to determine its feasibility and potential challenges to its implementation.

Method: We performed a retrospective audit from 1st September 2021 - 30th April 2024 on the following populations:



Patients unable to consent or enrolled in clinical trials were excluded. Frailty screening was performed primarily by haematologists and CCC co-screening commenced from September 2023. Dedicated E-referrals pathways were created and appointments offered within 4 weeks.

Results: Of the 94 eligible patients, only 30 were screened for frailty (31.9%). This was due to inconsistent screening by clinicians. A third of all screening was performed by CCC.

Table 1 Patient Demographics (n = 30)

Age (years) - median	80 (range 65-88)
Male (n)	16
NESB (n)	8
ECOG at diagnosis – median	1 (range 0-3)
CCI - median	4 (range 2-8)
G8 score - median	10 (range 5-14)
Malignancy – categories (n)	Aggressive lymphomas = 18; Indolent lymphomas = 9; Multiple myeloma= 3
Stage – median	Lymphomas: Stage IV Myeloma: RSS Stage III

Of those 30 patients, 23 were referred for CGA (76.6%). Of the 7 patients not referred for CGA, the most common reasons were rapid clinical deterioration (n=3) and patient refusal (n= 2).17 out of 23 patients had full CGA completed. The most common reason for not attending CGA post referral was death prior to review (n=3).

Conclusion:
Frailty screening in older people with haematological cancer is feasible and use of G8 screening tool adequately captures those most at risk of poor clinical outcomes. However, its implementation is challenging due to screening inconsistencies, rapid disease progression and low health literacy. Utilisation of CCC to conduct screening improves screening rate significantly.

Legend
CTX – Chemotherapy; RTX – Radiotherapy; CCC – Cancer Care Coordinator; ECOG - Eastern Cooperative Oncology Group
CCI – Charlson Comorbidity Index; NESB – Non English-Speaking Background

HO024

Real-world, multi-centre review of outcomes utilising harmonised lenalidomide, bortezomib and dexamethasone (RVd) protocols in transplant-ineligible (TI) newly diagnosed multiple myeloma (NDMM)

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Aim: RVd induction is a standard of care for NDMM. The pivotal SWOG0777[1] trial utilises twice weekly bortezomib which, although potent, is widely considered to confer unacceptable toxicity, particularly for TI patients[2-3]. For centres with centralised prescribing resources, divergence from published regimens poses issues of safety. To address this, following PBS listing in 2020, several NSW centres "harmonised" RVd with two pragmatic consensus regimens incorporating weekly bortezomib, based on RVd-Lite or SWOG0777. This multi-centre real-world study assessed outcomes in TI patients.

Method: 76 patients were prospectively followed from 6 hospitals from June 2020 until September 2023. By physician discretion, patients received 'Modified SWOG[1]' (28-day cycles of weekly bortezomib, lenalidomide 25mg D1-14 and dexamethasone 40mg weekly in split doses) or 'Modified RVd-Lite[4]'(35-day cycles of weekly bortezomib, lenalidomide 15mg D1-21 and dexamethasone 40mg weekly in split doses). Response and toxicity were assessed post-induction and 6-monthly.

Results: Median follow up time was 26.5 months. Amongst 76 patients, 35 received modified SWOG and 41 received modified RVd-Lite. Modified RVd-Lite patients were older (median 77 vs. 74 yrs) and more frail with greater proportion of ECOG 3 (9.8% vs. 0%) and IMWG score ≥2 (19.5% vs 5.7%). ORR 91.4% and ≥VGPR 71.4% achieved with Modified SWOG were similar to SWOG S0777[1] (ORR 90.2%, ≥VGPR 74.9%) with a comparable median PFS 40.2 months (95% CI: 20.8-59.5). Patients receiving Modified RVd-Lite achieved ORR 92.7% and ≥VGPR 58.5% similar to RVd-Lite[4] (ORR 86%, ≥VGPR 66%) with a median PFS of 24.4 months (95% CI 21.1-27.7) (Figure 1a). Median OS was not reached with either regimen (Figure 1b). Premature discontinuation due to toxicity occurred in 14 (18.4%) and peripheral neuropathy in 30 (39.5%) with rare grade ≥3 events (2/76, 2.6%).

Conclusion: Harmonised RVd regimens with weekly bortezomib demonstrated comparable efficacy to trial data with improved tolerability in TI patients.

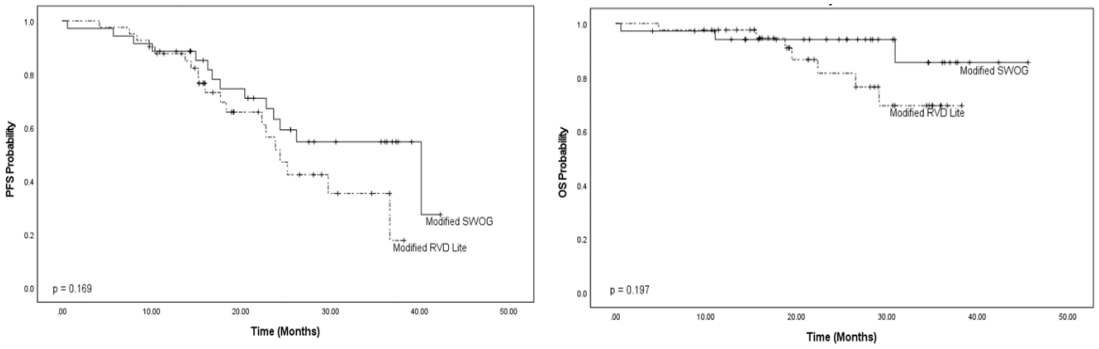

Figure 1: (a) PFS and (b) OS by RVd Protocol

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HO025

Subacute cognitive and psychological recovery from the immune effector cell associated neurotoxicity syndrome following chimeric antigen receptor T-cell (CAR-T) therapy.

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Aim: The study aimed to investigate cognitive and psychological recovery from the immune effector cell associated neurotoxicity syndrome (ICANS) in haematology patients one-month after CAR-T therapy.

Method: Seventy patients completed a comprehensive cognitive test battery and a self-report measure of psychopathology and cognitive concerns before and one-month after receiving commercial CAR-T for treatment of lymphoma (94%) or leukaemia (6%). Thirty-one (44%) patients experienced ICANS acutely. Bayesian repeated measures analysis of covariance examined the effect of interaction between ICANS group and time of the assessment on change in cognition and psychopathology. Models were adjusted for age, education, and sex.

Results: ICANS patients had greater decline in executive function from baseline to follow-up, compared with non-ICANS patients (BF_{10}=6.33). Of ICANS patients, five (16%) were impaired on the executive function domain one-month post-CAR-T, compared with only one patient (3%) in the non-ICANS group. There was no evidence for an effect of ICANS group over time in any other cognitive domain. Greater decline in executive function was associated with longer inpatient admission (BF_{10}=2869.19), higher cumulative dose of dexamethasone (BF_{10}=22.90), and baseline Eastern Cooperative Oncology Group performance status ≥1 (BF_{10}=8.91). A test of verbal delayed recall was the only individual psychometric measure with evidence for an effect of ICANS group over time (BF_{10}=99.01). We found an association of time with global psychopathology (BF_{10}=19.50), which represented a reduction in aggression and alcohol issues at follow-up.

Conclusion: There was a persisting reduction in executive function and verbal recall in the ICANS group a month post-CAR-T. There was no detectable effect of ICANS on other aspects of cognitive function, suggesting otherwise adequate subacute recovery. An improvement in self-reported symptoms of psychopathology indicates good psychological tolerance of CAR-T associated neurological toxicity. Cognitive monitoring, however, is indicated for ICANS patients beyond the subacute period.

HO026

Efficacy of asciminib against ABL-rearrangement of Ph-like Acute Lymphoblastic Leukaemia is dependent on the presence of the SH3 domain.

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Aim: Philadelphia-like Acute Lymphoblastic Leukaemia (Ph-like ALL) is a high-risk subtype with poor overall survival requiring novel treatment options. In addition to other gene fusions, it comprises *ABL1* and *ABL2* gene rearrangements (*ABL-r*), often including the SH2/SH3 domains. *ABL-r* may be amenable to treatment with asciminib, a highly specific allosteric inhibitor. We explored the efficacy of asciminib against *ABL-r* and the impact of SH2/SH3 domains on asciminib sensitivity.

Method: A computational model of *ABL2* (Arg) was developed. Ba/F3 cells were transduced with *ABL-r* fusion genes (n=8) from patient cells (n=9) and site-directed mutagenesis was implemented for the construction of the “isoforms” (deletion of SH2 and/or SH3 domain). The myristate pocket was conserved in all constructs. Asciminib efficacy was assessed by phospho-flow cytometry and annexin V/7-AAD cell death assays (LD_{50}). PDX models were established with *NUP214::ABL1* (n=3) and *ZC3HAV1::ABL2* (n=1) patient cells and treatment (asciminib 30mg/kg or dasatinib 20 mg/kg) commenced at 5% hCD45+ cells in the peripheral blood. Statistical significance (P-value) was calculated by one-way ANOVA and Kaplan-Meier survival curves.

Results: The computational model supported asciminib binding to Arg. Ba/F3 cells transduced with *NUP214::ABL1*, *RANBP2::ABL1* and *ZC3HAV1::ABL2* demonstrated sensitivity and kinase signalling inhibition by asciminib ($p<0.0001$ vs control). The remaining cell lines were resistant to asciminib. Generation of *NUP214::ABL1* and *ZC3HAV1::ABL2* "isoforms" indicated that the SH3 domain is critical for asciminib efficacy (Table 1). All cell lines were sensitive to other TKIs. Asciminib efficacy was demonstrated in pre-clinical *in vivo NUP214::ABL1* and *ZC3HAV1::ABL2* models. Asciminib significantly increased survival outcomes ($p<0.001$ vs control).

Conclusion: This is the first time asciminib has been demonstrated to be effective against ABL-r cells *in vitro* and *in vivo.* The data supports the addition of asciminib to the treatment regimens of patients with specific *ABL-r* where the presence of the SH3 domain is critical for asciminib-mediated therapeutic effect.

Table 1: Efficacy of asciminib against *ABL-r* of Ph-like ALL

Ba/F3 cell lines	Asciminib (LD_{50})	SH3 domain	SH2 domain
Empty vector (control)	24 µM	N/A	N/A
RCSD1::ABL1	34 µM	absent	partial (33 aa)
SNX2::ABL1	>50 µM	absent	partial (33 aa)
RANBP2::ABL1	3.3 µM	complete	complete
NUP214::ABL1	0.39 µM	partial (34 aa)	complete
NUP214::ABL1 SDM1	18 µM	partial (8 aa)	complete
NUP214::ABL1 SDM2	0.06 µM	partial (26 aa)	partial (81 aa)
NUP214::ABL1 SDM3	0.04 µM	partial (34 aa)	partial (69 aa)*
NUP214::ABL1 SDM4	0.05 µM	partial (34 aa)	partial (69 aa)*
RCSD1::ABL2	26 µM	absent	partial (33 aa)
PAG1::ABL2	24 µM	absent	partial (33 aa)
TPR::ABL2	29 µM	absent	partial (33 aa)
ZC3HAV1::ABL2	0.18 µM	complete	complete
ZC3HAV1::ABL2 SDM1	29 µM	partial (34 aa)	complete
ZC3HAV1::ABL2 SDM2	10 µM	absent	partial (33 aa)

*different SH2 domain regions deleted

Sensitive Moderate Resistant

HO027

The ubiquitin E3 ligase MARCH5 is a master regulator of apoptosis and its depletion potently sensitises multiple haematologic malignancies to venetoclax

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Aim: Despite the potent activity of venetoclax (VEN) in several haematologic malignancies (HMs), disease relapse is common due to the persistence of resistant sub-populations. We sought to identify novel targets exhibiting synthetic lethality with VEN across multiple blood cancers.

Method: We devised a novel genetic screen, "CRISPR-death", where VEN-resistant lines were transduced with the GecKO whole genome knockout (KO) library and cultured to eliminate cells with KO of essential genes. After short exposure to VEN, the rare dying (sensitised) cells were sorted by Annexin-V positivity, enabling guide-RNA sequencing prior to apoptotic DNA degradation. Discovered hits were therefore enriched for synthetic lethality, and further evaluated using degron-dTag, mass spectrometry (MS) proteomics, and xenograft models.

Results: KO of the ubiquitin enzymes *MARCH5* and *UBE2J2* recurrently emerged as top VEN-sensitisers across multiple screens. Degron-dTag depletion of MARCH5 resulted in profound, rapid and dose-dependent VEN sensitisation, exhibiting synergy and synthetic lethality across MCL, AML, myeloma and DLBCL cell lines (Fig 1). These results were recapitulated *in vivo,* where synthetic lethality was again demonstrated against a MCL cell line NSG xenograft. Beyond VEN-sensitisation, MARCH5 loss also markedly enhanced dependence on BCL-X_L. *MARCH5* KO in two breast cancer lines did not result in VEN sensitisation, suggesting haematologic selectively. We next confirmed that UBE2J2 is the dominant E2-enzyme required for MARCH5-mediated VEN-protection. Genetic variants of MARCH5 that impair UBE2J2 binding were unable to restore VEN-resistance to MARCH5 KO cells. Coupling the MARCH5 literature with MS proteomics, we identified multiple substrates of MARCH5 and strongly implicate mitofusin-2 (MFN2) as critical to MARCH5-mediated VEN protection.

Conclusion: "CRISPR-death" represents a novel method to identify synthetic lethal targets. Targeting MARCH5 and its interaction with UBE2J2 and MFN2 will likely sensitise many HMs to VEN.

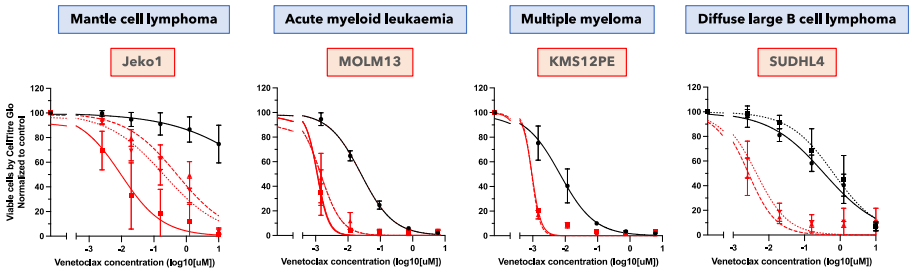

Figure 1. Black lines represent clones nucleofected with non-targeting guides (control). Red lines represent independent *MARCH5* KO clones. Cell viability was measured by CellTitre Glo at 24 hours after venetoclax exposure. Mean +/- SD of three independent replicates shown.

HO028

Functional High-Risk Multiple Myeloma (FHR-MM) following Lenalidomide-Bortezomib-dexamethasone (RVd) induction or bortezomib-cyclophosphamide-dexamethasone (VCD): An analysis from the Australian & New Zealand Myeloma and Related Diseases Registry (ANZ-MRDR).

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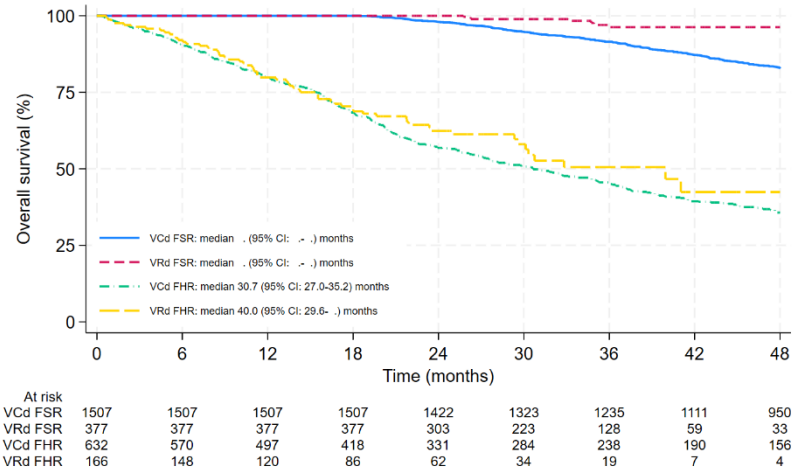
Aim: Approximately 20% of all newly diagnosed MM (NDMM) patients experience early progression (PD) despite optimal first-line (1L) therapy, described as FHR disease, and an unacceptably short median overall survival of 20 months(1). We have now performed a retrospective analysis comparing patients with FHR disease, defined by early relapse within 18 months of commencement of front-line therapy (ER18), who received induction with VCD (VCD-IND) and more recently RVd (RVd-IND).

Method: Patients were categorised as either FHR – PD and/or died within 18 months of 1L or non-FHR, alive and without PD >18 months post 1L. Significance tests for categorical variables were calculated using the chi-squared tests. Survival analyses were performed using a Kaplan-Meier approach, and comparisons between groups, the log-rank tests.

Results: A total of 2683 patients were categorised as either FHR or non-FHR. Following survival analysis, the estimated incidence of FHR disease was 28% (CI:26-30%) vs 23% (CI:20-27%) following VCD-IND and RVd-IND, respectively. Compared to patients without FHR, FHR patients were older, 69.2yrs (60.8-75.7) vs 64.3yrs (57.1-70.3, p<0.001), had poorer performance status, ECOG-PS 2-4, 23.7% vs 14.3%, p<0.001 and had more advanced disease, ISS Stage III, 42.7% vs 21.9%, p<0.001. The median PFS was 9.9 (9.1-10.8) vs 7.3 months (6.2-8.6), for FHR patients, VCD-IND and RVd-IND, respectively, compared to 46.2 and not reached in non-FHR patients, VCD-IND and RVd-IND, respectively. For FHR patients, there was no statistically significant difference in median PFS2 (median 19.2 vs 18.4 months, P=0.975) or OS (median 30.7 vs 40.0 months, P=0.305), VCD-IND versus RVd-IND, respectively (Figure 1).

Conclusion: The shift in standard practice from VCD-IND to RVd-IND has potentially reduced the incidence of FHR-MM in Australia. However, this has not translated to an appreciable improvement in outcome for patients who exhibit FHR disease despite RVd-IND.

Figure 1. Overall survival by FHR status and induction regimen



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HO029

CBL mutations in proliferative chronic myelomonocytic leukaemia cluster in the RING domain and express CD116 in CD34+ progenitor cells

Lim K[1], Kan W[3], Nair P[1,2,4], Kutyna M[1,2], Lopez A[1,3], Hercus T[3], Ross D[1,2,3,4,9], Lane S[5], Fong C[6], Brown A[3], Yong A[1,2,7,8], Yeung D[2,9], Hughes T[2], Hiwase D[2,3,9], Thomas D[1,2,3,9]

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Aim: In this study, we examined the clinical and molecular features and immunophenotype of newly diagnosed chronic myelomonocytic leukaemia (CMML) patients with *CBL* mutations enrolled in the Australian-based **PRE**cision **A**pproach to **Ch**ronic **M**yelomonocytic Leukaemia (PREACH-M; ACTRN12621000223831) trial.

Method: 24 patients aged between 56-86 years in multiple centres across Australia diagnosed with CMML based on the WHO 2016 criteria and harbouring *TET2*, *KRAS*, *NRAS* or *CBL* mutation at a variant allele frequency (VAF) ≥3% were included in this study. *CBL* mutation hotspots were identified. Blood mononuclear cells were immunophenotyped using anti-human CD45, CD14, CD16, CD34, CD114, CD115, CD116 and CD131 panel. RNA-Seq was performed on bone marrow samples.

Results: *CBL* mutations were detected in 11/24 (45.9%) patients and associated with increased bone marrow blast percentage, white cell count and spleen length compared to *CBL* wildtype patients without other Ras pathway mutations. Of patients with *CBL* mutations, 10/11 (90.9%; *P*=0.03) presented with splenomegaly, 8/11 (72.7%) classified as myeloproliferative-CMML and 4/11 (36.4%) as CMML-2. In 7/11 (63.6%) patients with *CBL* mutation, more than one *CBL* variant can be detected, with frequent *TET2* mutation co-occurrence (r^2=0.68, *P*=0.002). CMML, including those with *CBL* mutations, displayed an increased percentage (89.7 ± 1.6 vs. 50.3 ± 2.7%; *P*= 0.000003) of CD116 (granulocyte-macrophage colony-stimulating factor receptor subunit alpha)-expressing CD34+ progenitors compared to healthy controls. In CMML, mutations concentrate within the RING domain contrary to JMML, where linker region mutations are most common (*P*<0.0001).

Conclusion: The data underscores the association of *CBL* mutations with a proliferative phenotype and more advanced stages of the disease, and therefore, to increased risk of progression to acute myeloid leukaemia. The high proportion of CD116-expressing CD34+ progenitors indicate they may be targetable by anti-granulocyte-macrophage colony stimulating factor (anti-GM-CSF) neutralising antibody.

HO030

Quantitative Detection of KMT2A-rearranged Measurable Residual Disease has Strong Prognostic Impact Prior to Allogeneic Haematopoietic Cell Transplantation (HCT) in Acute Myeloid Leukaemia (AML)

Loo S[1,2,3], Potter N[4], Ivey A[5], O'Nions J[6], Moon R[5], Fong C[7], Anstee N[2], Tiong I[1], Othman J[4,8], Chua C[2,3,10], Fleming S[5], Renshaw H[6], Baker R[6], Russell N[8], Ritchie D[1], Bajel A[1], Hou H[9], Dillon R[3,8], Wei A[1,2]

[1]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, [2]Walter and Eliza Hall Institute of Medical Research, [3]Northern Hospital, [4]King's College, [5]The Alfred Hospital , [6]University College London NHS Foundation Trust, [7]Austin Hospital, [8]Guy's and St.Thomas Hospital, [9]National Taiwan University Hospital, [10]Monash Health

Aim: Despite allogeneic HCT in first remission, ~40% of patients with *KMT2A*-rearranged (*KMT2Ar)* AML relapse.[1] *KMT2A*r measurable residual disease (MRD) assessment using quantitative polymerase chain reaction (qPCR) is not standard practice.[2] A barrier to MRD monitoring is breakpoint heterogeneity within *KMT2A* and diverse fusion partners. Despite >90 fusion partners identified, >70% involve either *MLLT3, ELL, AFDN,* or *MLLT10.*[3] We analyse the prognostic impact of pre-HCT *KMT2Ar* MRD on post-HCT outcome in adult *KMT2Ar* AML. We also describe a novel reverse transcription droplet digital PCR (RT-dPCR) assay that enables *KMT2Ar* MRD to be monitored using a simplified multiplexed assay. The relevance is enhanced by menin inhibitors showing promising efficacy in *KMT2Ar* AML and potential for pre-emptive *KMT2Ar* MRD targeting.[4]

Method: Sixty-seven patients in Australia, UK and Taiwan were included. Archived pre-HCT RNA from bone marrow/peripheral blood were analysed by RT-qPCR in 58 patients or RT-dPCR in 9. Further assay details will be presented at the meeting. Relapse-free (RFS) and overall survival (OS) were estimated by Kaplan-Meier and Cox proportional hazards for variables impacting survival.

Results: Pre-HCT, 42% were MRD-positive with median level 0.16% (range, 0.0056-35.0394) (Figure 1). Two-year cumulative incidence of relapse was significantly increased among patients MRD-positive vs negative (75% vs 25%, Gray's test 0.0001), with corresponding inferior survival at median follow-up of 37 months: 2-year RFS 17% vs 59%(p=0.0009; Figure 2) and 2-year OS 38% vs 66%(p=0.011). Pre-HCT MRD detection was the only determinant of inferior RFS (HR 2.8, p=0.011) and OS (HR 2.4, p=0.036) on multivariate analysis.

Conclusion: This study, the largest that we know of, highlights the dismal prognosis associated with pre-HCT *KMT2Ar* MRD. With RNA fusion panels increasingly performed at diagnosis, *KMT2Ar* detection and MRD tracking will become commonplace. Pre-emptive MRD relapse treatment with menin inhibitors is currently being assessed in the AMLM26 INTERCEPT trial.[5]

Figure 1

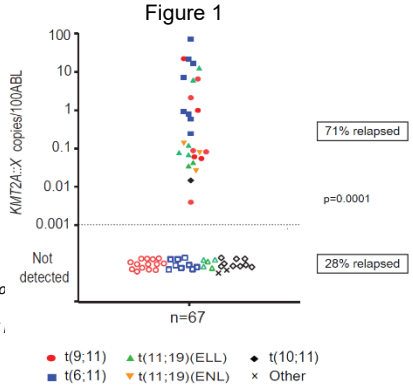
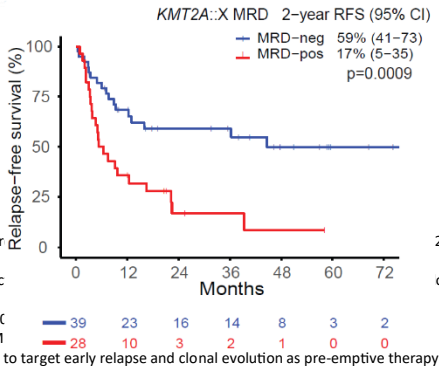


Figure 2



1. et al. Risk classification at diagnosis pr 2A-rearranged AML. *Blo*
2. d-lineage leukemia (MLL) gene detec oid leukemia. *Med Sci*
3. ecombinome of acute leukemias in 2(
4. menib in KMT2A-rearranged or NPM
5. 2 study investigating novel therapies to target early relapse and clonal evolution as pre-emptive therapy in AML (INTERCEPT): a multi-arm, precision-based, recursive,platform trial. Poster #1447. *American Society of Hematology (ASH).* 2022:Abstract #1447.

HO031

Treatment Outcomes and Quality of Life Data from WhiMSICAL - the Global Waldenström's Macroglobulinemia patient-derived data registry

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Aim: Waldenström Macroglobulinemia (WM) is a rare B-cell lymphoma with an incidence of around 3 cases per million people per year. In rare diseases, patient-reported outcomes play an essential role alongside clinical trials to improve our understanding. WhiMSICAL (Waldenström Macroglobulinemia Study Involving CArt-wheeL) is the only global WM patient-derived data registry. This study aimed to assess treatment outcomes and quality of life (QoL) data for Bendamustine-Rituximab (BR) compared to Bruton tyrosine kinase inhibitors (BTKi) in the first-line setting.

Method: Patients consent to the online rare cancer database, www.cart-wheel.org and then enter treatment and QoL information (EORTC-QLQ-C30). Recruitment is driven by the International Waldenström Macroglobulinemia Foundation. We analysed the data entered up until 17th May 2024. Time to next treatment (TTNT) was assessed from start of therapy to start of next therapy. Patients without a documented next therapy were censored at the time of last edit. QoL scores were compared between both first-line treatments.

Results: A total of 673 patients from 23 countries have entered data into the registry. Most were male (60%), with a median age at diagnosis of 62 years. There was no significant difference between the two treatment groups in terms of age, (median BR 62 years, mBTKI 65 years (p=0.18). The TTNT was not significantly different between first line BR versus mBTKI, median not reached vs 95 months, respectively (p=0.16) (Figure 1A). Patients on mBTKi had better reported EORTC QLQ-C30 global scale scores: mean 80.5±16.5, BR-treated patients mean 68.2±19 (p=0.001) (Figure 1B).

Conclusion: Patient-derived data from WhiMSICAL continues to accumulate data on important outcomes in WM with an increasing follow-up period. BR remains an excellent first-line option for patients with WM, however further longitudinal quality of life (QoL) studies are required to confirm the difference in QoL between BR and BTKi.

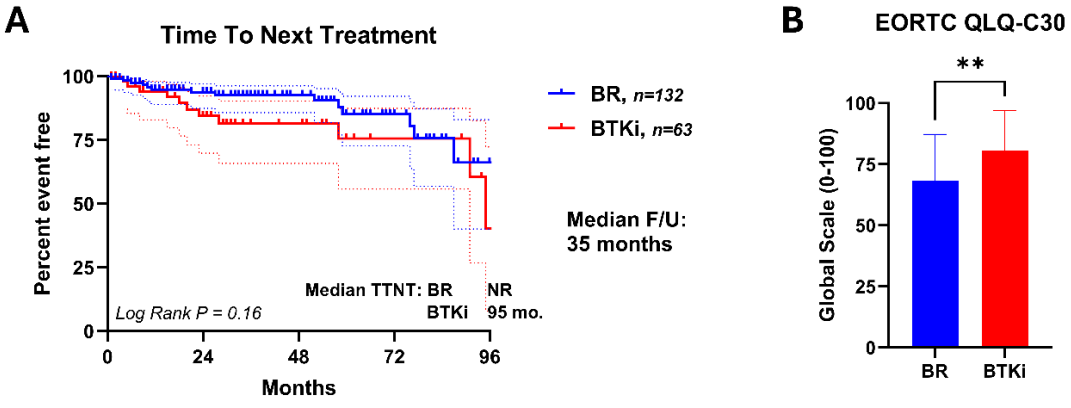

Figure 1. Comparison of first line bendamustine rituximab (BR) and Bruton tyrosine kinase inhibitors (BTKi). Time to next treatment was assessed by Kaplan-Meier survival analysis (A), with patients censored at date of last edit to their data. Patients who had entered quality of life data within 12 months of starting first-line BR treatment (n=49), or while still on first-line BTKi (n=44) were included in the analysis (unpaired T-test). NR – not reached, mo. – months, ** p<0.01

HO032

Frailty and Comorbidity are Significant Prognostic Factors in Adult Haemophagocytic Lymphohistiocyosis: A Multi-Centre Retrospective Study

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Aim: Haemophagocytic Lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome with historically poor overall survival (OS).(1–4) South West Sydney Local Health District (SWSLHD) is one of the largest health districts in Australia, with several hospital centres and an ethnically diverse, aging population of >1 million residents. We report our outcomes in adult patients with HLH.

Method: 37 patients with HLH aged ≥18 years diagnosed by a haematologist or immunologist 2014-2024 were identified from the SWSLHD HLH database. Demographics, disease-specific biomarkers (HScore, HLH2004 criteria, D-dimer, LDH), diagnoses, treatment and Charlson Comorbidity Index (CCI) were extracted from the medical record. Rockwood Clinical Frailty Score (CFS) was estimated by a geriatrician retrospectively. Statistical analysis was performed using JASP and MedCalc.

Results: Median age was 66 years (range 20-79 years) with 1.8:1 male/female ratio. Median HLH2004 criteria met was 5, with sensitivity of 61%. Median HScore was 215, with sensitivity of 73% for cutoff of ≥169. Mean CFS was 2.4, mean CCI was 3.5. Causes of HLH were haematological malignancy (17/37), infection (9/37), autoimmune/autoinflammatory (6/37), idiopathic (3/37) and primary (2/37).

Median OS was 17.0 months with 18/37 deaths. Median OS was 7.3 months in those ≥65 years vs not reached (NR) if <65 years (p=0.015), 2.8 months with CCI>3 vs NR if CCI ≤3 (p=0.005), 2.9 months with CFS≥4 vs NR and 2.9 months with presence of either CFS≥4 or CCI>3 vs NR without (p=0.001). Malignant HLH, HScore ≥169, HLH2004 criteria ≥5 met were not prognostic factors.

Conclusion: HLH patients in SWSLHD had favourable median OS compared with other retrospective studies. Frailty and comorbidity were highly significant prognostic factors associated with very poor OS, likely mediating the effect of age on OS. Patients with HLH should have baseline assessment of frailty and comorbidity.

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4. Birndt S, Schenk T, Heinevetter B, Brunkhorst FM, Maschmeyer G, Rothmann F, et al. Hemophagocytic lymphohistiocytosis in adults: collaborative analysis of 137 cases of a nationwide German registry. J Cancer Res Clin Oncol. 2020 Apr 1;146(4):1065–77.

HO032

Continuous Venetoclax for Relapsed CLL- Characteristics and outcomes of Long-term responders

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Aim: A subset of patients with relapsed and refractory (RR) chronic lymphocytic leukaemia (CLL) have a long-term response (>5 years) to continuous venetoclax. We aim to describe the frequency, characteristics and outcomes of these "long-term responders."

Method: Eighty-six patients with RR CLL commenced treatment with continuous venetoclax on four early phase clinical trials (M12-175, M13-982, M13-365, M15-889) at a single institution. Patients without progressive disease (PD) after 5 years of continuous venetoclax were defined as long-term responders. Progression free survival (PFS) and overall survival (OS) were analysed using Kaplan Meier methods. Next generation sequencing was performed on available samples for *BCL2* and *TP53* mutations. A land-mark analysis was undertaken at 2-years from start of venetoclax to assess impact of uMRD status ($<10^{-4}$ Peripheral blood, PB) on PFS.

Results: Twenty-nine (33%) patients were long term responders and have been followed for a median of another 50 months beyond 5-years. Table 1 compares their characteristics to those without long-term response. Amongst long-term responders, 18 (62%) subsequently ceased venetoclax because of PD (10/18), emergence of therapy-related myeloid neoplasm (3/18) or other reason (5/18). Median PFS post 5-years was 35.7 months and median OS has not been met. Of seven tested at PD, 3 (43%) had *BCL2* mutations and two had acquired *TP53* mutations. Nine patients received subsequent therapy with an overall response rate of 50% (4/8 with data available). In a land-mark analysis of all patients continuing venetoclax beyond 2 years (n=43), PFS at 5 years from commencement was 87.0% (95% CI 64.8%-95.6%) if uMRD achieved and 45.1% (95% CI 22.1-65.7%) if not.

Conclusion: Long term responses to continuous venetoclax occurs in approximately one third of patients and are more common in patients with favourable risk genomics who achieve uMRD at 2 years. Long term-responders show a continual pattern of relapse, frequent *BCL2* mutations at time of PD and therapy-related myeloid neoplasms can emerge in these heavily pre-treated patients.

Table 1: *Characteristics of long-term responders and comparator cohort*

	Venetoclax >5 years (n=29)	Venetoclax <5 years (n=57)	number	p
Pre-treatment clinical variables: Average Age	67.5	67.3	86	0.93
Median Prior Lines of Therapy	3	3	86	0.67
Fludarabine refractory	20 (69%)	9 (57%)	86	0.32
Bulk > 5cm	10 (34%)	26 (45%)	86	0.32
IGHV-m	7 (43%)	5 (15%)	49	**0.03**
TP53 abberant	12 (41%)	30 (52%)	76	0.50
Complex Karyotype (>3 abnormalities)	3 (11%)	20 (35%)	59	**0.04**
Treatment variable: With Rituximab	4 (14%)	12 (21%)	86	0.41
Response Variable: Complete Response	15 (52%)	29 (25%)	86	**0.02**

HO034

More efficient delivery of High-cost standard-of-care Therapies in Relapsed Multiple Myeloma using real-time feedback of Patient-reported outcome measures: the MY-PROMPT-2 trial

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[1]School of Public Health and Preventive Medicine, Monash University, [2]Cancer Care Research Unit, University of Sydney, [3]The Alfred Hospital, [4]School of Translational Medicine, Monash University , [5]Royal Prince Alfred Hospital, [6]University of Sydney, [7]Peter MacCallum Cancer Centre/Royal Melbourne Hospital, [8]Princess Alexandra Hospital, [9]School of Medical Sciences, University of Sydney, [10]Centre for Health Economics, Monash University, [11]St Vincent's Hospital, Sydney

Aim: Many patients with multiple myeloma (MM) stop therapy prematurely, often due to symptoms and impact on quality of life (QoL). Short duration on treatment (DoT) can reduce survival benefit. We hypothesise that making clinicians aware of emerging symptoms could optimise DoT, which would enhance treatment effectiveness and patient outcomes.
In patients with relapsed refractory MM (RRMM), receiving standard of care (SoC) lenalidomide, carfilzomib or daratumumab-based therapies, we aim to determine whether routine real-time patient-reported outcome measure (PROM) feedback to clinicians at patient visits improves event-free survival (EFS: time from randomisation to permanent discontinuation of treatment, progression or death) compared to SoC alone.

Methods: Parallel, non-blinded, multicentre Bayesian RCT using 1:1 allocation, stratified by SoC regimen and age.
Intervention: PROM results summary sent to clinicians at monthly visits for 12 months. PROMs:

- MyPOS: MM-specific, 30 items - symptoms/ mood/ healthcare support
- further SOC regimen-specific questions (≤5) for common side-effects

ePROM system: REDCap-based for easy implementation. PROMs are emailed to intervention patients 1 week before visits. PROM summary is emailed to clinician, patient, and site staff.
Questionnaires comparing health-related QoL (EORTC QLQ-C30) and treatment satisfaction (TSQM-9) are collected 3-monthly in both arms for 12 months.
Novel statistical trial design: Once ≥60 events have been observed between the 2 arms, EFS assessment starts. If the intervention arm is **inferior**, the trial is stopped, if it is **superior**, proof of concept, or recommendation for trial expansion can be declared.

Results: Recruitment is active at 7 sites with 14 participants recruited. Interviews for the qualitative sub-study have commenced.

Conclusion: This is the first multicentre trial in RRMM to test the benefit of real-time PRO reporting. The widely-used REDCap platform helps translation into practice, and the pragmatic design suits rare diseases allowing a smaller sample to guide the decision to adopt PROM reporting.

HO035

A Single Center Retrospective Analysis of Valganciclovir 900mg Daily for Cytomegalovirus Prophylaxis in high risk allo-HSCT patients.

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[1]The Alfred Hospital, [2]Monash University

Background: Cytomegalovirus (CMV) reactivation is one of the most clinically significant complications in allogeneic stem cell transplantation. Prophylaxis with letermovir is currently recommended but is not PBS-funded in Australia and therefore most Australian transplant centres use a pre-emptive approach. The Alfred Bone Marrow Transplantation Unit has adopted an alternate prophylaxis approach using oral valganciclovir.

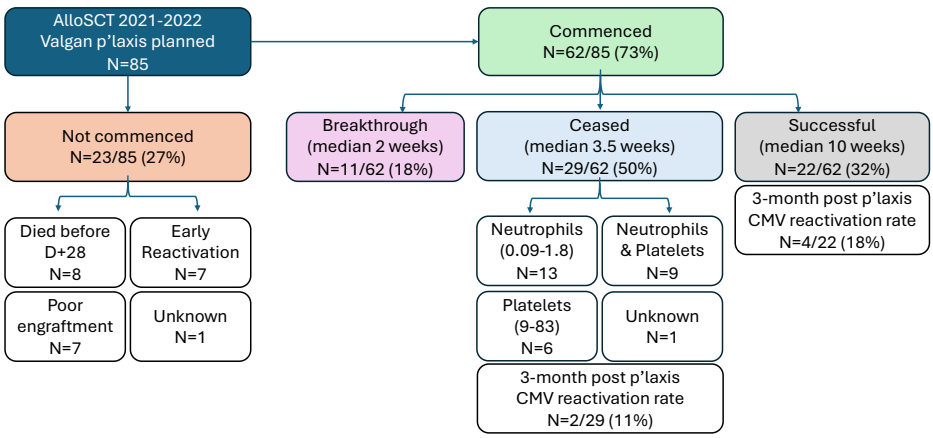
Aim: To determine the safety and efficacy of valganciclovir for preventing CMV reactivation.

Methods: Valganciclovir 900 mg daily from the time of engraftment (neutrophils > 1.0 x 10^9/L and platelets > 20 x 10^9/L) until day 100 was used for all high-risk transplants, defined as any CMV IgG positive donor and/or recipient undergoing an allogeneic stem cell transplant receiving post-transplant cyclophosphamide (PTCy), ATG or Alemtuzumab for GVHD prophylaxis. Breakthrough CMV reactivation was defined as a rising CMV viral load requiring CMV treatment. Toxicity was defined where the clinician stopped prophylaxis due to cytopaenias. Successful prophylaxis was defined as the ability to continue Valganciclovir 900 mg until D+100 without breakthrough CMV reactivation.

Results: We reviewed the clinical notes of 85 consecutive high-risk allogenic transplants performed in 2021 and 2022. Results are summarized in Figure 1. Overall, prophylaxis could not be started in 23 of 85 patients (27%) due to early death, poor engraftment or early CMV reactivation. Forty-two of the 62 patients commencing prophylaxis (49% of the total cohort) had failure due to either breakthrough reactivation or early cessation due to cytopaenias. Only 20 patients (24% of the total cohort) successfully received Valganciclovir prophylaxis although 4 of these 20 patients had reactivation after D+100. This rate of reactivation was as high as the 31 patients where Valganciclovir had to be ceased due to cytopaenias.

Conclusion: Valganciclovir 900 mg daily was poorly tolerated in the first 100 days post-transplant and not an effective method for preventing CMV reactivation.

Figure 1: CMV-related clinical outcomes of valganciclovir prophylaxis planned for the first 100 days after high-risk allogeneic transplantation.



HO036

Sensitive Genomic characterisation of the Clonal Haematopoietic landscape in individuals with Germline GATA2 Haploinsufficiency

Murphy E[1], Hunter S[1], Fox L[1], Nguyen T[1], Yap Y[1], Yerneni S[1], Thompson E[1,2], Tiong I[1], Blombery P[1,2]
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Aim: GATA2 haploinsufficiency syndrome is a germline disease which predisposes individuals to myeloid malignancy. The pre-malignant clonal haematopoietic (CH) landscape of individuals with GATA2 haploinsufficiency has not been extensively investigated to date. We aimed to characterise the clonal haematopoietic landscape of patients with GATA2 haploinsufficiency using ultra-sensitive molecular methodologies.

Method: Thirteen individuals with GATA2 haploinsufficiency were assessed using an 80-gene haematological malignancy UMI-corrected NGS panel (sensitivity 0.5% VAF). To further explore somatic variants at an ultra-sensitive level, a subset of the cohort underwent Twinstrand Duplex sequencing to detect variants at very low frequency (<0.01% VAF).

Results: CH was detectable in 9/13 patients by UMI-NGS, including in both the presence and absence of myeloid malignancy. *STAG2* was the most frequently mutated gene with variants observed in 5/13 patients (38%) including those without overt haematological malignancy. Sensitive variant detection identified multiple *STAG2* variants occurring together (range 1-10 per pt) consistent with oligoclonal clonal haematopoiesis. In one patient with longitudinal sampling, a single *STAG2* clone was observed to emerge from an oligoclonal *STAG2* mutated background. Notably, 3/13 patients harboured non-canonical *MPL* exon 12 variants. Finally, ultra-sensitive duplex sequencing and analysis using Twinstrand Duplex AML-29 App on the DNAnexus platform revealed marked further complexity, including multiple previously unrecognised *STAG2* variants as well as variants in *DNMT3A, ASXL1* and *TET2*.

Conclusion: We have described the clonal haematopoietic landscape of GATA2 haploinsufficiency at a sensitive level revealing (i) *STAG2* as a dominant early molecular lesion (ii) an oligoclonal model of CH presence (iii) enrichment of previously unrecognised *MPL* exon 12 variants and finally (iv) a high degree of clonal complexity at ultra-sensitive levels. Increasing understanding of the genomic landscape in GATA2 haploinsufficiency provides greater insights into disease progression and may ultimately inform clinical management.

HO037

A randomised trial of Topical Polaprezinc to prevent Oral Mucositis in patients undergoing Haematopoietic Stem Cell transplantation

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Aim: Oral mucositis (OM) is a common complication in hematopoietic stem cell transplantation (HSCT). Polaprezinc, an anti-ulcer drug, has been shown to be effective to prevent OM in several retrospective studies and a few small prospective studies when it was topically applied then ingested. This study aimed to evaluate the effectiveness of topical polaprezinc in patients undergoing HSCT.

Method: This was an open-label randomized clinical trial comparing polaprezinc (study drug) and sodium bicarbonate (control) mouthwashes for the prevention of severe OM in HSCT patients. Adult patients who underwent allogeneic or autologous HSCT after moderate to high risk conditioning regimens were included. Patients were randomized (1:1) to either the study arm or the control arm, and the randomization was stratified according to the conditioning regimens. The primary endpoint was the incidence of severe (WHO grade 3-4) OM. The secondary endpoints included duration of grade 3-4 OM, incidence and duration of Grade 2-4 OM, and patient-reported pain and functional limitations measured by the modified Oral Mucositis Daily Questionnaire. Data was analysed using the Fisher's Exact Test and the Mann-Whitney U test.

Results: In total, 108 patients (55 study arm, 53 control arm) were randomized and analysed. Baseline demographics, disease and treatment were similar between the arms. There were no differences in the incidence of severe OM (35% study arm vs 36% control arm). Duration of severe OM (median 6.5 days vs 5 days), patient-reported outcomes and other secondary endpoints were not significantly different. In both arms, patients reported more throat pain compared to mouth pain ($P<0.01$).

Conclusion: Topical polaprezinc had no effect in prevention of OM in HSCT patients. Further research is required to evaluate the systemic effects of polaprezinc. This study also highlighted that throat mucositis is the primary issue in HSCT.

HO038

Engineering Three-dimensional Scaffolds for early Ex Vivo Erythropoiesis

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Aim: Blood transfusion, the most prevalent method of tissue transplantation worldwide, relies heavily on donations. Yet, only 3% of Australians donate blood, while 33% need it[1].

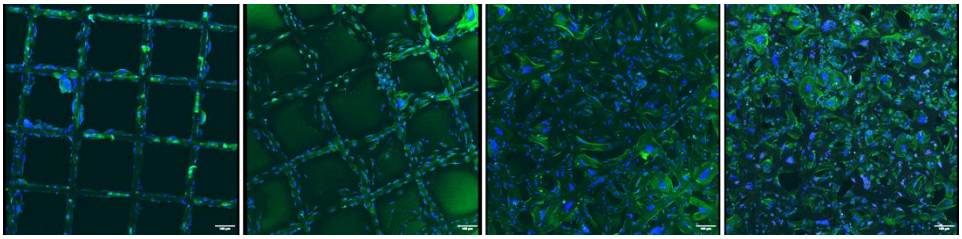
Ex vivo production of human blood cells offers a potential solution to donation shortages. However, significant technological challenges must be overcome before this becomes a cost-effective alternative. The cost to produce one unit of red blood cells (RBCs) using existing low-cell-density liquid suspension cell cultures is two orders of magnitude higher than a donor-based unit[2].

Biomaterial scaffolds show promise in supporting high-density cultures and consequently reducing costs, however, their impact on blood cell growth remains unclear. In this study, we established 3D cultures of peripheral blood mononuclear cells (PBMNCs) on 3D-printed fibrous scaffolds and demonstrated the expansion of hematopoietic progenitors and their early differentiation into RBCs.

Method: PBMNCs isolated from healthy donors were cultured on melt electrowritten (MEW) polycaprolactone (PCL) scaffolds for 8 days, in a culture medium supplemented with reduced cytokines, promoting hematopoietic progenitor proliferation and differentiation towards RBCs. Four scaffold architectures with varying curvature, porosity and surface area were investigated to assess their impact on culture. Cell adhesion, proliferation, and early erythroid differentiation were evaluated through image analysis and phenotypic immunocytochemical staining. Statistical analysis was performed using paired comparisons.

Results: We have successfully fabricated various architectures of marrow trabeculae-like MEW scaffolds. After 6 days, cultures with scaffolds exhibited a higher cell expansion compared to the liquid suspension (no scaffold) controls. Scaffolds fixed at day 8 of culture exhibited CD45, CD71, and CD235a erythroid markers.

Figure 1. PBMNCs after 8 days of culture on PCL MEW scaffolds. DAPI F-actin.



Conclusion: We have engineered a 3D *ex vivo* erythroid model, employing scaffolds of varying architectures, which serve as a platform for cell adhesion, proliferation, and early differentiation of erythroid progenitors, enabling high cell density blood expansion for efficient RBC production.

References:

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HO039

An individualised exercise intervention improves health outcomes for people with Multiple Myeloma: The MyeEx randomised waitlist-controlled trial

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Aims: Current treatments for people with multiple myeloma (MM) improve survival, but also result in high symptom burden, functional disabilities, and impaired health-related quality of life (HRQoL). Exercise may improve the health of people with MM, however evidence in this understudied population is lacking. The aim of this randomised waitlist-controlled trial was to investigate the influence of a 12-week individualised exercise intervention on HRQoL, as well as MM symptoms, pain, cardiorespiratory fitness, fatigue, and neuromuscular strength in people with MM.

Methods: People with a MM diagnosis were randomised to exercise (EX) or wait-list control (CON). The 12-week individualised program included twice-weekly sessions supervised one-on-one by an accredited exercise physiologist, with one additional home-based session prescribed per week. Each 60-minute session consisted of high-intensity interval training, moderate-to-hard muscle strength training and bone loading exercises. Outcomes were assessed using validated surveys (EORTC QLQ-C30 with MY20 module, FACT-BP, FACIT-F), cardiopulmonary exercise testing, and dynamometry.

Results: Participants with MM (n=60; mean age 65±9 years; 78% male) presented with lytic lesions (78%) and other skeletal complications (13%; back pain, osteoporosis, osteoarthritis). Twelve participants (20%) withdrew from the study due to medical conditions unrelated to the intervention (n=7) or loss of interest (n=5).

The EX group experienced improved HRQoL (EORTC QLQ-C30 summary score: +6.3, 95%CI 0.8, 11.9, p=0.03), mediated through improved bone pain (FACT-BP: +4.4, 95%CI 0.5, 8.3, p=0.03), and cardiorespiratory fitness ($\dot{V}O_2$peak: +3.1, 95%CI 1.4, 4.8, p=0.001), and MM symptoms (EORTC QLQ-MY20: -7.4, 95%CI -15.2, 0.5, p=0.07), compared to CON. No between-group differences (p>0.05) were observed in general pain, fatigue, or neuromuscular strength.

Conclusion: A 12-week individualised exercise intervention was effective at improving HRQoL, bone pain, cardiorespiratory fitness, and MM symptoms. The findings support the inclusion of exercise as part of standard care to improve the quality of life and health of people with MM.

HO040

Gut Dysbiosis may adversely impact treatment responses with TKIs in ABL-rearranged high-risk B-ALL

Page E[1,2], Cheney C[1,2], Schutz C[1], Ryan F[1,3], Yeung D[1,2,4,5], Blake S[1,3], Lynn D[1,3], White D[1,2,5,6]
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Aim: Acute Lymphoblastic Leukaemia (ALL) is an aggressive and frequently fatal disease, particularly in neonates and young adults/adults. The composition and function of the gut microbiota has been demonstrated to play an essential role in cancer initiation, progression, and response to therapy in other cancers. Here, we aimed to investigate its role in ALL progression and treatment response.

Method: Immunocompromised NOD.Cg-Prkdc^{scid}Il2rg^{tm1Wjl}/SzJ (NSG) mice were engrafted with blasts from two high-risk *ABL*-rearranged ALL patients to establish patient-derived-xenograft (PDX) models. Half of the mice (n=20/PDX) received antibiotic (ABX) drinking water to deplete the gut microbiota, confirmed by 16S rRNA gene sequencing of faecal samples collected over the experiments' course. Microbe diversity was assessed by Bray-Curtis Analysis. ALL progression was monitored via tail-vein bleeds and flow-cytometric analysis for human (h)CD45+ cells. Chemotherapy, targeted therapy (dasatinib) or combination (n=5/group) commenced once 5% hCD45+ was detected in the peripheral blood (PB). At endpoint (50% hCD45+ in PB), bone marrow, spleen and liver were harvested and H&E staining was performed. A survival analysis was carried out post-treatment cessation. Statistical significance was determined by One-way ANOVA and t-test.

Results: In two high-risk PDX-ALL models, ABX-microbiota depletion accelerated leukaemic engraftment (Fig 1A;p<0.0001). ABX-treated mice had increased spleen (p=0.0114) and liver (p=0.0133) weights and decreased survival (p=0.0227) compared to control (eubiotic) mice. The efficacy of chemotherapy was similar in both ABX and control mice, however, dasatinib was less efficacious in ABX-mice, which encountered treatment resistance and relapsed with leukaemia significantly earlier compared to eubiotic mice (Fig 1B;p=0.011).

Conclusion: High-risk ALL-PDX models demonstrate a more aggressive leukaemic phenotype when their gut microbiota has been depleted. Studies utilising different patient subtypes and targeted-therapies are underway in a novel germ-free-NSG model. Validating these preliminary data may suggest a healthy donor faecal-microbiota-transplant as a viable adjunct therapy to improve patient responses to targeted therapies.

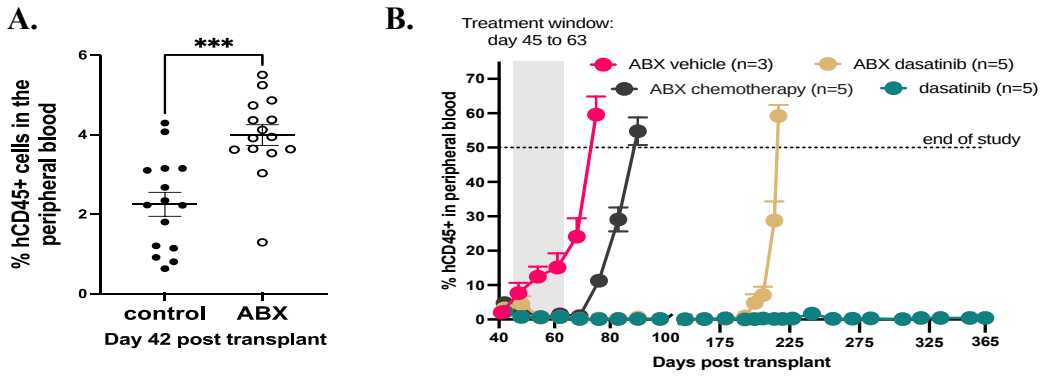

Figure 1: Antibiotic (ABX) induced depletion of gut microbiota decreases response to dasatinib and in a PDX model of *NUP214::ABL1* ALL. A) Leukaemic burden of *NUP214::ABL1* PDX mice with healthy or dysbiotic gut microbiota on day 42 post-transplant. **B)** Treatment commenced once 5% hCD45+ was detected in the peripheral blood (5 days on/2 days off for three weeks).

HO041

Single-institution experience of Steroid use in the management of Chimeric Antigen Receptor (CAR) T-cell therapy toxicity for Relapse/Refractory (R/R) large B-cell lymphoma (LBCL)

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Aim: CAR T-cell therapy has been available in Australia since February 2020 as a standard-of-care (SoC) publicly-funded treatment for fit patients with R/R LBCL after ≥2 lines of therapy. We evaluated our experience with steroid administration for the management of toxicities related to the use of tisagenlecleucel (tisa-cel) and axicabtagene ciloleucel (axi-cel).

Method: Data were collected in a prospective database for all patients with R/R LBCL who underwent SoC infusion with tisa-cel or axi-cel at the Peter MacCallum Cancer Centre / Royal Melbourne Hospital from February 2020 – February 2024.

Results: 145 patients received CAR-T cell therapy (52 tisa-cel, 93 axi-cel). Steroids were administered for the management of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) to 17% (n=9) and 77% (n=72) of the tisa-cell and axi-cel cohorts respectively (Table 1). In the axi-cel cohort CRS severity at time of first steroid dose was grade 1 in 56% (n=40). Grade ≥3 CRS occurred in 4% of patients (6% tisa-cel, 2% axi-cel), and grade ≥3 ICANS occurred in 11% of patients (2% tisa-cel, 17% axi-cel). In a one-month landmark analysis there was a trend towards longer duration of response (DOR) in those patients who received a cumulative dexamethasone equivalent dose greater than 0mg but less than 36mg compared to those who received no steroids or a cumulative dexamethasone equivalent dose ≥ 36mg (Figure 1). LDH > upper limit of normal pre-lymphodepletion was associated with higher cumulative steroid utilisation (Table 2).

Conclusion: Our single-institution experience highlights the frequent use of steroids in the management of CAR T-cell toxicity. Early steroid administration for lower-grade toxicity and low-dose steroid exposure was not associated with a reduced DOR and may prevent progression to severe toxicity. Further research is required to elucidate the potential impacts of steroid use on therapeutic outcomes in this population.

Table 1. Steroid Utilisation

Characteristic	Treatment Received		
	Axi-cel, N = 93[1]	**Tisa-cel**, N = 52[1]	**p-value**[2]
Steroids given	72 (77%)	9 (17%)	<0.001
Prophylactic Steroids given	4 (4.3%)	0 (0%)	0.3
Grade of CRS at first steroid dose			0.045
0	6 (8.3%)	1 (11%)	
1	40 (56%)	2 (22%)	
2	26 (36%)	5 (56%)	
≥3	0 (0%)	1 (11%)	
Grade of ICANS at first steroid dose			0.3
0	58 (81%)	6 (67%)	
1	11 (15%)	2 (22%)	
2	2 (2.8%)	0 (0%)	
3	1 (1.4%)	1 (11%)	
Days until first steroid	5 (3, 6)	6 (4, 11)	0.2
Duration of steroids (days)	5 (2, 11)	2 (0, 6)	0.2
Dexamethasone given	72 (77%)	9 (17%)	<0.001
Methylprednisolone pulse given	10 (11%)	0 (0%)	0.014
Dexamethasone equivalents (mg)	37 (12, 140)	16 (10, 24)	0.2

[1] n (%); Median (IQR)

[2] Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test

Figure 1. Axi-cel Duration of Response Curve

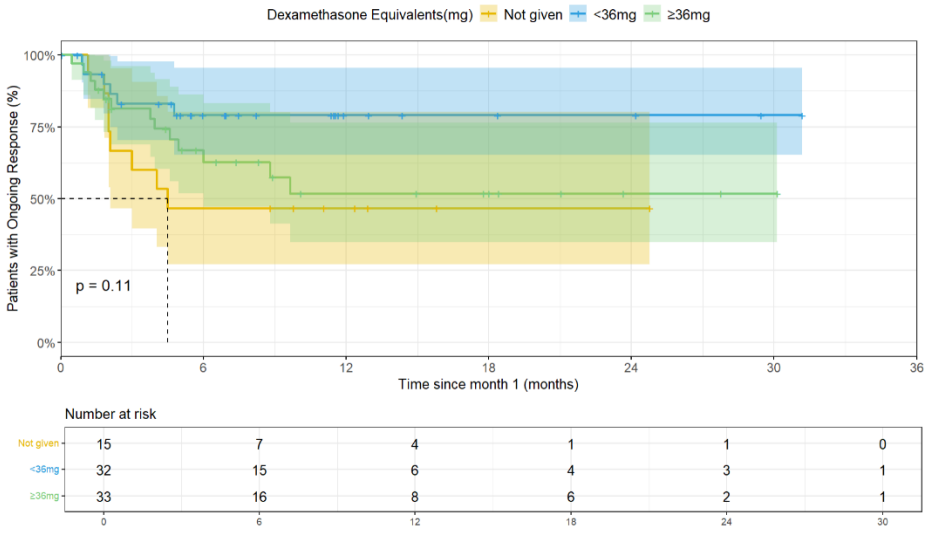

Table 2. Axi-cel Steroid Risk Factors

Characteristic	Equivalent Dose(mg)				Duration		
	Not given, N = 21[1]	**<37mg**, N = 36[1]	**≥37mg**, N = 36[1]	**p-value**[2]	**<7 days**, N = 45[1]	**≥7 days**, N = 27[1]	**p-value**[2]
LDH greater than ULN	8 (38%)	10 (28%)	23 (64%)	0.007	15 (33%)	18 (67%)	0.006
ECOG = 0	18 (86%)	23 (64%)	17 (47%)	0.015	29 (64%)	11 (41%)	0.050
Age greater than 65 years	6 (29%)	14 (39%)	19 (53%)	0.2	20 (44%)	13 (48%)	0.8
Refractory to most recent therapy	16 (76%)	22 (61%)	25 (69%)	0.5	28 (62%)	19 (70%)	0.5

[1] n (%)

[2] Pearson's Chi-squared test

Table 1. Steroid utilisation. **Table 2.** Risk factors for steroid use. **Figure 1.** Axi-cel DOR by steroid

HO042

Supportive Care research priorities for Acute Myeloid Leukaemia (AML) – results from a modified Delphi survey

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Aim: To identify and prioritise AML supportive care research priorities to inform a bi-national trial program.

Method: We employed a three-stage online modified Delphi process, inviting participants (clinicians and people with lived experience) from Australia and New Zealand through the Australasian Leukaemia and Lymphoma Group (ALLG), the Leukaemia Foundation and professional networks. Stage 1 called for supportive care research ideas, from which we developed research questions using content analysis. For stage 2, panellists rated each question's importance on a scale of 1 (most important) to 5 (least important). These data were analysed, and an *a priori* criteria were applied for a question to continue to stage 3, which was a mean score of <2 and ≥85% of respondents rating the question a 1 or 2. In the final round, participants ranked their top 10 research questions as well as the type of research needed to address the question (e.g. biological, RCT etc.).

Results: A total of 31 panellists completed round 1, 22 in round 2 and 22 in the final round. People with lived experience made up 32% of panellists in round 1, 45% in round 2 and 27% in round 3. Round 1 resulted in 66 research questions across 13 domains. In round 2, from the initial 66 questions, 16 (24%) met the criteria to progress to the next round. In the final round, panellists agreed on 10 priority research questions (table 1).

Table 1. Ranked supportive care research priorities for AML

Rank	Research Question	Research 'type' needed
1	What are the benefits and harms of prophylactic antibiotics in people with AML?	RCT
2	Which interventions are more effective to prevent bleeding in patients with severe thrombocytopenia?	RCT
3	Are long or short courses of antibiotics more effective in febrile neutropenia?	RCT
4	Can a frailty assessment guide risk stratification and decision making? (e.g. intensive vs non-intensive therapy)	Intervention development
5	How can nutrition support be optimised to support recovery from deconditioning?	Exploratory
6	What is the most effective regime to treat recurrent episodes of culture negative febrile neutropenia?	Intervention development
7	What is the effectiveness of an exercise intervention in improving survival, health and psychosocial outcomes for people with AML?	Intervention development
8	What is the optimal platelet count threshold for platelet transfusion?	RCT
9	What models of care are most effective at reducing infections?	Exploratory
10	How can criteria be established for better integration of palliative care at an earlier or optimal time point?	Exploratory

Conclusion: This Delphi process identified ten supportive care research priorities in AML across a range of domains, including infection prevention and treatment, bleeding prevention, nutrition, exercise and use of frailty assessments. This work, which incorporates the opinions of people with lived experience as well as clinicians, can be used to inform future clinical supportive care research.

HO043

Optical Genome mapping for Acute Myeloid Leukaemia diagnostics

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Aim: Accurate characterisation of tumour cytogenomic profile is critical for the diagnosis and prognosis of patients with acute myeloid leukaemia (AML). The current standard-of-care (SOC) pathway involves multiple assays: chromosome banding analysis (CBA), fluorescent in situ hybridization (FISH), and chromosomal microarray analysis (CMA). Optical genome mapping (OGM) has been proposed as a genome-wide assay capable of detecting multiple classes of genomic abnormalities. This study evaluated OGM performance in a real-world cohort of patients diagnosed with AML.

Method: OGM was performed on blood and bone marrow samples from 23 patients with AML who also underwent SOC diagnostic investigation. Whole genome sequencing (WGS) was also performed on 10/23 patients to orthogonally validate OGM findings.

Results: Out of 23 patients, 10 had normal karyotype while 13 had a cytogenomic abnormality that was diagnosis or prognosis defining. 11/13 abnormalities were detected by both SOC CBA/FISH/CMA and OGM (83% concordance), including: t(15;17)/*PML::RARA* (n=3), inv(16)/*CBFB::MYH11* (n=1), t(8;21)/*RUNX1::RUNX1T1* (n=1), t(16;21)/*RUNX1::RUNX1T3* (n=1), t(9;11)/*KMT2A::MLLT3* (n=1), *MECOM* rearrangement (n=3), and complex karyotype (n=2). Two notable discordances were observed. One was a del(7q) detected in 15% of cells by CMA below OGM sensitivity. The other was a small *MECOM* rearrangement cryptic to CBA but detected by OGM.

Beyond established cytogenetic markers, OGM identified additional structural variants in all patients. In one patient, this included somatic variants (*KMT2A* partial tandem duplication, microdeletion on chr12), and germline variants of uncertain significance confirmed by WGS.

Conclusion: In this cohort of patients with AML, OGM showed high concordance with SOC methods for established diagnosis-defining genomic abnormalities including detection of abnormalities not detectable by SOC analysis. Our orthogonal WGS data provides the opportunity for extensive analytical validation to determine the role of this technology in the diagnosis of patients with AML.

HO044

Transplant in Paediatric Haemaglobinopathy: The RCH experience

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Introduction: Sickle cell disease and transfusion-dependent thalassemia are inherited conditions associated with significant morbidity and reduced life expectancy. Recent advances in supportive management have led to a decrease in complications from these conditions, however allogeneic haematopoietic stem cell transplant (HSCT) remains the only curative option[1,2] The number of children in Australia with a major haemoglobinopathy is expected to continue to rise, with more families choosing to explore the option of HSCT, however limited information is currently available regarding outcomes of this procedure in Australia with no current national guidelines.

Case Series: The Royal Children's Hospital (RCH) has performed HSCT in seven children with sickle cell disease and seven children with transfusion-dependent beta thalassemia. Here we describe the RCH experience with transplant in major haemaglobinopathies, focusing on (1) pre-transplant management, (2) choice of conditioning regimes and (3) subsequent clinical outcomes. Pre-transplant factors to be considered include criteria for selection of transplant candidates (factoring in availability and type of transplant), and management of iron overload, hydroxyurea and blood products, with outcomes of interest including days to engraftment, length of hospitalisation, chimerism and overall morbidity/mortality.

Discussion: HSCT has traditionally been performed relatively rarely in children with major haemaglobinopathies in Australia[3]. Transplants in these children present unique challenges compared to those for malignant indications, especially where chronic transfusions programs are safe and with adherence to iron chelation and complications screening there is the expectation of good quality-of-life with long life expectancy. Guidelines around appropriate indications, optimisation pre-transplant and conditioning regimens are continuing to evolve in the setting of non-malignant transplant[1].

The RCH has developed a site-specific guideline for management of bone marrow transplant in these patients based on evolving evidence and clinical experience. Our experience highlights the need for a multidisciplinary approach to planning for HSCT in a cohort that is expected to continue to expand.

HO045

Long-term survival after Elranatamab Monotherapy in patients with relapsed or refractory Multiple Myeloma (RRMM): MagnetisMM-3

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Aim: In MagnetisMM-3 (NCT04649359), elranatamab induced deep and durable responses in patients with BCMA-naive RRMM. After a median follow-up of 17.6 months, the median overall survival (OS) was not yet mature (Tomasson, et al. ASH 2023; Abs 3385). Here, we report OS >2 years after the last patient's initial elranatamab dose.

Method: Eligible patients had disease refractory to ≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 antibody. Patients received subcutaneous elranatamab as 2 step-up priming doses then 76 mg once-weekly (QW). Patients who received ≥6 months of QW dosing and achieved partial response or better for ≥2 months were transitioned to Q2W dosing and to Q4W dosing after ≥6 Q2W cycles. Data cutoff was 26MAR2024.

Results: The median age of patients (N=123) was 68 years (19.5% were ≥75 years); 55.3% were male. The median number of prior lines of therapy was 5 (range, 2-22). At data cutoff, the overall response rate was 61.0% (37.4% complete response [CR] or better). Median duration of response (DOR), progression-free survival (PFS), and OS were not reached (95% CI, not estimable [NE]-NE), 17.2 (95% CI, 9.8-NE), and 24.6 (95% CI, 13.4-NE) months, respectively. The estimated rate for DOR at 2 years was 66.9% (95% CI, 54.4-76.7) among all responders and was 87.9% (95% CI, 73.1-94.8) in patients with CR or better. Since prior data cutoff (Sep 2023), there were 4 new deaths (disease under study, n=2; unknown reason, n=1; septic shock, n=1). There were no new safety signals. Five (4.1%) patients had secondary primary malignancies (SPMs; all squamous cell carcinoma [SCC]); all received prior lenalidomide and stem cell transplant.

Conclusion: After >2 years of follow-up, elranatamab demonstrated deep and durable responses and a median OS of 24.6 months in heavily pretreated, BCMA-naive patients with RRMM. SCC was the only reported SPM. No hematological SPMs were reported.

HO046

Sonrotoclax plus Dexamethasone was tolerable and demonstrated Antimyeloma activity in patients with Relapsed/Refractory (R/R) Multiple Myeloma (MM) harboring t(11;14)

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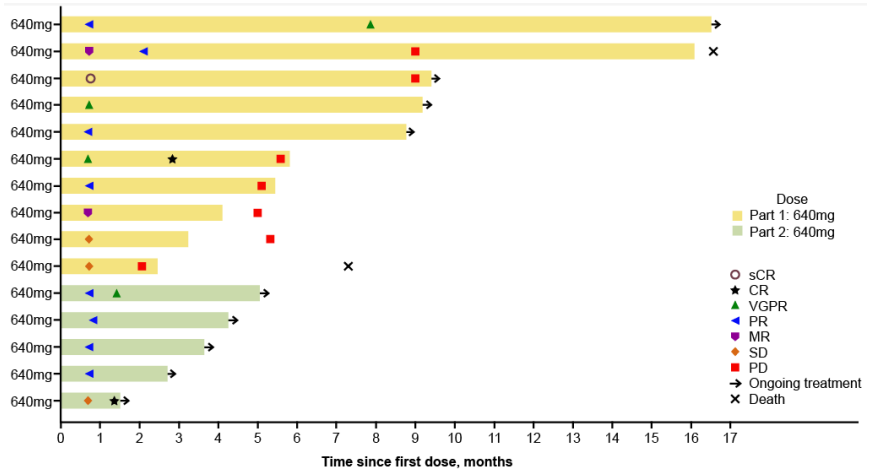
Aim: BGB-11417-105 (NCT04973605), an ongoing phase 1b/2 trial, evaluated the BCL2 inhibitor sonrotoclax (BGB-11417) as monotherapy or combination therapy in patients with R/R MM harboring t(11;14). Updated data for sonrotoclax 640mg plus dexamethasone are presented.

Method: Eligible patients had R/R MM, centrally confirmed t(11;14), and ≥3 (dose-finding) or ≥1 (dose-expansion) prior therapy. Patients received sonrotoclax 640mg orally once daily and dexamethasone 40mg weekly. AEs per CTCAE v5.0 and responses (IMWG criteria) were assessed.

Results: As of January 8, 2024, 20 patients (median prior therapies, 4; range, 1-12) were enrolled (640mg dose-escalation, n=10; dose-expansion, n=10). Median follow-up was 6.2 months (range, 0.3-16.6); 70% and 80% were refractory to anti-CD38 and immunomodulatory drugs, respectively. Thirteen patients (65%) remained on treatment (discontinuations: disease progression, n=3; AE, n=2 [hematuria, pancreatic cancer]; patient withdrawal, n=1; physician decision, n=1). The most common treatment-emergent AEs (TEAEs) were insomnia (30%) and diarrhea, fatigue, and nausea (each 25%). Three patients had hematologic TEAEs (thrombocytopenia, n=2 [grades 1 and 3]; neutropenia, n=1 [grade 1]). Three (15%) had serious TEAEs and 4 (20%) had grade ≥3 AEs; none were sonrotoclax related. No dose-limiting toxicities occurred. Two patients died on study (TEAE, n=1 [metastatic pancreatic cancer]; non-TEAE, n=1 [hepatocellular carcinoma–associated liver failure]; neither treatment related). Infections in >1 patient were COVID-19 and upper respiratory tract infection (n=2 each [10%]). In efficacy-evaluable patients, objective response rate was 80% (12/15; 95% CI, 51.9%-95.7%); very good partial response or better rate was 40% (6/15). Median time to response was 0.7 months. Median duration of response was 8.3 months (95% CI, 4.4-NR) and maximum was 15.4 months (ongoing; Figure).

Conclusion: With longer follow-up, sonrotoclax plus dexamethasone demonstrated a manageable safety profile, with low hematologic toxicity and infection rates. The combination provided deep and durable responses in this R/R population.



HO047

Final survival analysis of Daratumumab (DARA) plus Lenalidomide and Dexamethasone (D-Rd) vs Lenalidomide and Dexamethasone (Rd) in transplant-ineligible (TIE) patients (pts) with newly diagnosed multiple myeloma (NDMM): MAIA study

Quach H[1], Facon T[2], Kumar S[3], Orlowski R[4], Bahlis N[5], Moreau P[6], Goldschmidt H[7], Basu S[8], Hulin C[9], Zweegman S[10], Weisel K[11], Perrot A[12], Jacquet C[13], Raje N[14], Manier S[15], Chari A[16], Hansson M[17], Mohty M[18], Delforge M[19], Plesner T[20], Cook G[21], Leleu X[22], Venner C[23,24], Tiab M[25], Macro M[26], Frenzel L[27], Wang G[28], Pei H[29], Bolyard K[30], Carson R[28], Borgsten F[30], Usmani S[31]

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Aim: The phase 3 MAIA study demonstrated superior PFS (median 61.9 vs 34.4 months) and OS (median not reached vs 65.5 months) with D-Rd vs Rd in NDMM. Here we report updated OS results from the long-term analysis (median follow-up 7.5 years) and new subsequent antimyeloma therapy data.

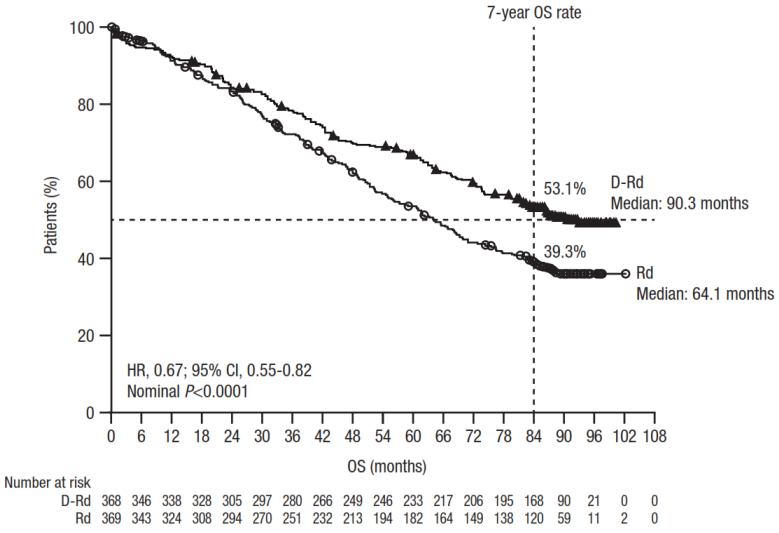
Method: TIE pts with NDMM were randomised 1:1 to receive D-Rd or Rd. All pts received 28-day cycles of Rd (R: 25 mg orally once daily on Days 1–21; d: 40 mg orally on Days 1, 8, 15, 22) with or without DARA (16 kg/mg IV once weekly for Cycles 1–2, once every 2 weeks for Cycles 3–6, and every 4 weeks thereafter) until disease progression or unacceptable toxicity. The primary endpoint was PFS. OS was a key secondary endpoint.

Results: 737 pts were randomised (D-Rd, n=368; Rd, n=369). After a median (range) follow-up of 89.3 (0–102.2) months, a 33% reduction in risk of death was observed with D-Rd vs Rd. Median OS was 90.3 months with D-Rd vs 64.1 months with Rd (HR, 0.67; 95% CI, 0.55–0.82; nominal P<0.0001; **Figure**). Among those treated, 140/364 (38.5%) D-Rd pts and 201/365 (55.1%) Rd pts received ≥1 subsequent line of antimyeloma therapy. Median time to subsequent therapy was longer with D-Rd vs Rd (not reached vs 42.4 months; HR, 0.51; 95% CI, 0.41–0.63; nominal P<0.0001). Overall, 285 (78.3%) and 345 (94.5%) D-Rd and Rd pts,

respectively, discontinued study treatment, primarily due to progressive disease (119 [32.7%] and 141 [38.6%]). Additional data on subsequent therapies and causes of death will be presented.

Conclusion: D-Rd continued to demonstrate a clinically significant survival benefit vs Rd in TIE pts with NDMM. Furthermore, 28.8% of Rd pts vs 6.3% D-Rd pts received subsequent DARA-based antimyeloma therapy. These data support frontline D-Rd in TIE pts with NDMM.

Figure. OS with D-Rd and Rd.



OS, overall survival; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.

HO048

RUNX1 STOP-loss mutations define a distinct prognostic subset within RUNX1-mutated acute myeloid leukaemia.

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[1]Alfred Health, [2]Australian Centre for Blood Diseases

Aim: The differential prognostic impact of types of *RUNX1* mutations in acute myeloid leukaemia (AML) has not been analysed. We term *RUNX1* STOP-loss (*RUNX1*-SL) mutations as those resulting in loss of the normal STOP codon from small insertion or deletions (INDELs) causing a frameshift (Figure 1a). We evaluated prognosis of *RUNX1*-SL mutations compared to *RUNX1* mutations that were not STOP-loss (*RUNX1*-NSL) and wild-type *RUNX1* (RUNX1wt).

Method: We retrospectively analysed 1619 patients with AML from two cohorts [German Acute Myeloid Leukemia Study Group from the European Genome-Phenome Archive (n=1475) and the Alfred Health (AH) AML database (n=144)]. RNA from bone marrow of *RUNX1*-SL mutation patients was converted to cDNA and Sanger sequenced. Survival analyses performed using R.

Results: Within the total combined population (n=1619), 30 patients harboured a *RUNX1*-SL mutation, 135 patients with a *RUNX1*-NSL mutation and 1454 *RUNX1*wt patients. *RUNX1*-SL mutations result in detectable mutant transcript (Figure 1b), suggesting the mutant mRNA is not degraded via nonstop decay surveillance pathways. *ASXL1* mutations were less common in *RUNX1*-SL compared to *RUNX1*-NSL (3% vs 22%, p=0.018), while the inverse was true for *MLL*-PTD (30% vs 7%, p=0.003) (Figure 1c/d). Median overall survival (OS) for *RUNX1*wt patients (27.1 months, 95% CI 23.1-32.8) and those with *RUNX1*-SL mutations [25.2 months, 95% CI 17.6 -not reached (NR)] was similar, and significantly longer than those with *RUNX1*-NSL mutations (13.6 months, 95% CI 11.9-21.6, p<0.001). Within the *RUNX1* mutated cohort, *RUNX1*-SL mutations were associated with improved survival compared to *RUNX1*-NSL mutations (HR 0.57, 95% CI 0.34-0.97, p = 0.04) (Figure 1e) and tracked with intermediate ELN 2022 risk, while patients with *RUNX1*-NSL tracked with adverse ELN 2022 risk (Figure 1f).

Conclusion: These results highlight the unique prognostic impact of harbouring a *RUNX1*-SL mutation in AML. *RUNX1*-SL mutations warrant consideration as a distinct intermediate-risk lesion, separate to the adverse risk *RUNX1*-NSL mutations.

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2. Yamato G, Shiba N, Yoshida K, Hara Y, Shiraishi Y, Ohki K, et al. RUNX1 mutations in pediatric acute myeloid leukemia are associated with distinct genetic features and an inferior prognosis. Blood. 2018 May 17;131(20):2266–70.

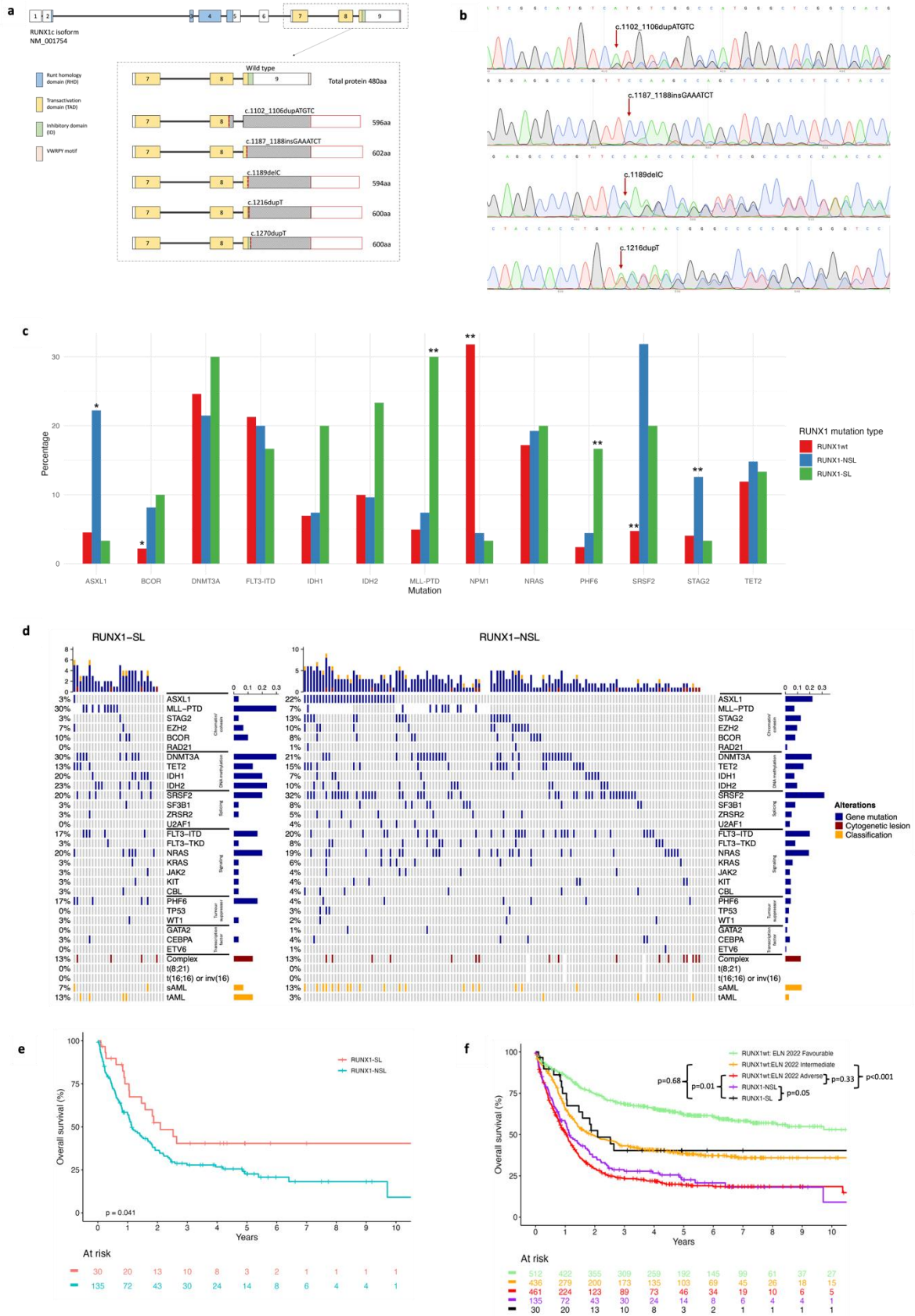

Figure 1: a) Pictorial representation of *RUNX1*-SL mutations in AH cohort (n=5) in relation to exons and functional domains of RUNX1c (major isoform of *RUNX1*). Shaded bar indicates frameshifted sequence and red dotted line indicates location of mutation. **b)** RNA sequencing visualised in SnapGene® for 4/5 AH *RUNX1*-SL patients with RNA available **c)** Mutation frequency by RUNX1 mutation status, in genes which were mutated by at least 10% in one of the RUNX1 mutation type subgroups, * highlights significant difference in frequency **d)** Oncoplot for *RUNX1*-mutated (n=165) cohort, separated by *RUNX1*-SL and *RUNX1*-NSL mutation, sAML=secondary AML, tAML= therapy-related AML, white boxes indicate testing for that lesion not performed **e)** Overall survival in the *RUNX1*-mutated population stratified by *RUNX1*-SL mutation vs *RUNX1*-NSL **f)** Overall survival in the total population stratified by ELN 2022 risk in *RUNX1*wt vs *RUNX1*-NSL mutation (purple) vs *RUNX1*-SL mutation (black)

HO049

Acquired copy number variants are highly correlated with Ph+ALL subgroups identified by transcriptomic analysis

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Aim: The ICC subclassifies Ph+ALL into *BCR::ABL1* with lymphoid-only versus multilineage involvement (a.k.a CML-like disease). Standard diagnostic assays cannot distinguish these subgroups, and differences in prognosis or optimal treatment remain unknown. Here, we use gene expression analysis to identify subgroups of Ph+ALL and correlate this with copy number variants (CNV) and treatment outcomes.

Method: mRNA sequencing (mRNA-seq) was performed on 115 Ph+ALL samples (n=12 children; n=26 adolescent young adults; n=77 adults). Gene deletions were detected by multiplex ligation-dependent probe amplification (SALSA MLPA P202 and P335). Lineage subclassification was determined with the AllCatchR_bcrabl1 classifier. tSNE was utilised for gene expression clustering. Kaplan-Meier plots and log-rank (Mantel-Cox) tests were performed in R.

Results: The e1a2 (p190) *BCR::ABL1* fusion transcript was found more frequently (77%) than e13a2 (p210; 17%) or e14a2 (6%). Hyperdiploid karyotype was present in 11% of cases. MLPA (n=103/115) revealed frequent deletions of *IKZF1* (78%), *CDKN2A/B* (53%), *PAX5* (43%), *BTG1* (26%) and *RB1* (17%); 47% of patients demonstrated an *IKZF1*plus profile. Gene expression analysis identified three patient clusters with distinct CNV patterns (Fig1a). Clusters A and B were classified as lymphoid-only, with enrichment of hyperdiploidy in cluster A and *IKZF1*plus (71%) in cluster B. Cluster C patients were classified multilineage, demonstrating frequent *IKZF1* deletion (77%) but lacking *PAX5*, *CDKN2A/B* or *RB1* deletions. Outcome data (n=50) showed decreased but not statistically significant relapse-free (RFS) and overall survival (OS) in lymphoid-only compared with multilineage Ph+ALL (RFS p=0.09; OS p=0.1, Fig1b). Patients with *CDKN2A/B* deletions had significantly lower RFS (p=0.024) and OS (p=0.026, Fig1c).

Conclusion: Ph+ALL patients exhibit distinct gene expression profiles associated with cell lineage and acquired CNVs. Patients with multilineage Ph+ALL lacked *PAX5* or *CDKN2A/B* deletions. Preliminary univariate survival analysis suggests *CDKN2A/B* deletions at diagnosis are associated with poorer outcomes.

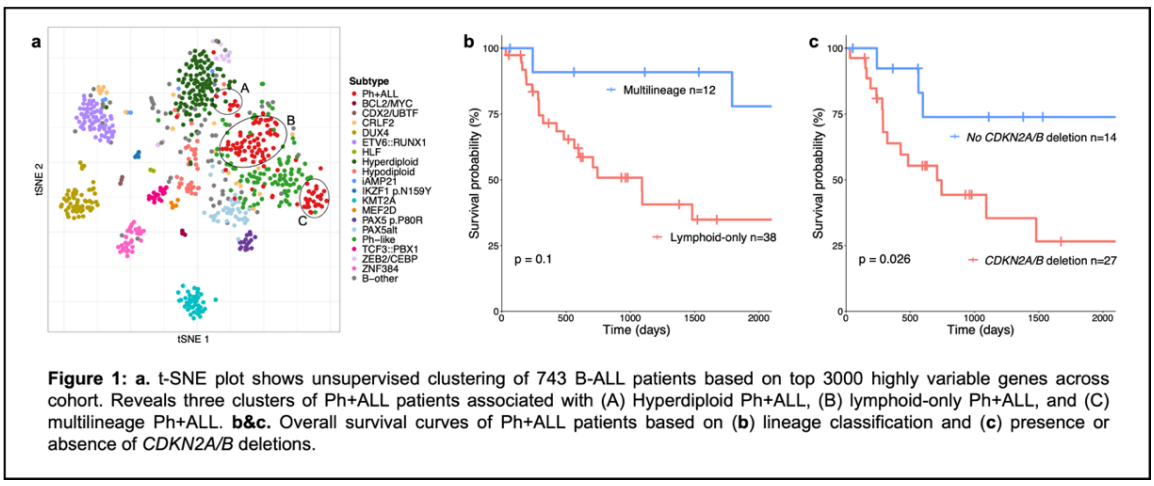

Figure 1: a. t-SNE plot shows unsupervised clustering of 743 B-ALL patients based on top 3000 highly variable genes across cohort. Reveals three clusters of Ph+ALL patients associated with (A) Hyperdiploid Ph+ALL, (B) lymphoid-only Ph+ALL, and (C) multilineage Ph+ALL. **b&c.** Overall survival curves of Ph+ALL patients based on (**b**) lineage classification and (**c**) presence or absence of *CDKN2A/B* deletions.

HO050

Co-occurrence of Obesity and Diabetes adversely impacts overall survival (OS) in Multiple Myeloma (MM) – an analysis from the Australian and New Zealand Myeloma & Related Disease Registry (ANZ MRDR).

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Aim: A key co-morbidity in MM is metabolic syndrome which comprises abdominal obesity, insulin resistance, dyslipidaemia and hypertension and increased risk of neoplasia related to insulin resistance and compensatory hyperinsulinaemia. These factors increase the complexity of management of myeloma including Dexamethasone use and may affect survival. This study aimed to map metabolic syndrome amongst MM patients in ANZ, to evaluate the impact of these factors on OS and progression free survival after first line treatment (PFS1) and ultimately to identify patient subpopulations who may benefit from targeted interventions.

Method: Data was provided by the ANZ MRDR. Patients with MM who commenced at least one line of treatment and those with recorded weight and height were included. Descriptive statistics were used to for baseline characteristics. Kaplan-Meier analysis with log rank test was used to calculate OS and PFS1. Multivariate Cox Regression analysis was performed to estimate hazard ratios (HR) for DM and metabolic syndrome (DM and Body Mass Index (BMI)>30).

Results: 3791 patients were included. 30.7% of patients had a BMI>30. Data on comorbidities was available in 90%. Of these, 12.1% had DM at diagnosis. DM was associated with worse OS (median 4.9 years [4.0-5.8] versus 6.7 years [6.2-7.2] in patients without DM, p<0.001) and worse PFS1 (median 26.8 months [21.6-32.0] versus 31.9 [30.1-33.6] without DM, p<0.01). Co-occurrence of diabetes + BMI>30 was associated with worse OS (Figure 1, Table 1) and was more common in the Maori (16.4%) and Polynesian People (20.3%) compared to Asian and European (5.1% and 4.9%). Only 12 patients were Aboriginal and Torres Strait Islander.

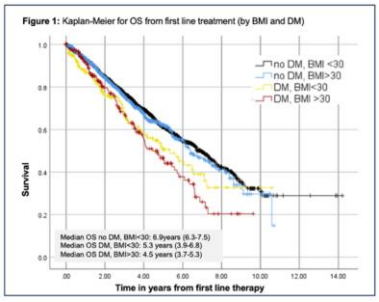

Table 1: Multivariable Cox regression, HR for all-cause mortality

Variable	HR (95% CI for lower and upper)	p-value
No DM, BMI<30	Reference	
No DM, BMI>30	1.10 (0.95-1.27)	0.21
DM, BMI<30	1.26 (0.99-1.6)	0.057
DM, BMI>30	***1.59 (1.28-1.98)***	***<0.001***
Gender female	Reference	
Gender male	1.13 (0.995-1.275)	0.06
Age <50	Reference	
Age 50-70	1.45 (1.09-1.95)	0.01
Age >70	3.30 (2.47-4.40)	<0.01

Conclusion:
Our data show that obesity when associated with diabetes, has prognostic relevance in myeloma and this population may benefit from targeted interventions.

HO051

Nivallo: A prospective phase I study of Nivolumab to promote the graft versus tumour effect in Haematological Malignancies persisting or progressing after Allogeneic stem cell transplantation.

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[1]Royal Melbourne Hospital, [2]Peter MacCallum Cancer Centre, [3]University of Melbourne, [4]Austin Health

Aim: The efficacy of allogeneic stem cell transplantation (alloSCT) in haematological malignancies (HM) is due to the immunologically mediated graft versus tumour (GVT) effect. We examined the safety and efficacy of the PD-1 inhibitor nivolumab in HM persistence or relapse after alloSCT (NCT03146468 and ACTRN12617000473369).

Method: Eligibility: HM persistence or relapse following alloSCT, immunosuppression cessation, absence of GVHD and donor CD3+ chimerism > 30%. Nivolumab was given in 2 weekly intervals for a maximum of 48 weeks. Primary endpoint was GVHD at 8, 24 and 48 weeks. Secondary endpoint was overall response rate (ORR).

Results: 49 were potentially eligible. 33 did not participate due to rate of disease progression (26%), GVHD (30%), T-cell chimerism <30% donor (5%) or concurrent illness (5%) or physician preference. 16 were enrolled, 2 did not pass screening. 14 patients received nivolumab. The median age was 52 (24-67). All had CD3+ chimerism > 70%. Patient details are in table 1.

Eleven patients relapsed from complete remission (CR) a median of 321 days (range 97-1500d) after alloSCT. Three (1 of Hodgkin lymphoma (HL) (155d), mantle cell lymphoma (MCL) (56d) and chronic lymphocytic leukaemia (CLL) (75d)) had progression of HM at first assessment post-alloSCT.
54 adverse events occurred. 10 SAE occurred, 4 were dose limiting toxicities (2 each of acute GVHD and pneumonitis).
Four achieved CR (2 HL, 1 T-ALL, 1 MCL) and 2 PR (1 HL, 1 NKT lymphoma) even after limited nivolumab exposure (1, 2 and 7 doses) in three patients with further dosing ceased due to GVHD (2), patient preference in 1 and pneumonitis in 1. All patients with AML ceased nivolumab due to progression.
Conclusion:
Nivolumab following alloSCT is feasible but limited by GVHD or pneumonitis. Promotion of GVT appears possible in lymphoid malignancy. Alternative strategies are required for AML relapse after alloSCT.

Trial number	Age	Sex	transplant indication	lines of therapy prior to allo	prior auto	prior allo	Status pre-transplant	Donor	Conditioning regimen
4	45	M	AML	1	N	N	CR	UD	FluCy(HD)

2	53	M	AML	4	N	Y	CR	UD	BuCy
11	24	F	AML	1	N	N	CR	UD	BuCy
12	47	F	HL	5	Y	N	PR	MSD	FluCy(HD)
7	38	M	HL	7	Y	N	CR	MSD	FluMel
1	26	M	HL	4	Y	N	PR	dUCB	FluCyTBI
9	66	M	B-ALL	2	N	N	CR	UD	CyTBI
10	52	M	T-ALL	1	N	N	CR	MSD	CyTBI
8	57	M	MCL	5	Y	N	PR	UD	FluCy(LD)
3	52	F	CLL	2	N	N	CR	UD	CyTBI
13	53	M	CLL	8	Y	N	PR	UD	FluMel
14	56	F	MF	0	N	N	untreated	MSD	FluMel
15	67	M	MDS	0	N	N	untreated	UD	BuCy
16	29	M	NK/T cell lymphoma	3	N	N	CR	UD	FluMel

HO052

Flow cytometric CAR-T cell enumeration and clinical correlation with cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

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Aim: To describe the *in vivo* kinetics of CAR-T cells in patients undergoing standard of care axicabtagene and tisagenlecleucel and correlate with CAR T toxicity (CRS and ICANS).

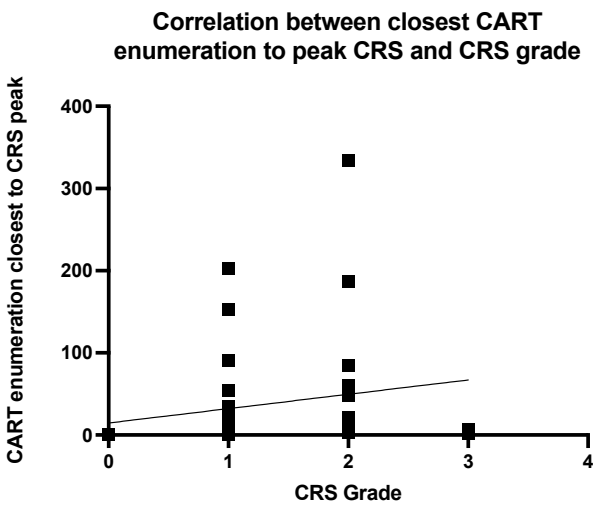
Method: CAR-T cells in peripheral blood were enumerated by flow cytometry. Whole blood was red cell lysed and stained with lyophilised PE-labelled monoclonal Anti-FMC63 antibody, CD3, 4, 8, 14, 20, and 7AAD. Spearman's rank correlation coefficient was used to assess the relationship of CAR-T numbers to CRS/ICANS grade.

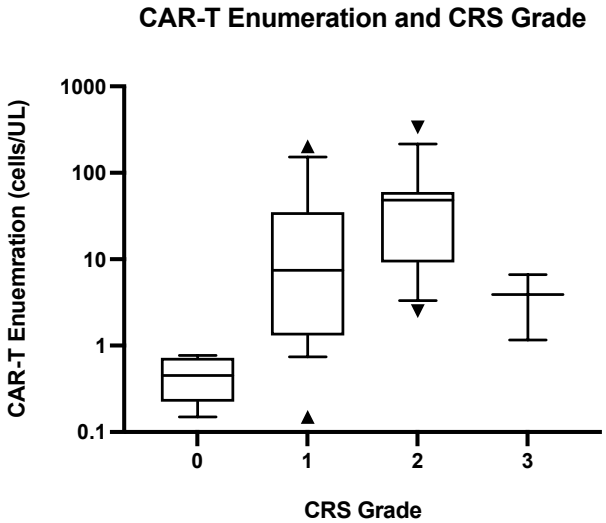
Results: 59 patients received CAR-T treatment (axi-cel n=33, tisa-cel =24, brexu-cel n=2) between June 2021 and December 2023 at Westmead Hospital. The most common indication was DLBCL (64%), followed by other HGBCL (17%), FL (9%), PMBCL (7%), and B-ALL (3%). 83% of patients had CRS; with a median grade of 1, a mean of 2.4 days between infusion and onset, and a mean duration of 6.5 days. 34% of patients had ICANS; with a median grade of 0, a mean of 5.6 days between infusion and onset, and a mean duration of 9.1 days. The higher the grade of CRS and ICANS, the longer the duration and the longer the time to peak toxicity.

We identified 245 enumeration values in the study period (median per patient 5, range 1 to 15). The mean time from infusion to peak CAR-T enumeration was 14 days (range 5-30). The median peak value was 21.6 CAR-T cells / uL (range not detected to 334). The median duration of detectability was 81 days (range 0 days to ongoing).

There was a moderate correlation between the closest CAR-T enumeration to CRS peak and CRS grade (r 0.46, p = 0.002.) There was no correlation between the closest CAR-T enumeration to ICANS peak and ICANS grade (r 0.02, p=0.919.)

Conclusion: Flow cytometric enumeration is a useful tool in understanding the *in vivo* kinetics of CAR-T, and may have clinical utility in tracking IEC toxicity. Regular and protocolised enumeration with prospective analysis is required.





HO053

Anti-tumoural T-cell immunity against B-cell receptor neoantigens explains the superior survival of IGHV-mutated chronic lymphocytic leukaemia

Sabdia M[1], Burgess M[2,3], Law S[1], Kazakoff S[4], Swain F[2,3], Fast E[5], Chen B[5], Thurgood L[6], Tobin J[1,3], Mollee P[3], Patch A[4], Gandhi M[1,3]

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Introduction: Chronic lymphocytic leukaemia (CLL) is the most common haematological malignancy. Outside of alloSCT it remains incurable. The mutational status of the immunoglobulin heavy chain variable (IGHV) region, part of the B-cell receptor (BCR), independently predicts outcomes in patients treated with chemoimmunotherapy. IGHV-mutated (M-CLL) has superior survival compared to IGHV-unmutated (U-CLL). Immune-mediated mechanism(s) behind this observation are yet to be explored. Neoantigens are immunogenic peptides, unique to malignant cells, that can arise from mutations. If harnessed, neoantigens have potential as novel immunotherapeutic strategies. CLL has a low tumour mutational burden (TMB), with few somatic-mutations/neoantigens. However, traditional TMB concepts exclude BCR-mutations, which may create 'BCR-neoantigens'.

Aim: To compare the frequency of BCR and somatic neoantigen-specific T-cells (NST-cells), and characterise NST-cell immunity, in U-CLL vs. M-CLL

					Discovery	Validation	p val
N					24	21	ns
Median age (range)					69 (44-90)	68 (43-89)	ns
Gender				Male	18	12	ns
				Female	6	9	ns
Subtype				U-CLL	13	12	ns
				M-CLL	11	9	ns
Chromosomal alterations	del11q	5	3	ns			
	del13q	14	10	ns			
	del17p	1	3	ns			
	tri12	0	1	ns			

Table 1: Patient characteristics

Methods: A discovery (Brisbane 24pts) / validation (Adelaide 21pts) approach was used (Table 1). Samples from both CLL cohorts underwent paired whole exome and tumour RNAseq. HLA-I/II neoantigens were called using pVACtools. Single-cell RNAseq (scRNAseq) was used to identify and characterise NST-T cells.

Results: Within the discovery cohort, somatic-neoantigens were comparable between M-CLL and U-CLL (Figure 1). Driver-mutations and driver-neoantigens were also comparable. However, BCR-neoantigens were 4x more abundant in M-CLL (Figure 1A). Chromosomal alterations did not impact neoantigen burden. Similar results were observed in the validation cohort (Figure 1B). The majority of neoantigens were HLA-II. Bulk RNAseq (via CIBERSORT) was consistent with scRNAseq in showing antigen experienced memory T-cells were the dominant CD4+ T-cell subtype. NST-cells against driver (XPO1, SF3B1, TP53) and BCR-neoantigens in CLL were characterised.

Conclusion: BCR-neoantigens are enriched in patients with M-CLL and likely influence its superior prognosis compared to U-CLL. The identification of BCR and driver-neoantigens, in combination with the enrichment of antigen experienced T-cells, support the further investigation of neoantigen immunotherapies for the treatment of CLL and other haematological malignancies.

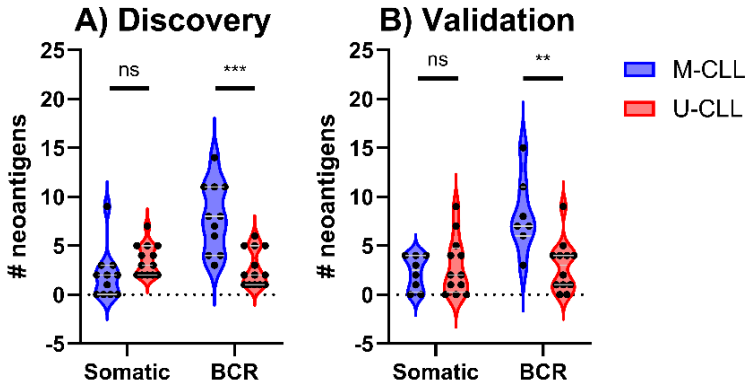

Figure 1. Somatic and BCR neoantigens in CLL.

HO054

Endothelial-targeted CD39 as a novel treatment for Acute Multi-organ injury in Sepsis

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Introduction & aim: Outcomes in sepsis are stubbornly poor and need a new approach. The current treatments do not address the inflammatory cytokine storm and endothelial activation leading to microvascular thrombosis and coagulopathy, recognised as common underlying processes contributing to acute organ failure, including sepsis associated encephalopathy (SAE). We have developed a novel therapeutic 'Anti-VCAM-CD39' localising the potent anti-inflammatory, vasodilatory and antithrombotic properties of the ectonucleotidase CD39 to the inflamed microvasculature by binding to the receptor vascular cell adhesion molecule-1 (VCAM-1) expressed on activated endothelial cells (ECs). For this project we **aimed** at validating the effect of *'Anti-VCAM-CD39*' in a sepsis murine model.

Method: Sepsis was induced in C57BL/6 mice with intraperitoneal injection of LPS (lipopolysaccharide) at 5mg/kg. '*Anti-VCAM-CD39'* (0.8 mg/kg, intravenous) was administered 1h later. Tissues were collected and interrogated with qRT-PCR, immunoblotting and immunofluorescence. Plasma adenosine and pro-inflammatory cytokines quantification was performed by ELISA and flow cytometry (LEGENDplex) respectively.

Results: Treatment with anti-VCAM-CD39 at 0.8mg/kg improved clinical outcomes and reversed core hypothermia. This coincided with significant reduction in plasma cytokines (IL1β, IL-6 and TNF-α (p=0.025, 0.03 and 0.05 respectively, treated versus untreated) at 6h. Systemic adenosine levels increased at 24h (p=0.03). Within the lung anti-VCAM-CD39, treatment inhibited the development of Acute Respiratory Distress Syndrome (ARDS) verified by H&E staining of lung tissues, and decreased endothelial activation (ICAM, e-selectin), hypoxia (HIF1a), and local pro-inflammatory cytokines (IL-6, MCP1). Heart stress characterised by upregulation of Atrial Natriuretic Peptide (Nppa) was alleviated at 24h. In the kidneys, anti-VCAM-CD39 significantly decreased the transcription of ICAM1, and pro-inflammatory cytokines IL-6, MCP1, while dropping the expression of Lcn2/NGAL, an early tubular kidney damage marker (p=0.04 treated versus untreated) at 6h. Similarly, it decreased the transcription of endothelial stimulation markers and pro-inflammatory cytokines in the brain at 6h.

Conclusion: Collectively, our results show that '*anti-VCAM-CD39"* could be a beneficial addition to antibiotics in the context of sepsis, alleviating the cytokine storm and the resulting tissue damage.

HO055

MRI and Neurocognitive Assessment of Chemobrain in Acute Myeloid Leukaemia.

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Aim: “Chemobrain” is commonly reported by patients treated for Acute Myeloid Leukaemia (AML), but objective detection by conventional imaging techniques is elusive. We aimed to detect “chemobrain” in AML patients using a comprehensive neurocognitive assessment and imaging platform.

Methods: We performed an observational, longitudinal cohort study in adults commencing chemotherapy for AML, powered to capture an expected 25% incidence of “chemobrain.” Participants underwent neurocognitive assessment (NCA) and brain MRI at three timepoints: pre-treatment (T1), end of treatment (T2), and 6 months later (T3). MRI comprised anatomical assessment, functional MRI, and quantitative susceptibility mapping (QSM) to examine brain iron as a neuro-inflammation imaging biomarker. Longitudinal changes of minimum 2.0SD were considered significant. Analysis was performed using FSL, CONN and SPM2 software to perform first- and group-level analysis with non-parametric statistics.

Results: 20 patients were enrolled during 2019-21; of these, 15 and 10 remained alive/enrolled for evaluation at T2 and T3 respectively. Overall NCA scores for the cohort between T1-T2 were similar; however, three participants (20% of those evaluable at T2) performed significantly worse (-2.0SD) at T2 in Language or Verbal Memory, returning to baseline at T3. Correlation analyses identified interesting potential associations between poor Language performance and volume loss in grey matter (p=0.021), frontal lobe (p=0.01), temporal lobe (p=0.02; including all subregions). ROI analysis of T1-T2 fMRI revealed significantly decreased functional connectivity between the ACC and the left language regions (IFG and pSTG; p=0.008). Diffusion analysis demonstrated decreased fibre density in the rostral corpus callosum (p=0.039), increased fibre density in the right Fornix tract (p=0.023), and increased fibre cross-section in the left ATR (p=0.007) and FPT (p=0.039). QSM of brain iron did not demonstrate any consistent correlations.

Conclusions: Collectively, these pilot data identify a subset of AML patients who develop objective worsening of language performance during treatment, correlating with alterations in volume, fibre density and connectivity in key language regions. These data support further evaluation of fMRI and language-focused NCA in AML patients.

HO056

Impact of bridging therapy on outcome following chimeric antigen receptor T-cell (CAR-T) therapy for large B-cell lymphoma (LBCL) in third-line and beyond: an Australian single-centre real-world experience

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Aim: Autologous anti-CD19 CAR-T-cell therapy is an established standard-of-care (SOC) for relapsed/refractory (R/R) LBCL, but successful delivery requires disease control through the manufacturing period. The impact of bridging therapy (BT, defined as anti-lymphoma therapy given between apheresis and commencement of lymphodepleting (LD) chemotherapy) on outcome is incompletely understood and confounded by baseline risk factors (patient and disease status). We describe our institutional practice in choice of BT and evaluate the impact of BT on known risk factors, such as LDH and total metabolic tumour volume (TMTV), and subsequent progression free survival (PFS) following CAR T-cell infusion.

Method: Data were collected retrospectively for all patients with R/R LBCL treated with SOC axicabtagene ciloleucel (axi-cel) or tisagenlecleucel (tisa-cel) in our Department between 2020-2024. We performed univariable and multivariable Cox proportional hazards (CoxPH) modelling of candidate risk factors for PFS at two time points: (1) apheresis, and (2) pre-LD chemotherapy.

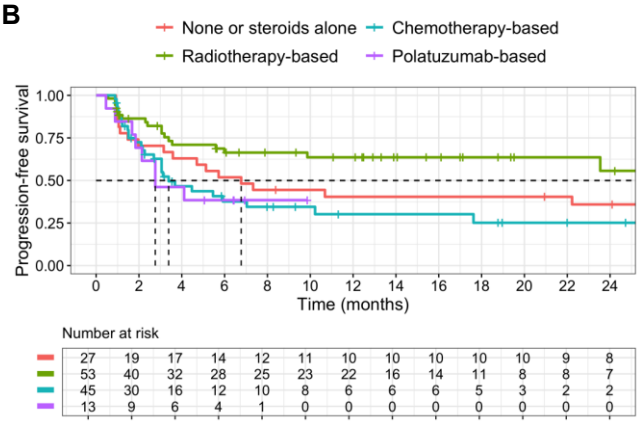
Results: 154 patients received CAR T-cell therapy (53 tisa-cel, 101 axi-cel), of which 136 (89%) received BT. Baseline characteristics are shown in Fig. 1A, divided according to whether radiotherapy (RT) was used as part of BT or not. The RT group included a higher proportion of patients with disease that was refractory to last therapy, stage 1-2, and that received axi-cel, but was not significantly different in LDH and TMTV. PFS at 12 months was 0.47 (95% CI: 0.39–0.57) for all patients, 0.39 for tisa-cel (95% CI: 0.28–0.55) and 0.52 for axi-cel (95% CI: 0.42–0.64). We observed improved PFS in patients bridged with a radiotherapy-based regimen (defined as radiotherapy combined with no or steroids-only systemic BT), Fig. 1B. On univariable CoxPH modelling we found that high LDH and TMTV <80mL were negatively associated with PFS at the pre-LD time point but not apheresis (not shown), suggesting that the impact of these risk factors is modifiable with BT. On multivariable CoxPH modelling of PFS, inclusion of radiotherapy as part of BT was associated with a Hazard Ratio of 0.64 (95% CI: 0.37–1.09, p=0.10) for all patients, Fig 1C, 0.41 (95% CI: 0.20–0.83, p=0.01) for axi-cel patients, and 1.36 (95% CI: 0.57–3.20, p=0.49) for tisa-cel patients.

Conclusion: Radiotherapy BT prior to CAR T-cell therapy for R/R LBCL was associated with high rates of durable response in our cohort. Further data maturation and statistical modelling is required to isolate the impact of radiotherapy independent of other baseline variables.

A

	All (N=154)	No RT (N=80)	RT (N=74)	p
Product				
Tisa-cel	53 (34%)	35 (44%)	18 (24%)	0.02
Axi-cel	101 (66%)	45 (56%)	56 (76%)	
Age, years				
med (min - max)	64.5 (31 - 81)	66.5 (32 - 81)	63 (31 - 80)	0.21
Histology				
HGBL	12 (8%)	6 (8%)	6 (8%)	0.73
DLBCL	101 (66%)	49 (61%)	52 (70%)	
tFL	20 (13%)	11 (14%)	9 (12%)	
tMZL/tWM	6 (4%)	5 (6%)	1 (1%)	
Richters	5 (3%)	3 (4%)	2 (3%)	
PMBCL	4 (3%)	2 (2%)	2 (3%)	
Most recent therapy				
Relapsed	58 (38%)	38 (48%)	20 (27%)	0.01
Refractory	96 (62%)	42 (52%)	54 (73%)	
CD3+ count (aph.), cells/uL				
med (min - max)	819 (82 - 5200)	953 (82 - 5200)	719 (138 - 3601)	0.35
ECOG (aph.)				
0	100 (65%)	48 (60%)	52 (70%)	0.24
1	54 (35%)	32 (40%)	22 (30%)	
LDH (aph.)				
Normal	69 (49%)	38 (54%)	31 (44%)	0.31
High	73 (51%)	33 (46%)	40 (56%)	
TMTV (aph.), mL				
med (min - max)	43 (0 - 2809)	35 (0 - 2809)	58 (0 - 1562)	0.06
Stage (aph.)				
1-2	47 (35%)	19 (27%)	28 (45%)	0.04
3-4	86 (65%)	52 (73%)	34 (55%)	
Extranodal disease (aph.)				
No	51 (38%)	31 (44%)	20 (32%)	0.24
Yes	82 (62%)	40 (56%)	42 (68%)	
Systemic BT				
None or steroids alone	78 (51%)	27 (34%)	51 (69%)	<1e-4
Chemotherapy	45 (29%)	36 (45%)	9 (12%)	
Polatuzumab +/- chemo.	13 (8%)	7 (9%)	6 (8%)	

B



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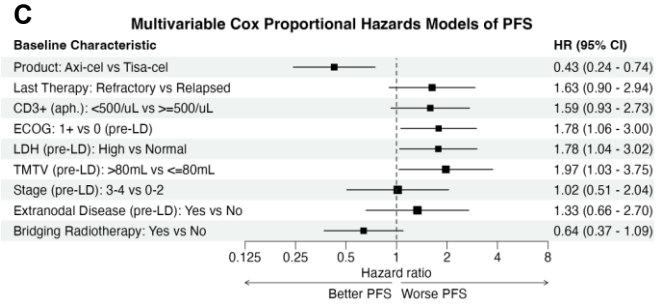

HO057

Targeting TACI Signaling Enhances Immune Function and Halts Chronic Lymphocytic Leukemia Progression

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Aim: CLL progression links to immune deficiency, but the mechanisms of immune cell dysfunction remain incompletely understood. Prior research highlighted TACI's role in IL-10 control and autoimmunity. However, its role in anti-tumor immunity and CLL progression is unexplored. This study investigates TACI signaling in CLL cell regulation within the microenvironment and its impact on CLL progression.

Method: We utilized the Eμ-TCL1 mouse model to generate CLL mice lacking TACI, exploring the effect of TACI loss on CLL cells in adoptive transfer models over 5 weeks. Microarray analysis and real-time PCR revealed TACI's influence on CLL transcriptomic signature. Additionally, we investigated TACI's direct role in CLL cell migration and its impact on T cells using patient-derived CLL cells in culture assays and in Patient-Derived Xenograph *(*PDX) mouse models.

Results: Our results showed that loss of TACI signaling effectively halted CLL progression and boosted immune functions, preventing CLL development. Specifically, when $TACI^{+/+}$ TCL1 or $TACI^{-/-}$ TCL1 CLL cells are transferred into wild-type recipient mice, we observed inhibited CLL progression and lower CLL incidence in mice engrafted with $TACI^{-/-}$ TCL1 CLL cells compared to mice receiving $TACI^{+/+}$ TCL1 cells. Mechanistically, these mice displayed normalised levels of IL-6 and IL-10, and restored T cell subsets proportions in the T-cell compartment compared with $TACI^{+/+}$ TCL1-Tg mice. TACI-deficient CLL cells also expressed lower levels of inhibitory receptors PD-L1 and PD-L2, restored circulating immunoglobulin levels and responses to a T cell-dependent antigen. We further demonstrated that TACI promotes CLL cell migration and homing into the spleen, where these cells actively promote an immunosuppressive microenvironment which further supports CLL cell immune evasion and growth. The direct role of TACI in controlling CLL cell migration and homing, and compromising anti-tumor immunity, was confirmed studying patient-derived primary CLL cells in culture and PDX models.

Conclusion: Disrupting TACI signaling offers, for the first time, an opportunity to control CLL progression while preserving vital immunity, in contrast to existing treatments that significantly impact immune function and cause infection-related complications.

HO058

Ciltacabtagene autoleucel (cilta-cel) vs Standard of care (SoC) in patients with Functional high-risk (FHR) Multiple Myeloma (MM): CARTITUDE-4 subgroup analysis

Sidiqi H[1], Costa L[2], Weisel K[3], van de Donk N[4], Sidana S[5], Cohen Y[6], Purtill D[7], Touzeau C[8], Fernández de Larrea C[9], Martinez-Lopez J[10], Lendvai N[11], Slaughter A[12], Lonardi C[13], Zhao M[14], Li K[15], Vogel M[16], Koneru M[17], Patel N[17], Florendo E[17], Filho O[17], Mateos M[18]

[1]Department Of Health Fiona Stanley Hospital, [2]University of Alabama at Birmingham, [3]University Medical Center Hamburg-Eppendorf, [4]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, [5]Stanford University School of Medicine, [6]Tel Aviv Sourasky (Ichilov) Medical Center, and Sackler Faculty of Medicine, Tel Aviv University, [7]Fiona Stanley Hospital, [8]Centre Hospitalier Universitaire de Nantes, [9]Amyloidosis and Myeloma Unit, Department of Hematology, Hospital Clínic of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, [10]Hematological Malignancies Clinical Research Unit, Hospital 12 de Octubre, Universidad Complutense, Centro Nacional de Investigaciones Oncológicas, CIBERONC, [11]Johnson & Johnson Innovative Medicine, [12]Cilag GmbH International, [13]Johnson & Johnson Innovative Medicine, [14]IQVIA, [15]Johnson & Johnson Innovative Medicine, [16]Johnson & Johnson Innovative Medicine, [17]Legend Biotech USA Inc., [18]Hospital Universitario de Salamanca, Instituto de Investigación Biomédica de Salamanca (IBSAL), Centro de Investigación del Cáncer (IBMCC-USAL, CSIC)

Aim: In CARTITUDE-4, a single cilta-cel infusion significantly improved PFS vs SoC (hazard ratio [HR], 0.26 [95% CI, 0.18–0.38]; P<0.0001) in patients with lenalidomide (len)-refractory MM after 1–3 prior lines of treatment (LOT). This *post-hoc* subgroup analysis of CARTITUDE-4 reports outcomes with second-line cilta-cel vs SoC, including patients with FHR MM.

Method: Patients were randomised to cilta-cel (apheresis, PVd or DPd bridging therapy, and then cilta-cel infusion [target dose, 0.75×10^6 CAR+ viable T cells/kg] 5–7 d after the start of lymphodepletion) or SoC (PVd or DPd until progressive disease [PD]). FHR was defined as PD within 18 months after receiving autologous SCT or the start of frontline therapy. Efficacy was assessed in randomised patients (intent-to-treat) and safety in patients who received any part of study treatment.

Results: 136 patients received cilta-cel (n=68) or SoC (n=68) as second-line treatment. Of these, 79 had FHR MM (cilta-cel, n=40; SoC, n=39). Median PFS was longer with second-line cilta-cel vs SoC, including in patients with FHR MM (**Table**). Overall survival was immature at the time of analysis. A greater proportion of patients who received cilta-cel vs SoC as second-line treatment had an overall response, ≥CR, MRD negativity, and longer median DOR, with similar observations among the FHR subset. Similar proportions of patients experienced grade ≥3 TEAEs with cilta-cel vs SoC as second-line treatment (96% vs 96%), including the subset with FHR MM (100% vs 97%). Among patients who received second-line treatment, 22 died (cilta-cel, n=11; SoC, n=11), 16 of whom had FHR MM (n=7; n=9).

	Cilta-cel as 2L treatment – all patients (n=68)	SoC as 2L treatment – all patients (n=68)	Cilta-cel as 2L treatment – FHR MM (n=40)	SoC as 2L treatment – FHR MM (n=39)
Median PFS, mo (95% CI)	NR (NE–NE)	17 (11–NE) HR=0.35 (95% CI 0.2–0.7) P=0.0007	NR (18–NE)	12 (8–NE) HR=0.27 (95% CI 0.1–0.6) P=0.0006
12-mo PFS, % (95% CI)	78 (66–86)	59 (46–69)	77 (60–87)	49 (32–64)
ORR, n (%)	61 (90)	54 (79) OR=2.3 (95% CI 0.8–6.0) P=0.0979	35 (88)	31 (80) OR=1.8 (95% CI 0.5–6.1) P=0.3400
≥CR, n (%)	48 (71)	24 (35) OR=4.4 (95% CI 2.1–9.0) P<.0001	27 (68)	15 (39) OR=3.3 (95% CI 1.3–8.4) P=0.0102
MRD negativity (10^{-5}), n (%)	43 (63)	13 (19) OR=7.3 (95% CI 3.3–15.9) P<0.0001	26 (65)	4 (10) OR=16.3 (95% CI 4.8–55.1) P<0.0001
Median DOR, mo (95% CI)	NR (NE–NE)	20 (14–NE)	NR (16–NE)	16 (8–NE)

CR, complete response; DOR, duration of response; MRD, minimal residual disease; NE, not estimable; NR, not reached; OR, odds ratio; ORR, overall response rate; PFS, progression free survival.

Conclusion: In patients with len-refractory FHR MM after 1 prior LOT, cilta-cel improved outcomes vs SoC and had a safety profile consistent with the known mechanism of action of CAR-T treatment , suggesting cilta-cel may overcome the poor prognosis associated with FHR MM.

HO059

Clonal haematopoiesis of indeterminate potential (CHIP) is not associated with decline in kidney function in healthy older adults.

Singh J[1,2,3], Polkinghorne K[1,4], Wolfe R[1], Wong N[2], Byars S[2], Leichter A[2], Lacaze P[1], McNeil J[1], Orchard S[1], Phung J[1], Ramshaw H[5], Thao L[1], Wood E[1,4], Woods R[1], Curtis D[1,2,6], McQuilten Z[1,4,6]
[1]Monash University, [2]Australian Centre for Blood Diseases, [3]Fiona Stanley Hospital , [4]Monash Health , [5]Monash Antibody Discovery Platform and Robocore, Monash University, [6]Alfred Health

Background: Studies on the impact of CHIP on kidney function have been inconsistent.

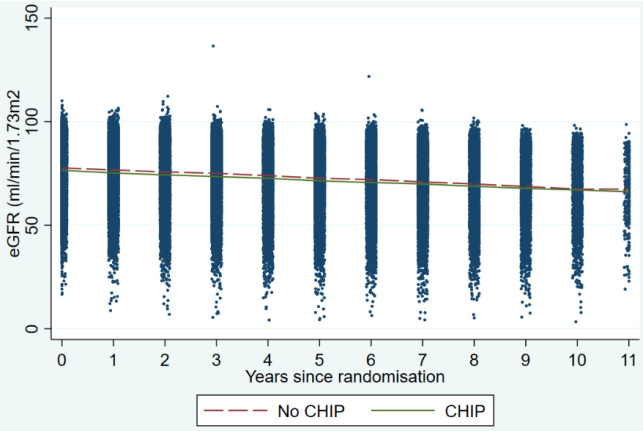
Aim: To investigate the association between CHIP and kidney function over time.

Method: The ASPREE project enrolled healthy Australians ≥70 years without cardiovascular disease, dementia, independence-limiting physical disability, 5-year life-limiting illness, or contraindication to aspirin. Targeted sequencing for CHIP was performed on peripheral blood as part of the ASPREE-CHIP sub-study. Participants were followed for a median of 8.4 years with yearly serum creatinine and urine albumin:creatinine ratio (ACR). We assessed the association between CHIP and longitudinal eGFR (CKD-EPI 2021 creatinine equation) or log(ACR) with linear mixed effects models allowing for a random intercept and slope for participants. Fixed covariates included baseline age, sex, diabetes, hypertension, prior history of cancer, smoking and frailty. CHIP status was included as a fixed covariate to assess impact on baseline kidney function, and as an interaction term with time to assess impact on longitudinal change.

Results: Our analysis included 9434 people with known CHIP status, of whom 2124 (22.5%) had CHIP. Median eGFR at baseline was 79ml/min/1.73m^2 (IQR 68-90), and ACR was 0.8mg/mmol (IQR 0.5-1.4). Participants had a median of eight eGFR and seven ACR measurements over time. In the multivariable model, neither baseline eGFR nor log(ACR) differed between people with and without CHIP. Per year, eGFR declined by 1.04ml/min/1.73m2 and logACR increased by 0.07 units. Neither of these was significantly different in individuals with CHIP (Figure 1), including those with large clones (variant allele fraction (VAF) >10%; n=532) or non-*DNMT3A* mutations (n=974).

Conclusion: In a cohort of healthy older adults there was minimal decline in kidney function over time, and no difference between those with and without CHIP after adjusting for age and other covariates. Discrepancies between studies may relate to differences in population characteristics and outcome measures.

Figure 1: eGFR over time



HO060

Combination treatment with novel BCL2 inhibitor sonrotoclax (BGB-11417) and zanubrutinib induces high rate of complete remission in patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL)

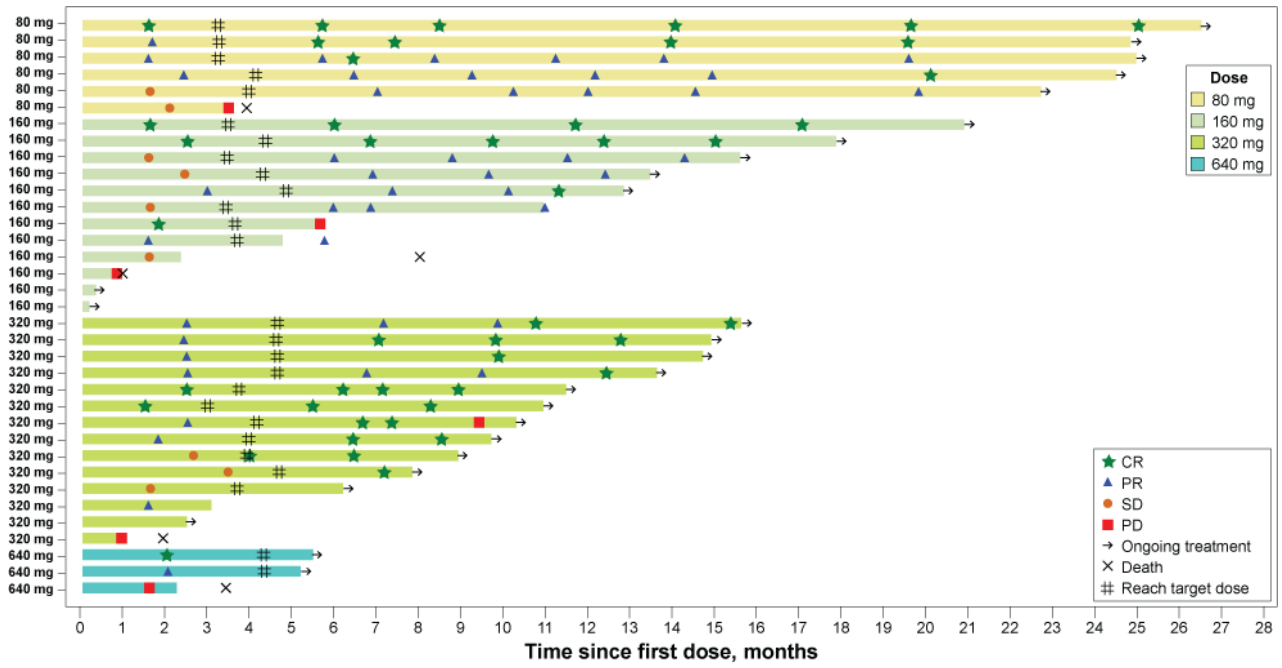
Tam C[1], Opat S[2], Hoffmann M[3], Soumerai J[4], Lasica M[5], Epperla N[6], Hou J[7], García-Sanz R[8], Schetelig J[9], Weinkove R[10,11], Fang Y[12], Patel S[13], Ding W[13], Guo H[14], Cordoba R[15]
[1]Alfred Hospital And Monash University, [2]Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, [3]University of Kansas Medical Center, [4]Massachusetts General Hospital Cancer Center and Harvard Medical School, [5]St Vincent's Hospital Melbourne, [6]The James Cancer Hospital and Solove Research Institute at Ohio State University, [7]University of Pittsburgh Medical Center, [8]Hospital Universitario de Salamanca, [9]Universitatsklinikum Carl Gustav Carus An Der Technischen Universitat Dresden, [10]Te Rerenga Ora Blood and Cancer Centre, Te Whatu Ora Health New Zealand Capital Coast & Hutt Valley, [11]Cancer Immunotherapy Programme, Malaghan Institute of Medical Research, [12]BeiGene (Beijing) Co, Ltd, [13]BeiGene USA, Inc, [14]BeiGene (Shanghai) Co, Ltd, [15]Hospital Universitario Fundación Jiménez Díaz

Aim: Sonrotoclax is a more selective and pharmacologically potent BCL2 inhibitor than venetoclax in biochemical assays. Zanubrutinib, a next-generation BTK inhibitor (BTKi), is approved for R/R MCL and improved PFS and OS vs ibrutinib. Data for sonrotoclax + zanubrutinib in R/R MCL from the ongoing BGB-11417-101 (NCT04277637) study are presented.

Method: Patients with ≥1 prior treatment received zanubrutinib (320mg QD/160mg BID) 8-12 weeks before sonrotoclax ramp-up (80/160/320/640mg QD); expansion cohorts followed. Endpoints included safety (CTCAE v5.0) and ORR (Lugano 2014 criteria). TLS was assessed per Howard 2011 criteria.

Results: As of 31Oct2023, 35 patients were enrolled (80mg, n=6; 160mg, n=12; 320mg, n=14; 640mg, n=3). Three patients were in zanubrutinib lead-in; 29 had started sonrotoclax. Overall, patients had a median of 1 prior treatment; 11 had prior autologous stem cell transplant and 3 had prior BTKi. Dose escalation occurred per protocol at all defined doses. No DLTs occurred; MTD was not reached up to 640mg. Sonrotoclax 160 and 320mg were chosen for expansion. Of 9 patients who discontinued treatment, 6 discontinued both drugs and 3 did not complete zanubrutinib lead-in due to early PD. Five patients died from PD (3 during zanubrutinib lead-in). TEAEs in ≥20% were neutropenia (31%), contusion (29%), thrombocytopenia (23%), and diarrhea (23%). Neutropenia was the most common grade ≥3 TEAE (20%). No TLS or atrial/ventricular fibrillation occurred. In 27 response-evaluable patients, ORR was 85% (18 CR; [67%]). In the dose-expansion, ORRs were 91% (320mg: 10/11; 10 CR) and 88% (160mg: 8/9; 4 CR [44%]) (Figure). Median time to CR was 6.4 months. In 2 patients with progression on prior BTKi, 1 CR and 1 PD were observed.

Conclusion: Sonrotoclax + zanubrutinib was well tolerated and showed promising efficacy in R/R MCL, including deep and durable responses. Expansion of the 320mg cohort is ongoing.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SD
PD
Ongoing treatment
Death
Reach target dose
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Time since first dose, months

HO061

Preliminary efficacy and safety of the Bruton tyrosine kinase (BTK) degrader BGB-16673 in patients with relapsed or refractory (R/R) CLL/SLL: results from the phase 1 BGB-16673-101 study

Tam C[1], Parrondo R[2], Thompson M[3], Frustaci A[4], Allan J[5], Ghia P[6,7], Vinogradov I[8], Trotman J[9], Choi M[10], Chen X[11], By K[12], Fabre S[12], Paik J[12], Agarwal A[12], Seymour J[13]

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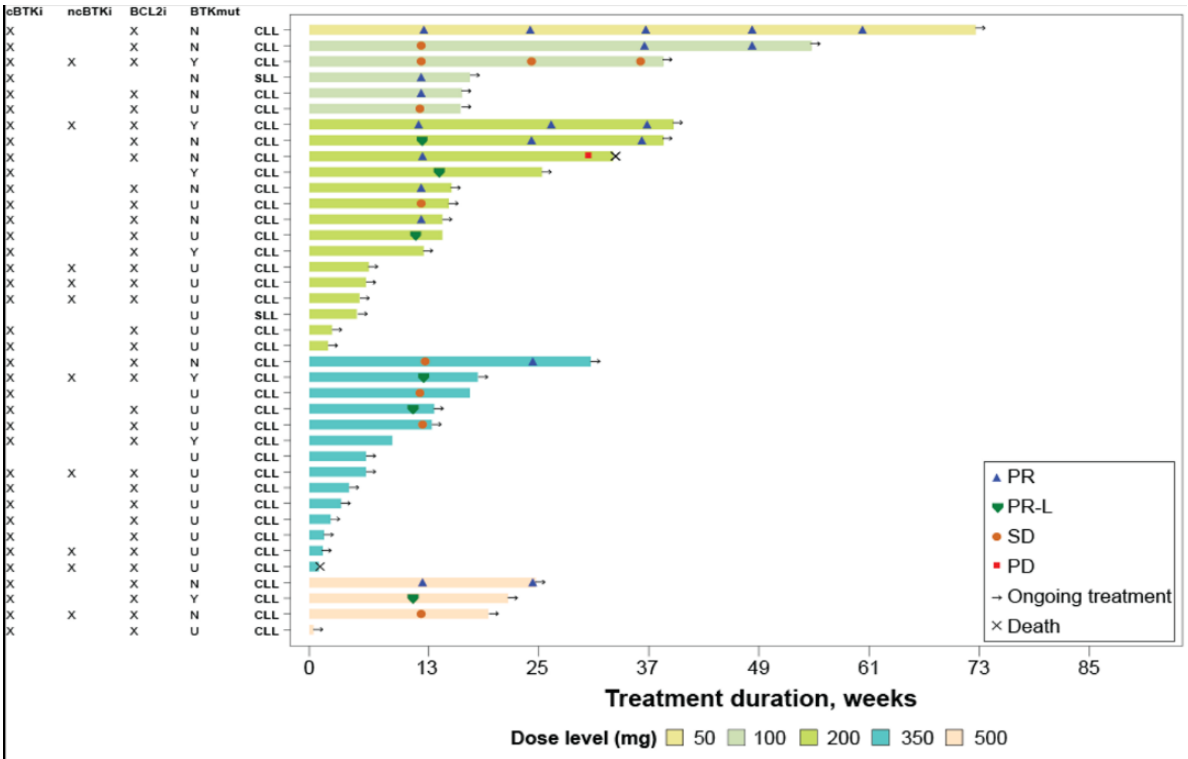
Aim: BGB-16673, a heterobifunctional small molecule, induces BTK degradation via ubiquitination. In preclinical models, BGB-16673 degraded wild-type and mutant BTK proteins resistant to covalent (cBTKi) and noncovalent BTK inhibitors (ncBTKi). Updated data for CLL/SLL from the first-in-human study, BGB-16673-101 (NCT05006716), are presented.

Method: Patients had CLL/SLL and ≥2 prior therapies, including cBTKi (US/EU/Australia). BGB-16673 was dosed orally QD in 28-day cycles. Planned dose escalation had 6 levels (50-600mg QD). Primary endpoints included safety (CTCAE v5.0 and iwCLL hematologic toxicity criteria) and maximum tolerated dose (MTD). Dose-limiting toxicity (DLT) was assessed in cycle 1. Response was assessed per iwCLL 2018 criteria (SLL: Cheson 2014).

Results: As of 9Nov2023, 42 patients were enrolled and 39 were treated. Patients had a median of 4 (range, 2-8) prior therapies, including cBTKis (n=37), BCL2 inhibitors (n=34), and ncBTKis (n=10). Of tested patients, 54% (20/37) had del(17p) and/or *TP53* mutation, 87% (27/31) had unmutated IGHV, and 43% (12/28) had ≥3 karyotypic abnormalities. Median follow-up was 3.3 months (range, 0.1-16.7). One DLT occurred (200mg; grade 3 maculopapular rash). MTD was not reached. The most common treatment-emergent AEs (TEAEs) were contusion (31%; no grade ≥3), fatigue (31%; no grade ≥3), diarrhea (26%; no grade ≥3), and neutropenia (23%; grade ≥3, 18%). One patient (500mg) had grade 3 hypertension. No atrial fibrillation was observed. TEAEs led to 2 deaths (septic shock, pneumonia; each unrelated to treatment), 2 discontinuations (subdural hemorrhage, thyroid cancer), and 1 dose reduction (grade 2 arthralgia). Thirty-five patients (90%) remain on therapy (discontinuations: 1 progressive disease; 3 AE). In 24 response-evaluable patients, ORR was 67%, with 23/24 responses ongoing, including in patients with prior cBTKi (n=16) and ncBTKi (n=2), and with and without BTK mutation (Figure).

Conclusion: BGB-16673 demonstrated preliminary tolerability and antitumor activity in heavily pretreated patients with CLL/SLL, including those with BTK inhibitor-resistant mutations.



X = patient had the indicated prior therapy; BTK mutation status was classified as present (Y), absent (N), or unknown (U).
cBTKi, covalent BTK inhibitor; mut, mutation; ncBTKi, noncovalent BTK inhibitor; PR-L, PR with lymphocytosis

HO062

Serum Biomarkers ST2, REG3a, and MAGIC Algorithm Probability (MAP) Kinetics Predict Non-Relapse Mortality (NRM) in Allogeneic Stem Cell Transplant Patients Independent of Acute Graft-Versus-Host-Disease (aGVHD).

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Aim: The Mount Sinai Acute GVHD International Consortium (MAGIC) Algorithm Probability (MAP), which combines serum levels of Stimulation-2 (ST2) and Regenerating Family Member 3 Alpha (REG3a), predicts lethal acute GVHD (aGVHD) in allogeneic transplant (alloSCT) patients via a Day 7 post-transplant blood test. (1,2). This study examines the kinetics of these biomarkers and MAP score within the first three weeks post-alloSCT in patients who develop aGVHD and 6-month NRM.

Method: We conducted a single-center prospective study of consecutive alloSCT patients at the Alfred Hospital from February 2022-2024. Serum samples were collected at baseline (D0), D7, D14, and D21 post-transplant. ST2 and REG3a concentrations were measured using enzyme-linked immunosorbent assays (ST2/IL-33R Quantikine ELISA Kit/Human Reg3A DuoSet ELISA DY5940-05; R&D systems). Patients were reviewed weekly for aGVHD occurrence until D120, then at least monthly. The MAP score was calculated using the established formula provided in previous publications (1).

Results: Eighty-seven alloSCT patients completed serum ST2 and REG3a analysis and follow up. The median age was 60.5 years (range 18-74). Donor types included sibling (28.7%), matched unrelated (42.5%), and haploidentical (27.5%). Post-transplant cyclophosphamide was the main GVHD prophylaxis method (79.3%). The 6m NRM was 13.8%. Increases in ST2, REG3a and MAP score significantly correlated with 6m NRM (ST2 relative risk (RR) 5.5 (95% CI 1.5-21.6), p=0.011; REG3a RR 11.5 (95% CI 1.9-62.0), p=0.004; and MAP RR >20 (95% CI 2.0–NA, p=0.0002). No patients with a decreasing MAP score experienced 6m NRM (Figure 1a). The most common cause of NRM was infection without prior aGVHD (66.7%). One patient died from steroid-refractory aGVHD. Increases in ST2, REG3a or MAP scores were not associated with MAGIC grade 2-4 or gastrointestinal aGVHD. An increase in MAP score was significantly associated with worse overall survival (p<0.0001; Figure 1b), with no significant difference in relapse rates (p=0.5).

Conclusion: Our study demonstrates that increases in ST2, REG3a levels and MAP score early post-alloSCT predict 6m NRM and worse overall survival, independent of aGVHD occurrence. The kinetics of the MAP score have potential utility in prognosticating transplant-related outcomes to guide the clinical management of alloSCT patients.

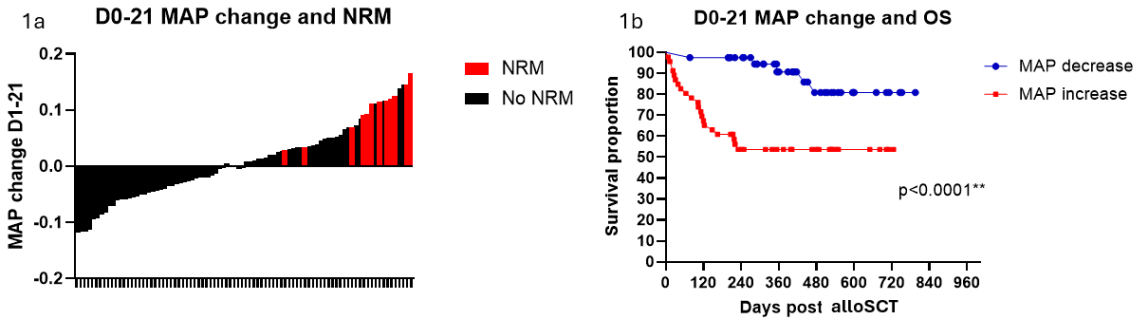

Figure 1a: Waterfall plot showing patient MAP score change and NRM; Figure 1b: Kaplan-Meier survival curve demonstrating OS according to MAP score change.

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HO063

Genomic screening in advanced haematological cancers: Lessons from the first 155 cases in the Australian Molecular Screening and Therapeutics in Leukaemia and Lymphoma (MoST-LLy) program

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Aim: In an attempt to overcome the poor prognosis experienced by patients with relapsed or refractory haematologic malignancies, we have developed an Australian clinical platform trial, the Molecular Screening and Therapeutics in Leukaemia and Lymphoma (MoST-LLy), ACTRN12616000908437. This protocol links broad genomic sequencing with a suite of innovative molecularly targeted clinical trials in advanced myeloid and lymphoid malignancies. This program aims to improve access to molecular sequencing, accelerate drug development and improve clinical outcomes.

Method: MoST-LLy aims to recruit 480 high-risk blood cancer patients who have failed standard of care therapies, or where no standard of care exists. Genomic screening used the 523-gene TSO500 panel with expedited turnaround, paired with reporting through a haematology-specific Molecular Tumour Board (MTB). Recruitment is ongoing to two investigator-initiated phase 2 trials (MoST15, combined durvalumab and acalabrutinib in DLBCL; ACTRN12621000507886 and MoST16, pamiparib in high-risk myeloid malignancies, ACTRN12621001183875) and two additional linked studies (IMpress in high-risk MDS/AML, NCT05583552 and PREACH-M in CMML, ACTRN12621000223831).

Results: At data censor May 31 2024, 5 recruiting sites were open: Brisbane, Adelaide, Perth, Hobart and a national teletrials remote consenting hub to facilitate enrolment at rural and regional locations. Molecular profiling has been completed on 139/155 consented patients (63 lymphoma and 76 leukaemia). Clinical trial recommendations were shortlisted by actionable variants in the TOPOGRAPH knowledgebase. Ninety-three of 139 patients profiled (67%) received a clinical trial recommendation, resulting in 39 people (28%) receiving further therapy on a biomarker-linked or histology-based trial as above. The turnaround time from consent of patient to MTB recommendation was 21 days for lymphoma patients and 33 days for leukaemia patients. Molecular findings revealed a high rate of deleterious TP53 mutations in DLBCL (33% of cases) and leukaemia (11%). Tumour mutational burden was significantly higher in lymphoma patients compared to myeloid malignancies.

Conclusion: The MoST-LLy platform has implemented a national research infrastructure, providing real-time access to broad genomic screening and efficient linkage of patients to biomarker-linked studies and accelerated access to novel treatments.

HO064

Overcoming barriers in delivering treatment for patients with DLBCL in outer metropolitan hospitals – the Rockingham General Hospital (RGH) experience

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Aim: Access to DLBCL treatment is inequitable in outer metropolitan and regional Australia[1 2]. We aim to describe treatment outcomes for DLBCL at RGH, an outer metropolitan hospital with limited access to novel therapies.

Method: This is a single centre, retrospective, observational study of 55 patients treated at RGH between 2012 to 2024. Survival analysis was conducted via Kaplan-Meier estimate.

Results: At time of diagnosis, median age was 75.1 years and 30.9% had ECOG>1. 52.7% of patients were male. 55.6% had bulky disease, 58.2% GCB subtype and 12.7% MYC and BCL2 and/or BCL6 rearrangements. With a median follow-up of 3 years (range 0.1-11.4), 3-year PFS and OS was 73.5% and 76% respectively. Forty-five patients (81.8%) achieved CR with 1L therapy. Ten patients (18%) were refractory, six patients (11%) subsequently relapsed. Fourteen patients received 2L therapy with a median PFS and OS after 2L of 161 days and 281 days respectively. Of those who received 2L therapy, six patients (42.9%) patients remain in remission. Three patients were referred for autoSCT; one died from disease progression prior to transplant and two patients remain in remission. Two patients were referred for clinical trials and died from disease progression. Four patients with inadequate response to 2L therapy subsequently received epcoritamab in RGH; three remain in remission, one of whom previously progressed through tisagenlecleucel (CAR T-cell therapy) at three months.

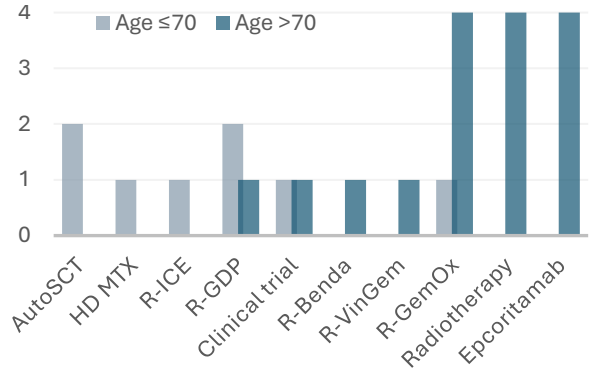

Figure 1 Therapy received in refractory-relapsed setting by age group

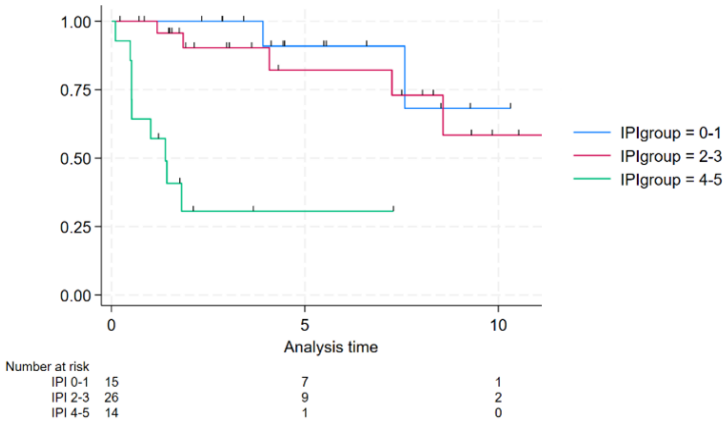

Figure 2 PFS by International Prognostic Index (IPI) score; log-rank p-value 0.0000

Conclusion: Despite an older comorbid population[3] with higher likelihood of bulky disease at presentation[4], patients who received treatment in our hospital had similar outcomes compared to historical outcomes[5 6]. Survival of transplant-ineligible patients at relapse is poor with limited

access to clinical trials and novel therapies. Novel treatments like off-the-shelf bispecific antibodies could revolutionise therapy for patients in regional and outer metropolitan areas, with four patients having safely received treatment at time of analysis.

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HO065

A dual targeting approach with neoepitope-directed monoclonal antibodies can improve outcomes for CALR-mutant myelofibrosis

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Aim: Mutations within calreticulin (*CALR*) are the second most common genetic aberration in myelofibrosis (MF). Patients with *CALR* mutations respond poorly to JAK-inhibitors and currently no mutation-specific approach exists. We engineered neoepitope-specific monoclonal antibodies (mAb, 4D7 and 9H11) that have striking biological activity.

Method: Rats immunised with CALR-mutant peptide were screened by ELISA. Engineered TF-1 cells expressing TpoR and $CALR^{mut}$ were cultured with mAbs, and downstream signalling was assessed. Primary MF CD34+ cells were differentiated into megakaryocytes in the presence of mAbs. *CALR*-dependent in vivo models were established in NSG mice.

Results: We engineered mAbs with the mutant-CALR neoepitope peptide and clones 4D7 and 9H11 showed superior activity, in addition to binding different epitopes. These mAbs inhibited cell proliferation of TF-1 TpoR $CALR^{mut}$ cells. Interestingly, a synergistic effect of 4D7 and 9H11 was observed when used in combination, with a greater reduction in proliferation at a lower dose. Additionally, mAbs blocked constitutive phospho-STAT5 and phospho-ERK signalling and induced an apoptotic response. We evaluated activity in primary $CALR^{mut}$ CD34+ cells through megakaryocyte differentiation and showed inhibition of megakaryocyte progenitors by at least 85% when mAbs were used in combination ($P<0.0001$). Bone marrow engraftment in NSG mice showed significantly reduced tumour burden ($P=0.005$), prolonged survival, reduction of hCD33+ in peripheral blood and reduction of splenomegaly in treated mice compared to controls. Moreover, the combination of mAbs showed a significantly prolonged survival compared to monotherapy, with some indicating no signs of disease at end of study. Both antibodies were humanised with no loss of efficacy or toxicity. Notably, h9H11 showed a significant survival advantage over conventional therapy, ruxolitinib, and when combined with ruxolitinib, demonstrated prolonged survival in vivo.

Conclusion: These results suggest an advanced immunotherapeutic approach to eliminate *CALR*-driven clones by simultaneously targeting distinct epitopes and demonstrates a clinical utility in *CALR*-mutant patients that develop ruxolitinib-resistance.

HO066

Dynamic assessment of RBC-transfusion dependency (RBC-TD) improves the Molecular International Prognostic Scoring System (IPSS-M) risk stratification of MDS

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Aim: RBC-TD predicts poor survival and dynamic assessment of RBC-TD improves the Revised -International Prognostic Scoring System (IPSS-R) (Hiwase *et al* Am J Hematol 2017). Integrating genomic profiling with haematologic and cytogenetic parameters, the IPSS-M improves the risk stratification of MDS; however, it does not include RBC-TD. This study evaluates the prognostic value of RBC-TD along with IPSS-M in an independent cohort of MDS in the South Australian-Myeloid Neoplasm (SA-MN) Registry.

Method: IPSS-M categories were estimated, and mean values were assigned to the missing 18.6% of genetic mutation data (Bernard *et al* NEJM Evidence 2022). RBC-TD was defined as ≥8 RBC units within sixteen weeks. Overall survival (OS) was estimated with the Kaplan-Meier (KM) method. Cox proportional-hazards modelling was used to assess the effect of RBC-TD with covariates IPSS-M, age and sex.

Results: Of 398 patients, there were 342 (85.9%) with MDS and 56 (14.1%) with MDS/MPN. The median age at diagnosis was 70.2 (IQR 65-78) and 64.8% were male. The median OS was 33.1 months (95% CI 28.4-43.3). According to IPSS-M, 10.6%, 29.9%, 13.6%, 10.1%, 17.6% and 18.3% were classified as Very Low (n=42), Low (n=119), Moderate Low (n=54), Moderate High (n=40), High (n=70), and Very High (n=73), respectively, with significant survival difference between the groups (Figure 1A). At diagnosis, 23.4% were classified as RBC-TD, which was associated with inferior OS, particularly in high-risk IPSS-M categories (Figure 1B). Importantly, RBC-TD was associated with poor survival independent of IPSS-M categorisation and age at diagnosis (Figure 1C).

Conclusion: The RBC-TD provides dynamic risk information independent of IPSS-M and, should be considered for guiding treatment including potentially curative allogenic stem cell transplantation.

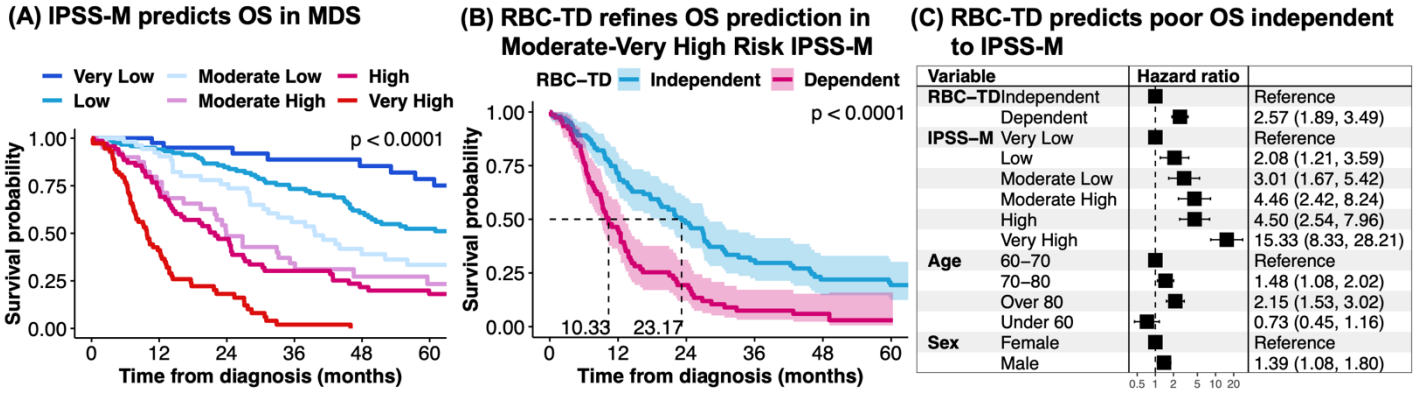

Figure 1: Dynamic assessment of RBC-TD improves the IPSS-M risk stratification of MDS. (A) KM curves of OS by IPSS-M. (B) KM curves with 95% CIs of OS by diagnostic RBC-TD in Moderate to Very High-Risk IPSS-M. (C) Forest plot of Cox proportional-hazards with 95% CIs of OS with diagnostic RBC-TD, IPSS-M, age and sex.

HO067

Defining the spectrum of UBA1 variants in haematological malignancy

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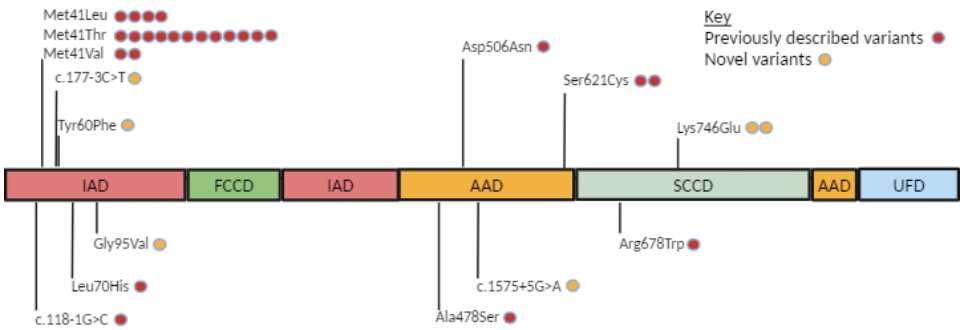
Aim: *UBA1* variants, typically missense Met41 variants, are implicated in the pathogenesis of VEXAS syndrome. Recently, potential causative variants have been identified in other domains of *UBA1* in VEXAS syndrome, however, the spectrum across haematological malignancy is relatively unknown. We describe the unbiased assessment of *UBA1* across a large cohort of patients with haematological malignancy.

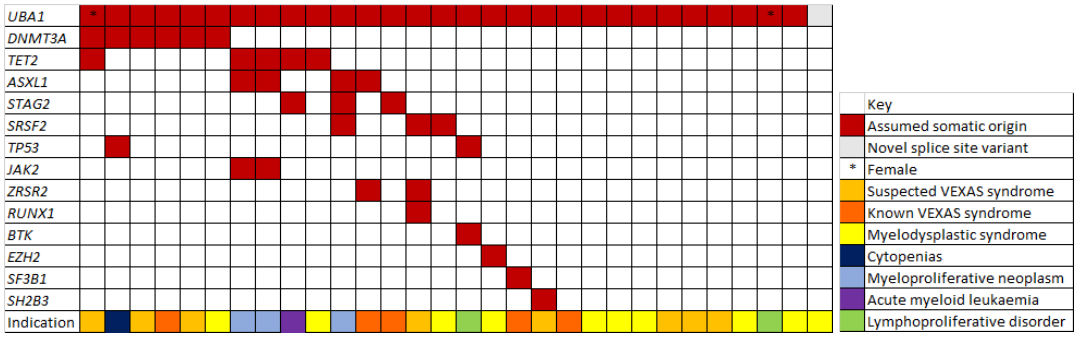
Method: All *UBA1* coding exons by unique molecular index-corrected NGS (along with 79 other genes recurrently mutated in haematological malignancy) were assessed in consecutive samples referred for diagnostic testing over a 6 month period and correlated with clinicopathological features.

Results: *UBA1* variants passing filters for somatic origin were detected in 31/4298 patients (0.7%), at variant allele frequency 2-85% (median 51%), including 2 females with variants at 2% and 22%. Recurrent variants included Met41 missense variants (n=18), Ser621Cys (n=2) and Lys746Glu (n=2). Samples with *UBA1* variants included bone marrow aspirate (n=20), peripheral blood (n=10) and cerebrospinal fluid (n=1). Correlative bone marrow morphology described vacuolated precursors in 9/20 samples, all with Met41 variants.

UBA1 variants were detected in 8/46 patients (17%) with suspected VEXAS syndrome, including 7 Met41 variants and an Ala478Ser variant. 5 Met41 variants were detected in patients with known VEXAS syndrome. Other primary indications with *UBA1* variants included myelodysplastic syndrome (5 Met41 and 5 non-Met41 variants), myeloproliferative neoplasms (3 non-Met41 variants), lymphoproliferative disorders (3 non-Met41 variants), acute myeloid leukaemia (non-Met41 variant) and cytopenias (Met41 variant). Additional gene variants were detected in 19 patients, recurrently in *DNMT3A*, *TET2*, *ASXL1*, *STAG2, SRSF2*, *TP53*, *JAK2* and *ZRSR2*.

Conclusion: *UBA1* Met41 variants are most typical in VEXAS syndrome, however other UBA1 variants are more frequent in other haematological malignancies. *UBA1* variants co-segregate with mutations in genes associated with clonal haematopoiesis and myeloid neoplasms. Further study is needed to understand the pathogenicity and clonal evolution of *UBA1*-mutated haematological malignancies.




UBA1
DNMT3A
TET2
ASXL1
STAG2
SRSF2
TP53
JAK2
ZRSR2
RUNX1
BTK
EZH2
SF3B1
SH2B3
Indication
Key
Assumed somatic origin
Novel splice site variant
Female
Suspected VEXAS syndrome
Known VEXAS syndrome
Myelodysplastic syndrome
Cytopenias
Myeloproliferative neoplasm
Acute myeloid leukaemia
Lymphoproliferative disorder

HO068

PBSC mobilisation and ASCT outcomes following VRD and Cyclo+G or G-CSF alone in myeloma (MM)

Xia W[1,2], BAI L[1,2], REID C[3], WONG K[3], CHEN Q[1,2], STEVENSON W[2,3], KERRIDGE I[2,3], WARD C[2,3], KLIMAN D[3], COYLE L[3], FAY K[3], MACKINLAY N[3], GREENWOOD M[2,3]

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Aim: VRD is the Australian standard induction for ASCT-eligible MM patients. Scheduling/dosing of VRD and PBSC mobilisation regimens vary between centres and patients. We aimed to describe PBSC mobilisation kinetics and engraftment outcomes following VRD using different mobilisation regimens.

Method: We conducted a retrospective analysis of 92 patients undergoing VRD induction, PBSC mobilisation and ASCT at RNSH from 2020-23. All patients received 3 or 4 cycles of VRD induction. Patients aged <70 were mobilised with Cyclophosphamide 2g/m^2 plus GCSF 5ug/kg bd to achieve sufficient PBSC for 1 or 2 ASCT. Patients aged ≥70 were mobilised with G-CSF 5ug/kg bd as a single agent to achieve sufficient PBSC for 1 ASCT. Plerixafor 0.24mg/kg was used if PB CD34 was <10/uL and WCC >5x10^9/L after finishing Cyclo+G or G-alone cycles.

Results: Median age 66 (40-78) yrs. 53.3% (49/92) were male. Median follow up 527(80-1328) days. 80/92 (87%) patients received Cyclo+G, 12/92 (13%) received G-alone. Age ≥65 yrs had lower CD34 mobilization/collection than <65 yrs (PB CD34 69 vs 112/uL, p=0.032 harvested 5.57 vs 8.43 x10^6/kg, p=0.017). 76/80 (95%) of Cyclo+G patients mobilised sufficient CD34 for 1 or 2 ASCT. 9/12 (75%) G-alone group were mobilised successfully for 1 ASCT. In comparison to Cyclo+G group, G-alone collected fewer CD34 (3.70 vs 6.83 x10^6/kg, p <0.001) and had slower platelet engraftment, platelet reached 50 and 100x10^6/mL needed 23 vs 20 days (p=0.024 and <0.01) and had higher rate of mobilisation failure vs Cyclo+G group, 25% (3/12) vs 5% (4/80), p=0.015.

Conclusion: Patients aged ≥65 yrs using G-alone mobilised fewer CD34, less often proceeded to ASCT, had longer time to platelet recovery and higher rates of mobilisation failure and longer time to platelet engraftment post ASCT. Alternative mobilisation strategies in elderly could be explored.

HO069

Procoagulant platelet responses are increased in Essential Thrombocythaemia and decrease with cytoreduction

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Background: Essential thrombocythaemia (ET) is associated with increased risk of arterial and venous thrombosis. Thrombotic risk does not directly correlate with platelet count but can be reduced by cytoreductive treatment such as hydroxyurea in high-risk patients (1). The procoagulant platelet subset facilitates rapid thrombin generation after activation. We have previously shown increased thrombin induced procoagulant platelet in ET, especially in JAK2V617F mutated patients (2). We hypothesised procoagulant platelet as a promising biomarker for thrombosis in ET.

Aim: This study aimed to assess influence of cytoreductive therapy on platelet procoagulant response in ET.

Method: Patients were recruited at Concord Hospital (n=119) with median follow up of 63.2 months since recruitment. Whole blood flow cytometry procoagulant platelet (defined as cell-death marker GSAO+ and P-selectin+) assays were performed, with prospective clinical and laboratory data collection.

Results: In May 2024, 88% of patients are alive. 81% were JAK2 V617F positive with mean allelic burden of 16.4%. Compared with healthy controls, JAK2V617F$_{mut}$ patients had significantly higher procoagulant response to strong dual agonist (thrombin 5 U/mL, collagen 10 µg/mL) (p=0.0025).

15 treatment naïve patients had procoagulant platelet measurement before and after commencing cytoreduction. All were on aspirin (100-200mg/d). 12 were treated with hydroxyurea. Percentage of procoagulant platelets formed in response to dual agonists reduced by mean 6.9% (±12.2, p=0.044) after commencing cytoreduction. Persistently reduced procoagulant response was observed in 12 out of 15 subjects at the most recent timepoint, with average treatment duration of 448 days. 3 patients had recurrent or new thrombotic events. 2 of the 3 occurred in patients whose procoagulant response did not show a downward trend with cytoreduction.

Conclusion: Procoagulant platelet response is elevated in ET patients and reduces with cytoreductive treatment, suggesting a potential pathophysiological role in treatment response. Further study is required to understand the underlying mechanisms.

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HO070

High tumour-intrinsic expression of STING underpins potent and TP53 independent pro-apoptotic activity by STING agonists in primary AML

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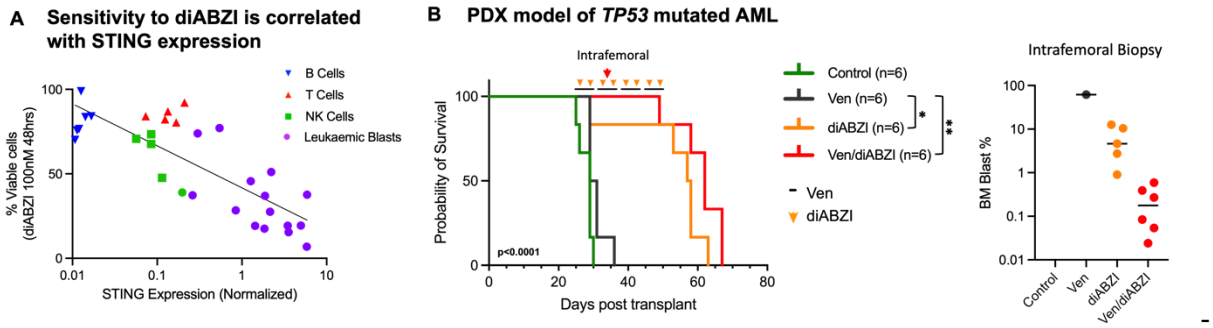
Aim: Acute myeloid leukaemia (AML) continues to have poor prognosis, especially if *TP53* is mutated (*TP53*m). Activation of the stimulator of interferon genes (STING) pathway canonically induces type 1 interferon production but in certain cellular contexts can also drive apoptosis. We aimed to investigate the cell-intrinsic effects of STING agonists in AML and to determine its efficacy against *TP53*m AML.

Method: We tested the small molecule STING agonist diABZI (SYNthesis Med Chem). Drug sensitivity assays were performed using human AML derived cell lines and primary patient samples. Intracellular flow cytometry was used to measure STING expression. *In vivo* testing was conducted using cell line and patient-derived xenografts (PDX). Mice received no treatment (control), venetoclax (50mg/kg orally 5-days/week), diABZI (1.5mg/kg IV biweekly), or combination venetoclax/diABZI for 2-4 weeks (n=5-6 per group). Survival analysis was performed using the log-rank test with Bonferroni correction.

Results: In primary samples, gated leukaemic blasts from 26 patients demonstrated significantly higher levels of STING protein than normal B, T and NK cell populations. 70% of AML blasts were highly sensitive to 100nM diABZI, compared to normal T or B lymphoid cells exposed to the same conditions (Figure 1A). CRISPR-based modifications in AML cell lines confirmed that diABZI-induced cell death was STING dependent, but independent of TP53. *In vivo*, diABZI prolonged survival in MOLM-13 *TP53* wildtype and knock-out cell line models, with significantly enhanced survival when combined with venetoclax. In a PDX model of *TP53*m AML, diABZI-based therapy improved survival and induced marked and rapid reduction in bone marrow leukemic burden (Figure 1B).

Figure 1



Conclusion: STING agonists exert tumour intrinsic, potent, and *TP53* independent activity against primary AML, with efficacy enhanced when combined with venetoclax. Our data demonstrates the potential of STING agonists as a novel therapeutic strategy for AML, especially against *TP53*m disease, supporting further clinical trial investigation.

ANZSBT Oral Presentations

AO001

Engineering cell culture platforms for manufacturing and testing blood cell therapies.

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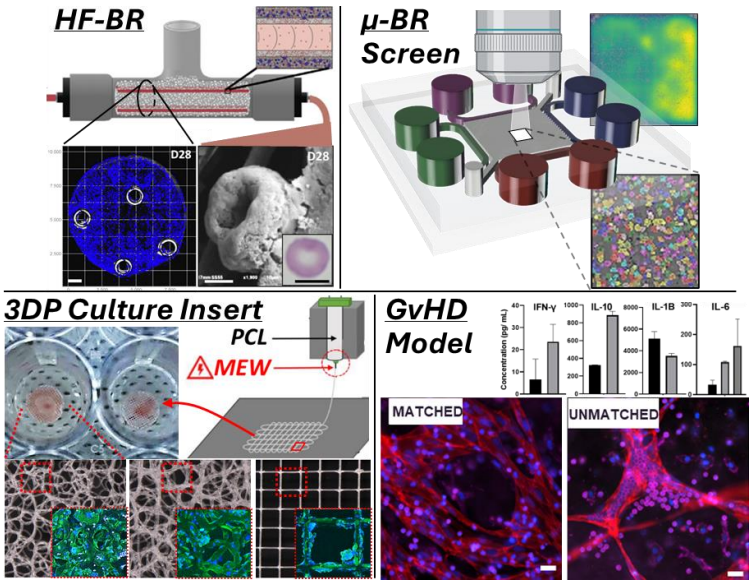
Aim: Blood-derived cell and gene therapies (CGTs) are widely anticipated to be the next step-change in medicine, curing previously incurable diseases, with a predicted 2027 valuation of $120m[1] due to their 70 clinical indications.[2] But CGT's promising future is impeded by (1) high costs associated with CGT manufacturing in cell cultures[3] and (2) the slow translation of allo-CGTs for off-the-shelf treatments. Currently, cultured CGTs can cost upwards of $300,000 per dose and no consensus management guidelines exist for allo-CGT rejection management.[4]

Methods and Results: By recreating *ex vivo* hematopoietic microenvironments in laboratory cell cultures, our new research group at UQ engineers 3D culture platforms to optimise cost-efficient manufacturing processes for CGTs and to screen patient reactivity to donor CGTs to optimise transplant management. This work began in the UK by engineering (Fig 1a) hollow fibre bioreactors for umbilical cord blood mononuclear cell (CB MNC) expansion to 10^9/mL densities with red cell (RBC) differentiation and harvest,[5–9] and continues in Brisbane with: (b) CB hematopoietic stem cell (HSC) microbioreactors to screen high density expansion in hydrogels, (c) 3D printed scaffolds as an inexpensive cell culture insert to enhance peripheral blood (PB) and CB MNC production of RBCs, and (d) hydrogel cocultures of blood outgrowth endothelial cells (BOECs) with MNCs from matched or mismatched donors as a model of transplant-associated endothelial activation and thrombotic microangiopathy.[10]

Conclusions: Our lab engineers 3D cultures which mimic physiological haematopoiesis to enhance blood CGT manufacturing and provide realistic models of haematopoietic disease.

Fig. 1: Overview of Culture Technology. (**a**) Hollow fibre bioreactors (**HF-BRs**) enabled the highest-density human blood culture to date (>10^9 CB-MNCs/mL).[5–9] (**b**) Our microbioreactors (**μ-BRs**) screen optimal conditions for high-density CB-HSC expansion in hydrogels. (**c**) Our **3D printed inserts** support high-density RBC production. (**d**) Our BOEC-MNC hydrogels recreate hematopoietic-endothelial interactions to predict **transplant response**.



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AO002

SCIg in the scrub: what matters to patients

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Background: Western New South Wales Local Health District (WNSWLHD) provides subcutaneous immunoglobulin (SCIg) to 78 patients across 250,000 square kilometres. WNSWLHD successfully implemented a SCIg home injection program across 10 facilities, epitomized by the initiative dubbed 'SCIg in the scrub. ‘SCIg in the scrub’ aligns with the WNSWLHD strategic goal of delivering world class health care to rural NSW.

Aim: To evaluate the experiences of rural and remote patients receiving SCIg treatment under the WNSWLHD model of care.

Method: A retrospective study was conducted in October 2023 using a modified 2013 IDF National Immunoglobulin Treatment Survey, distributed electronically and via paper to all 78 participants. The survey achieved a response rate of 62% (n=48).

Result: Key findings include:

- 94% (n=45) stated they were satisfied with the program
- 85% (n=41) respondents reported SCIg was easy to fit into their life
- 81% (n=39) reported SCIg as an effective treatment for their condition.
- Rich qualitative data was themed indicating significant QoL improvements. Although not formally measured, it aligns with known QoL data.

These results confirm the sustainability and preference for SCIg among rural and remote populations in New South Wales.

Conclusion: This study confirms SCIg as a viable option for managing lifelong medical conditions among rural and remote patients, affording them a measure of autonomy in managing conditions beyond their control. Of the participants, 65% transitioned from Intravenous Immunoglobulin (IVIg). As consultants became more confident in the model, they initiated immunoglobulin-naïve individuals directly onto SCIg, comprising 35% (n=17) of the participants. Engaging participants and seeking feedback are integral to effective model implementation. Survey responses, alongside participant quotes and opportunities for improvement, have been shared with facility leads and trainers. The 'SCIg in scrub' framework fosters inclusivity, ensuring equitable access to evidence-based treatment options across diverse healthcare landscapes.

Reference: 2013 IDF National Immunoglobulin Treatment Survey: Immune Deficiency Foundation

AO003

Developing a Model to predict need for Red Blood cell (RBC) transfusion, using machine learning tools

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Aim: To describe early experience from the National Transfusion Dataset (NTD) project in developing a model to predict RBC transfusion in haematology-oncology in-patients.

Method: Structured data were extracted from electronic medical records of haematology-oncology patients at The Alfred, and combined with unstructured data, extracted using the CogStack tool, to inform development of a model to predict RBC transfusion. CogStack utilises natural language processing and AI to extract information.

From 10,286 in-patient episodes with clinical notes, FBE results and ICD code data were classified by transfusion status: 1) Not transfused at all (6,936); 2) Transfused with product other than RBC (1,170); 3) Transfused RBC only (1,158) or 4) Transfused RBC and other product(s) (1,022). Discharge summaries and clinical notes captured after transfusion were excluded.

The K-Best algorithm was used to identify which data fields best distinguished between classifications. A random 5% of episodes were withheld during model training and testing to validate the model later. Stratified five-fold cross-validation was used for training and testing, and Synthetic Minority Over-Sampling Technique (SMOTE) applied to each fold during training to handle group size imbalance. Several classification algorithms were assessed to see which worked best.

Results: With K-Best set at 150 data fields the CatBoost classification algorithm performed best. During testing, it achieved accuracy: 95.37%, precision: 88.9%, recall: 89.5%, F1-Score: 89.2%. During validation on the set-aside data, its results were accuracy: 95.3%, precision: 86.6%, recall: 92.5%, F1-Score: 89.5%.

Conclusion: The results indicate the model was able to learn patterns to discern between patients who required RBC transfusion from those who did not. The consistency between the testing and validation results indicate the model generalised well on unseen data. Further refinement is underway. Future work will explore the potential to deliver real-time alerts, based on the model, on a platform designed in conjunction with hospital staff.

AO004

Practice change to improve the use of irradiated red blood cells to minimise the risk of transfusion-associated graft-versus-host disease (TA-GVHD)

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Aim: Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare iatrogenic complication of transfusion with a high mortality rate that can be prevented by irradiation of cellular blood products. A previous audit (1) at our institution showed a high number of at risk patients receiving non-irradiated red cells. Repeat audits were performed to assess the effectiveness of the preventative strategies introduced.

Method: Transfusion management plans were introduced for Haematology/Oncology patients. A warning flag was entered into in the Laboratory Information System (LIS) on the basis of this plan. In addition, education was provided to the clinical and laboratory staff about irradiation requirements. Pharmacy dispensing records were used to identify patients receiving purine nucleoside analogues for two time periods: October 2020 to September 2021 and October 2021 to September 2022. Diagnosis, treatment dates and red blood cell (RBC) transfusions were retrieved from the LIS and electronic medical record.

Results: The audit results in Table 1 show that the preventative strategies introduced to reduce the transfusion of inappropriate blood products have been partially effective.

Time Period	Jan 2008 to Oct 2018	Oct 2020 to Sept 2021	Oct 2021 to Sept 2022
Number of Patients receiving implicated medications	310	50	43
Alemtuzumab	48 (15%)	0 (0%)	0 (0%)
Bendamustine	29 (9%)	9 (18%)	3 (7%)
Cladrabine	17 (5%)	2 (4%)	3 (7%)
Dacarbazine	164 (52%)	34 (68%)	31 (72%)
Fludarabine	52 (17%)	5 (10%)	6 (14%)
Patients with Transfusion Management Plans	N/A	18 (36%)	16 (37%)
Number of patients receiving RBC transfusions	42 (14%)	15 (30%)	11(26%)
Number of transfused patients receiving some non-irradiated RBCs	28 (67%)	5 (33%)	1 (9%)

Table 1. Summary of Audit Results

Totally six patients transfused inappropriate products between October 2020 and September 2022. Four were incorrectly prescribed by the clinician, and two were due to the wrong product being selected by the Laboratory staff and the incorrect product specifications not being detected at administration. All patients with transfusion management plans were issued with suitable RBCs.

Conclusion: Education and the introduction of transfusion management plans has decreased the number of incorrect blood products transfused, but errors still occur.

Reference: 1. Yuen H, Rushford K, Dunstan T *et al*. Irradiated blood product use in patients at risk for Transfusion-Associated Graft-Versus-Host Disease. *Vox Sanguinis* (2019) 114 (Suppl 1) 68.

AO005

Towards safer neonatal transfusion with cord blood-derived cultured red blood cells.

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[1]Australian Red Cross Lifeblood

Aim: Transfusion of red blood cells (RBCs) to low-birth-weight neonates can be lifesaving but presents risks of severe side effects. RBCs are donated by adults - which differ from neonatal RBCs in size and haemoglobin content, yet comparative data are incomplete. RBCs cultured from cord blood stem cells (CB-derived cRBCs) may be more similar to native cord blood which could be a safer blood product for neonatal transfusion. This study compares cord-derived cRBCs to native RBCs from adult (PB) and cord (CB) blood to develop our understanding of neonatal RBCs.

Method: CD34+ stem cells were isolated from CB and PB and cultured for 21 days (n=6). Growth was assessed daily, and enucleation rate was assessed at day (D)7, 10, 14, 17 and 21. The expression of RBC surface markers was investigated by flow cytometry. Data were analysed by two-way ANOVA or student's t-test. $P<0.05$ was considered significant.

Results: Expansion of CB-derived cRBCs was significantly higher than PB-derived cRBCs ($p=0.04$) while enucleation rate was lower ($p=0.036$). Flow cytometric analyses revealed that membrane structural proteins were expressed in high percentage of cells (above 85%) by all groups. Higher percentage of CB-derived cRBC expressed maturation proteins, CD71 and CD98 compared to RBCs from CB and PB. Only 1.1% and 0.9% of RBC from CB and PB respectively, were nucleated compared to the 9.1%±8.3 of the CB-derived cRBCs.

Conclusion: Our findings indicate that, although cultured RBCs from CB and PB show different enucleation rates, they are phenotypically similar immature RBCs, while 98% of RBCs from cord blood are mature red cells. These data provide the basis for further functional investigations to assess the feasibility of cultured RBCs from cord blood as a new blood product for neonatal transfusion.

AO006

High-throughput genotyping of blood donor antigens: Red cells, platelets, neutrophils, and leukocytes

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[1]Australian Red Cross Lifeblood, [2]Blood Transfusion Genomics Consortium

Aim: Australian Red Cross Lifeblood is in the final stages of assessing and validating a new high-throughput blood donor genotyping array, which has been developed by the Blood transfusion Genomics Consortium[1]. This innovative research array enables comprehensive typing of human erythrocyte (HEA), platelet (HPA), leukocyte (HLA), and neutrophil antigens (HNA), as well as donor health information. We aim to highlight our initial results from screening of Australian first-time blood donors.

Method: Genomic DNA was extracted from 380 first time donor samples using the QIAsymphony SP instrument (QIAGEN Pty Ltd) and processed utilising the Applied Biosystems™ Axiom™ Propel XPRES 2x384HT workflow (Thermo Fisher Scientific Inc). Target DNA was hybridised to the Applied Biosystems™ Axiom™ BloodGenomiX™ Array, washed, probes ligated and features stained, and imaged by the automated GeneTitan multichannel instrument. Samples were analysed and those which met quality control metrics were reported using the Axiom™ BloodGenomiX™ Reporter Software. This predicts 261 HEA antigens across 38 blood group systems divided into core and research screen variants, in addition to multiple HLA Class I, HPA and HNA types. Frequency analysis was performed using the R language and environment for statistical computing (R Studio, Version 2032.6.0.421, MA, USA).

Results: Preliminary data for 376 donors identified 10 donors who were antigen negative for clinically significant high frequency red cell or platelet antigens. Additionally, one donor was predicted Fy(a–b–) (*FY*02N.01/*02N.01*). Several donors were also identified with low frequency antigens that are not currently routinely screened for.
Data from a further 8000 blood donors (both new and repeat) is expected and will result in comprehensive typing for this donor population.

Conclusion: Beyond enhancing blood transfusion safety, inventory management, and meeting the growing demand for precision-matched blood products, this array will identify blood donors with rare phenotypes—a crucial factor in optimizing the blood supply chain.

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AO007

Environmental Impacts of Patient Blood Management: Uncovering Sustainability Risks with LCA Analysis. Shall we be concerned?

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Aim: Performing a Life Cycle Assessment (LCA) of blood bag can provide a quantitative overview of the environmental impact. The aim of this study was to assess the environmental impact of PVC-based blood bags, and determine if implementation of PBM can significantly contribute to the wellbeing of environment.

Method: This retrospective observational study included all blood bags issued for transfusion for one year. The number of avoidable transfusion events were evaluated based on relevant guidelines. Data related to LCA, from cradle to grave was obtained for PVC-based blood bags using relevant LCA model. Based on LCA studies, different environmental impact categories were quantified. USEPA tool was used to analyse the results of the study. The primary outcome variable was measured in carbon dioxide equivalent (CO_2) emissions.

Results: Based on LCA data obtained for a single blood bag, the overall prediction was made for x & y as in Table 1.

Table 1- Evaluation of LCA based parameters for total transfused 48406 blood bags (x) and avoidable transfusion related 10849 blood bags (y)

Environmental Parameters	Emission per bag (n)	Total emission (n*x)	Avoidable emission (n*y)
CO2 emission (kg)	2.02*	97,780	21914
Methane emission (kg)	0.451	21,831	4892
Oil fuel usage (kg)	10.3	4,98,581.8	111744
Coal usage (kg)	92.5	44,77,555	10,03,532.5
Natural gas usage (m3)	9.63	4,66,149.78	104475

An average blood bag generated 277 kg of CO2 equivalent. 2853 metric tonne of CO_2 emission could have been avoidable. Coal was the chief source of energy (85.1%). 163 metric tonnes of CO_2 equivalent of greenhouse gas emission were avoidable.

Conclusion:
It is significant that blood bags are associated with both resource depletion as well as contributes to climate change. Based on our calculations, it can be deduced that transfusion practitioners can reduce carbon emissions and maximise resource efficiency by improving blood ordering practices, one of the many advantages of PBM practices.

AO007

Blood transfusion practices in intensive care units: a prospective observational bi-national study

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Aim: Blood transfusions in intensive care units (ICU) are common. However, for many areas, insufficient evidence has meant guidelines have been unable to make evidence-based recommendations. Our aim was to report current ICU blood transfusion practice, how it compares with transfusion guidelines, and how it has changed since the publication of the 2011-12 guidelines.

Method: A bi-national, multicentre, prospective cohort study of all adult patients admitted to participating Australian and New Zealand (ANZ) ICUs over a one week period in 2021-22 followed until ICU discharge. We investigated transfusion types, triggers, consistency with guidelines, variation, transfusion costs, and compared current practice with prior published practice. Univariable and multivariable linear and logistic regression analyses were performed.

Results: Of 927 patients admitted to 40 ANZ ICUs, 217 (23.4%) received a transfusion during their ICU admission: 192 (20.7%) received red blood cells (RBC), 63 (6.8%) received platelets, 49 (5.3%) received fresh frozen plasma (FFP), and 29 (3.1%) received cryoprecipitate. Massive transfusion protocols were implemented nine times for six (0.7%) patients. Compared to national transfusion guidelines, 89.0% of RBC, 30.3% of platelet, 27.4% of FFP, and 20.0% of cryoprecipitate transfusions were consistent. After adjusting for confounding variables, variation in transfusion practice between sites was found. Compared to ICU transfusion practices in 2008, after adjusting for confounding variables, ICU patients who received RBC and FFP were transfused more units each, and variation in total transfusions increased for RBC, platelets and FFP.

Conclusion: Blood transfusions are common in ICU, but practice is heterogenous and frequently inconsistent with national guidelines, and the number of units transfused per patient has increased since prior to the publication of the guidelines.

AO009

The Fibrinolytic potential of Cryopreserved Platelets

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Aim: Cryopreservation of platelets is an attractive storage option as it facilitates an extension of the shelf-life from 7 days to at least 2 years. Cryopreserved platelets display greater procoagulant potential than platelets stored at RT. However, the phenotypic changes induced by cryopreservation may distort the delicate balance between coagulation and fibrinolysis. The aim of this study was to determine the fibrinolytic potential of cryopreserved platelets.

Method: Platelets were frozen at -80°C according to standard methods using 5.5% DMSO, then thawed and resuspended in fresh plasma before testing (n=10). Fresh components (day 1) were tested in parallel. The abundance of surface bound fibrinolytic mediators was assessed by flow cytometry. Soluble proteins were measured by ELISA or a coagulation analyser. Clot formation was induced with thrombin and calcium, and retraction was measured after 2 hours by weighing. Clot lysis was assessed by thromboelastography (TEG) in the presence of exogenous tPA.

Results: The supernatant of thawed platelets contained a higher concentration of soluble fibrinolytic mediators: fibrinogen, plasminogen, TAFI, FXIII, PAI-1, and tPA, compared to fresh platelets. This was primarily due to thawed platelets being resuspended in fresh plasma. Thawed platelets also displayed a higher surface abundance of PAI-1 and FXIII, compared to fresh platelets. The clots formed by thawed platelets underwent retraction. However, the extent of retraction was strongly associated with the platelet concentration ($r=-0.6825$; $p<0.0001$) and was augmented by the presence of fresh platelets. tPA-induced fibrinolysis, measured by LY60, was not statistically different between fresh (4±3%) and thawed (13±12%; $p=0.056$) platelets.

Conclusion: The ability of platelets to modulate fibrinolysis is multifaceted, and although differences in the abundance of fibrinolytic mediators were observed in thawed platelets, this did not translate to a deficit in fibrinolytic capacity. This work provides a more complete understanding of the overall haemostatic capacity of cryopreserved platelets.

AO010

Resuscitation of Adult Shocked Trauma Patients using major Haemorrhage Protocols guided by Viscoelastic Haemostatic Assays versus Standard Laboratory tests

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Aim: The resuscitation of major trauma patients with critical bleeding may follow a formulaic approach using high ratios of blood components or a viscoelastic haemostatic assay (VHA) guided approach. Data from randomised controlled trials suggest equipoise among the two strategies. The aim of this study was to compare the two strategies for resuscitation of shocked trauma patients.

Method: This was a registry-based cohort study including patients from two level I trauma centres in Australia- one where a formulaic approach is used, with no use of VHA during trauma resuscitation and the other that practices a VHA-guided resuscitation strategy. The primary outcome was the total volume of blood components transfused in the first 24 hours, adjusted for differences in baseline characteristics and time to death. Secondary outcomes were volumes of each blood component and in-hospital mortality.

Results: During the study period between 01 Jan 2020 and 31 Dec 2022, there were 152 eligible patients categorised to the formulaic group and 40 categorised to the VHA group. Prehospital times were longer in the formulaic group (2.0 vs 1.4 hrs), and more patients in the VHA group (38% vs 17%) were transfused prehospital blood components. All other baseline characteristics were similar. Formulaic resuscitation was associated with significantly more blood components transfused (adjusted incidence rate ratio 1.5; 95%CI: 1.4-1.7, p<0.001). Using a formulaic approach, patients were administered more red blood cells, plasma and platelets, but fewer cryoprecipitate. There was no significant association with the formulaic approach and in-hospital mortality (adjusted odds ratio 2.3; 95%CI: 0.7-7.1, p=0.15).

Conclusion: Given the cost and potential adverse effects of blood component transfusions, a VHA-guided transfusion strategy presents an attractive option, particularly among centres receiving high volumes of shocked trauma patients. Further trials, enrolling the population most likely to benefit from precision transfusion strategies, is indicated.

AO011

What Steps and Healthcare Resources are required to give Red Blood cell (RBC) Transfusion? A prospective time-based activity-driven study of transfusion in patients with Myelodysplastic Syndromes (MDS).

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Aim: MDS patients often need transfusion. Safe transfusion depends on a complex interplay of processes, but data is lacking on the individual steps, decision pathways, resources and costs involved. We aimed to identify and quantify all healthcare resources used in each step of the pathway for MDS patients receiving inpatient (IP) and outpatient (OP) RBC transfusions.

Method: In this prospective study from May-October 2022 involving MDS-related transfusion, we observed multiple patients and processes including: pre-transfusion phlebotomy, laboratory processes, transfusion in one IP and two OP wards. Each step was process-mapped, timed and all consumables, equipment and staffing recorded.

Results: 79 MDS patients were transfused 256 RBC units, during 169 transfusion episodes (77 OP;92 IP). 32 process maps (22 laboratory, 10 clinical including phlebotomy and pharmacy) were developed, describing >600 activities.

Table 1 shows the processes, steps, decision points, time and resources for transfusing 1 RBC unit. For a routine uncomplicated patient (no alloantibodies/special requirements, automated group & screen, computer crossmatch), the entire process took, on average, 440 minutes for OP (ward A:478 minutes, ward B:401 minutes) and 303 minutes for IP (Table 2). For complex patients (alloantibodies/special requirements), total time is up to 918 minutes for OP and 743 minutes for IP (Table 2). Laboratory processes are the most complex, taking 87% of total time (647/743minutes) for complex IP, 77% (647/841minutes) for complex OP. For routine patients,

Table 1 Transfusion process for 1 RBC unit

Process	**Steps, *N***	**Decision points, *N***	**Time (mins), mean (range)**	**Staff, *N***	**Consumables/ equipment, *N***
OP Phlebotomy	36	1	18 (10-26)	2	47
IP Phlebotomy	32	2	33 (31-37)	1	35
Laboratory (same for OP & IP)	Routine*: 165 Complex#: up to 417	Routine*: 20 Complex#: 53	Routine*: 207 (189-217) Complex#: 647 (602-793)	3	103
RBC administration					
OP ward A	105	38	253 (194-353)	9	156
OP ward B	86	36	176 (146-215)	6	77
IP ward	38	23	63 (52-77)	4	47

**Routine: no alloantibodies, no special blood products required #Complex: alloantibodies or special blood products required*

laboratory processes take 68% (207/303minutes) total time for IP and up to 52% (207/401 minutes) total time for OP.

Table 2: Total time (phlebotomy + laboratory + RBC transfusion) in minutes (mean)

Patient type	**OP ward A* time (mins), mean (range)**	**OP ward B* time (mins), mean (range)**	**IP time (mins), mean (range)**
Routine	478 (393-596)	401 (345-458)	303 (272-331)
Complex	918 (806-1172)	841 (758-1034)	743 (685-907)

**OP MDS transfusion occurs in one of 2 day wards*

Conclusion: This is the first detailed study of the complex processes required for RBC transfusion in MDS patients. Health economics analysis is currently underway and will help in future resource planning. Detailing the many steps and decision points also identifies potential ‘weak links in the chain’, which can improve transfusion procedural safety and efficiency.

AO012

Overcoming Barriers to Support Patients to access Subcutaneous Immunoglobulin in Australia

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Aim: In Australia, immunoglobulin (Ig) is available to eligible patients under the national blood arrangements funded by all Australian governments and administered by the National Blood Authority (NBA). Ig can be infused intravenously (IVIg) in the hospital setting, or subcutaneously (SCIg) by patients in their own home.

Evidence shows that SCIg treatment offers better patient-centred quality of life, reduced adverse effects from more frequent administration at lower doses resulting in more consistent Ig levels in blood, and improved cost-effectiveness thus reducing costs for health systems. However, only 16% of eligible patients access SCIg treatment and SCIg patients comprise 28% of patients being treated publicly, compared to 3.4% being treated privately. Why is this?

Method: A review was undertaken to better understand the barriers to patients accessing SCIg. Consultations occurred with a broad range of stakeholders including governments, clinicians, blood bank, and pharmacy staff, suppliers and patients.

A stakeholder panel subsequently considered strategies to address identified barriers and understand the limitations and feasibility. Potential strategies were evaluated against agreed criteria to identify preferred options.

Results: Barriers identified include funding and resourcing for equipment and SCIg specific health-care services, clinician and hospital preferences for IVIg, low awareness of SCIg benefits, and supply and access issues.

Conclusion: The strategies recommended to overcome barriers and support patients to access SCIg in Australia include:

- ensuring appropriate funding and resourcing is available to support SCIg programs;
- improving awareness of the benefits of SCIg treatment;
- updating guidelines and policies to provide clearer guidance on when SCIg should be offered to patients; and
- improving reporting to track uptake and better understand SCIg usage trends.

Implementation of these recommendations is in progress, noting the importance of the shared responsibility with stakeholders for success.

AO013

Blood volume in Preterm Infants is Substantially Lower than Estimates in Current Clinical guidelines

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Aim: The accepted wisdom is that preterm infants have a higher blood volume than at term; this is reflected in the Australian transfusion guidelines (100 vs 80 mL/kg). However, these estimates are based on early studies with methodological flaws that overestimated blood volume, particularly in preterm infants. Limited studies report blood volume in very preterm infants on the first day after birth, when substantial fluid shifts occur. We aimed to determine if current Australian transfusion guidelines accurately reflect blood volume in a modern cohort of preterm infants less than 24 hours old.

Method: The inclusion criteria were 1) preterm infants born <32 weeks gestation, 2) admitted to The Women's and Children's Hospital Adelaide and 3) receiving packed red cell transfusion at <24 h old (*n*=10). Blood volume was measured using haemoglobin subtype analysis. A one sample t test was used to compare blood volume against transfusion guidelines.

Results: Preterm infants were 25^{+1} (SD 1^{+4}) weeks gestational age (30 % male), birth weight 755 (SD 141) g. Postnatal age at measurement ranged from 1-7 h, averaging 4 (SD 2) h after birth. Blood volume was significantly lower than clinical guidelines, averaging 58 (SD 19) mL/kg ($p<0.0001$). All values were lower than guideline estimates for preterm infants, (maximum value 86 mL/kg). Red cell volume averaged 20 (SD 6) mL/kg, and plasma volume averaged 38 (SD 13) mL/kg.

Conclusion: Blood volume of preterm infants is 42% lower than estimates in the Australian Transfusion guidelines. This finding highlights the urgent need for a comprehensive study of changes in blood volume in sick and stable preterm infants across the first days of life and how this compares to infants born at term. An understanding of blood volume changes after birth is critical to providing effective support while in intensive care and hence improving outcomes for preterm infants.

AO014

Red cell alloimmunisation and haemolytic disease of the foetus and newborn in First Nations, rural and remote mothers and babies in the Northern Territory

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Aim: First Nations hospitalised patients in the Northern Territory (NT) have a higher prevalence of red cell (RC) alloantibodies, with RC transfusion an independent predictor of risk.1,2 We investigated the consequences of these alloantibodies for rural, remote and First Nations pregnant women and babies across the NT.

Method: Five-year retrospective (2015-2020) cohort study of all births to mothers ≥16 years admitted to NT public hospitals. Outcomes of interest included alloantibody prevalence/specificity, hospital of delivery, and prevalence of (non-ABO) haemolytic disease of the foetus/newborn (HDFN).

Results: 9327 mothers were included. First Nations mothers had a significantly higher prevalence of RC alloantibodies (7.9% (262/3337) vs 1.2% (70/5990), (Chi2 p<0.001), and clinically significant alloantibodies (predominantly Rh system, Fig.1): 1.2% (40/3337) vs 0.3% (17/5990) (p<0.001). In the 262 alloimmunised First Nations women, 374 alloantibodies were detected, with 317 (84.8%) non-clinically significant (eg. Lewis) (Fig.1). Of 11727 total birth episodes, prevalence of clinically significant RC alloantibodies was 1.12% (48/4285) vs 0.24% (18/7442) for First Nations vs non-First Nations births (p<0.001), and 1.09% (41/3775) vs 0.31% (25/7952) for birth episodes where the mothers' primary place of residence was remote versus regional. Women in remote NT with clinically significant alloantibodies were more likely to deliver in Darwin or Alice Springs rather than the remote hospital nearest to Country (89% vs 37%). In 66 births to women with clinically significant alloantibodies, for First Nations versus non-First Nations babies, 11 (0.26% births) vs 5 (0.07% births) were DAT positive with RC elution positive for the corresponding maternal RC alloantibody, 8/4285 (0.19%) vs 4/7442 (0.05%) developed (non-ABO) HDFN (Fisher's exact p=0.038), and 8/4285 (0.19%) vs 2/7442 (0.03%) required treatment (phototherapy/IVIG/exchange transfusion).

Conclusion: RC alloimmunisation and non-ABO HDFN disproportionately affect First Nations mothers and babies in remote NT and are associated with increased need for tertiary care further away from Country.

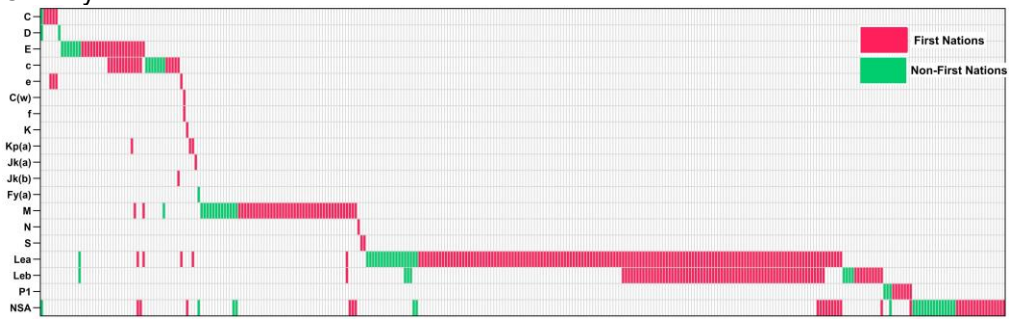

Fig 1. Alloantibody specificities in NT pregnant women. NSA: non-specific antigen

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AO015

Rethinking D-Positivity: Molecular Testing Guidelines and Clinical Implications

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Aim: Accurately determining RhD status in pregnant women is a critical service provided by pathology laboratories, fundamental to effective management and the prevention of alloimmunisation-related complications. The *RHD* gene is highly polymorphic, with over 300 variants identified across different population groups. These variants can display variable reactivity with monoclonal anti-D reagents, highlighting the limitations of serological detection methods. The ANZSBT guidelines recommend molecular qualification for serologically weaker D expressions (≤1-2+). However, partial D variants, which can form allo-anti-D, sometimes exhibit strong (3+) reactivity. Observational data from our study suggest that patients of African ethnicity often exhibit 3+ reactivity. This raises questions about the suitability of existing guidelines as a "one-size-fits-all" approach.

Method: Red cells were phenotyped using Grifols CAT methodology. Between 2022 and 2023, Healius transfusion laboratories referred 328 samples, serologically RhD-positive (3+), to the Australian Red Cross Lifeblood for molecular typing (RHD BeadChip, Immucor), deviating from the current guidelines. This decision was based on observational evidence of 3+ alloimmunisation and reports from Lifeblood that identified 3+ patients from African ethnicity as DAR variants.

Results: Of the 328 RhD-positive patients, 216 (65.85%) were weak D type 1-3 and were managed as RhD-positive. The remaining 112 (34.15%) revealed 24 different *RHD* variants or "Possible D" types, resulting in a change in clinical management from RhD-positive to RhD-negative. Among these 112 patients, DAR (n=30) was the most prevalent D variant.

Conclusion: Serologically RhD-positive (3+) samples are currently not included in the guidelines for RHD genotyping. However, this study identified 112 non-weak D type 1-3 samples, prompting a change in management for these patients. Depending on the typing reagent and/or method used, the RhD phenotype profile can vary significantly. These findings may support a review of the ANZSBT guidelines for weak D molecular testing, emphasizing the need for tailored approaches to diagnostic testing with consideration given to population makeup, the diversity of various RhD phenotypes, their variants, and the risk of alloimmunisation.

AO016

What we Learnt setting up Blood Bank in Australia's First Heart hospital

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Victorian Heart Hospital (VHH) is Australia's first cardiac hospital, opened on the 8th of March 2023. VHH is a 200 bed hospital with an Emergency Department, 7 Catheterisation laboratories, Intensive Care Unit, 3 Theatres, a helicopter pad for transport from country Victoria regions, with a large volume of complex patients with significant Blood Banking needs
VHH Blood Bank is a category B laboratory and is part of the Monash Health Pathology network
Apart from the standard new laboratory set up processes, there were additional considerations and processes related to our specific patient cohort.

This is what we did:

- We worked closely with the Clinical Haematology team, Theatre, ICU and ED stakeholders to cater for the specific cardiac patient demographic including anticoagulant reversal products (andexanet)
- Optimisation of our massive transfusion protocol (MTP) noting large number of MTP activations (83 in 12 months)
- Implementation of a post cardiac bypass specific 'emergency coagulation pack' (65 in 12 months)
- Validation and introduction of the pneumatic tube system for transporting fresh products to Theatre
- Introduction of new process for albumin storage in Theatre and ICU
- Participation in the CLIP II study-use of cryopreserved platelets in cardiac patients
- Evaluation of group and screen testing on intraosseous specimens, noting large number of cardiac arrest patients with decreased peripheral venous access

Other challenges included:

- Maintaining staff training and competency and relevant inventory for paediatric Blood Banking in a predominantly adult hospital environment, eg birth of baby to a mother in VHH Theatre
- A small team that is core trained and required to work on a 24/7 rotational roster and on call
- Inventory considerations related to being a satellite laboratory servicing complex patient cohort

AO017

The effects of Storage and Leucoreduction on packed red cell (PRBC) and risk of Supernatant-mediated TRALI.

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Aim: Biological response modifiers (BRMs) thought to be associated with non-antibody-mediated TRALI accumulate during blood product storage. Evidence surrounding the effect of leucoreduction of PRBCs on risk of TRALI development risk has been conflicting. This study aimed to evaluate which pathways were relevant to risk of PRBC-supernatant mediated TRALI whether storage duration and leucoreduction in PRBCs modified PRBC supernatants (SN) risk of TRALI.

Method: Leucodepleted and non-leucodepleted PRBC units were processed on day 2 (D2) or day 42 (D42). Supernatants were obtained by dual centrifugation, heat-treated (56°C for 30mins) and then pooled, aliquoted and frozen. Human lung microvascular endothelial cells (HLMVECs) were grown to confluence and then treated with lipopolysaccharide (LPS). After 6 hours, freshly isolated neutrophils were added and allowed to settle for 30 mins. PRBC SN pools from D2 and D42 (with or without leucoreduction) were added to the wells (10% v/v) and incubated for a further 30 mins. Microscopic counting was performed using Trypan blue staining to identify dead cells. Significance was determined using a one-way ANOVA ($p<0.05$), followed by Dunnett's post-hoc test.

Results: No significant reduction in HLMVEC viability was observed following PRBC SN treatment of HLMVEC without LPS and neutrophils. In the presence of neutrophils, a significant decrease in viability was seen in LPS treated cultures exposed to day 42 PRBC SN with (62.14 ± 3.57% viability vs. 75.24 ± 6.94 viability, $p=0.0238$) and without leukoreduction (58.56 ± 9.10% viability vs. 73.43 ± 5.04% viability, $p=0.0128$) in comparison to cultures exposed to D2 PRBC SN. No significant difference was seen between cultures exposed to supernatants from stored leucoreduced or non-leucoreduced cells.

Conclusion: In this model, evidence of a two-hit neutrophil activation pathway for HLMVEC death following exposure to the stored PRBC SN was observed. Storage duration of PRBC increased the risk of BRM mediated TRALI development, but leucoreduction did not.

AO018

RH blood group genetic diversity in a Kenyan donor population: Implications for chronically transfused patients in Kenya.

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Aim: Serologic typing for ABO and D is standard practice in transfusion services. Extended serology and genotyping for antigens including those from the RH, Kell, Duffy, Kidd and MNS blood group systems is also recommended to reduce risk of red cell alloimmunisation. In some jurisdictions Rh serology typing is limited to D and genotyping is not available. This study, for a Kenyan blood donor population, was to determine the *RHD/CE* blood group genotype profile, predict phenotype profiles and compare to RhD serological results.

Method: Whole blood samples (n=191) comprising 114 D-negative, 74 D-positive and 3 weak D from volunteer donors from the Kenyan National Blood Transfusion Service (KNBTS) were investigated. Genomic DNA was extracted and next generation sequencing was performed using a targeted custom blood group sequencing panel on the Illumina MiSeq[1]. Variant Calling Format (VCF) files were annotated using wANNOVAR[2]. Two scientists independently interpreted genotypes and predicted phenotypes by matching VCF file variants to variants in the ISBT Blood Group Allele Tables.

Results: For D-negative (n=114) phenotyped samples, MPS-based genotyping showed 109/114 comprised only alleles predicting the D-negative phenotype. The remaining 5/114 had alleles predicted as D-positive (partial D). For D-positive (n=74) phenotyped donors, MPS predicted 61/74 D-positive. In contrast, 13/74 had alleles predicting D-negative (n=2), weak D (n=2) and partial D positive (n=9) phenotypes. Samples (n=112) predicted to be D-negative exhibited four alleles: *RHD*01N.01, RHD*08N.01 (RHDΨ)* and the *RHD-CE-D* hybrid allele [(*RHD*03N.01*). Ten different *RHD* alleles predicted a conventional D-positive phenotype. Sequences for 18/191 samples were predominantly homozygous for the *RHCE* reference alleles while the remaining 173/191 were *RHCE* variant alleles.

Conclusion: *RH* variant alleles in the selected Kenyan donor population are diverse, indicating the need for extended serology and genotype matching of red blood cells, especially for chronically transfused patients.

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THANZ Oral Presentations

TO001

A Health experience in using Andexanet Alfa to treat Oral factor Xa anticoagulant-associated Critical bleeding

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I**ntroduction :** Andexanet alfa administration has been associated with rapid reduction in both anti-Xa activity and free Factor Xa (FXa) inhibitor levels. Recent evidence has shown its efficacy in achieving haemostatic stability during acute bleeding but with increased thrombotic events. Andexanet received provisional approval by the Therapeutic Goods Administration in July 2023.

Aim: To audit the outcomes in patients with critical bleeding on apixaban or rivaroxaban in whom a decision to administer andexanet was made.

Method: A retrospective review of clinical outcomes in patients administered andexanet for the management of critical bleeding on apixaban or rivaroxaban was conducted. Cases were identified by reviewing andexanet dispensing records at our institution, a tertiary teaching hospital in Melbourne, between 1 January and 1 May 2024. For each case, electronic medical records were reviewed. Primary endpoints included haemostatic efficacy using the rating system from the andexanet registration trials, and arterial/venous thrombosis or death at 30 days. Secondary endpoints were the time from presentation to the availability of drug level and andexanet administration.

Results: Four cases of Intra-Cerebral Haemorrhage (ICH) were included (Table 1), comprising three primary and one secondary traumatic ICH. All cases had anti-Xa >75ng/ml at presentation and were administered low-dose andexanet. Two cases showed haematoma expansion by >35% within the first 12 hours post andexanet (i.e. poor haemostatic efficacy) while the other two demonstrated excellent haemostatic efficacy. At the 30-day follow-up, no thrombotic events were observed, but one patient had died. Regarding functional recovery, two had significant functional impairment while one patient had near complete functional recovery, as assessed by the modified Rankin Scale.

Conclusion: Monash Health used andexanet to treat apixaban or rivaroxaban-related bleeding in four cases over a four-month period. All cases had life-threatening intracranial bleeding. Poor haemostatic efficacy was observed in 50% (2/4) with a 30-day mortality of 25% (1/4) and no thrombotic complications. Only one patient achieved significant functional recovery at 30 days.

Case number:	1	2	3	4
Age:	74 year old	90 year old	54 year old	85 year old
Gender:	Male	Male	Male	Female
Anticoagulant /dose	Rivaroxaban 15mg OD	Apixaban 5mg BD	Apixaban 5mg BD	Rivaroxaban 20mg OD
Indication for anticoagulation:	Atrial Fibrillation	Atrial Fibrillation, previous unprovoked proximal leg DVT	Unprovoked DVT/PE	Aortic Valve Replacement
Time of last thrombotic event pre presentation:	Nil	2015	2018	Nil
Last dose of anticoagulant pre presentation:	Unknown	Unknown	5hr pre presentation	Unknown
Type of bleeding:	ICH	ICH	ICH	Traumatic Intracranial bleed
Vital signs at presentation: BP, HR, GCS	GCS 13, SBP 170/100, HR 107	GCS 15, SBP 170, HR 73	GCS 15, SBP 160, HR 115	GCS 13, SBP 215, HR 106
Presentation:	Presented with low GCS	Headache with no focal neurology	Headache and L sided neurology	Low GCS
Comorbidities:	Type II diabetes Mellitus, Hypertension	Hypertension	Spina bifida, renal transplant	IHD, Breast cancer, Parkinson's Disease
Imaging pre Andexanet:	CT brain: 20 x 33x 26 mm Right thalamic bleed with mass effect and midline shift (76minutes)✶	CT brain: large occipital intraparenchimal haematoma with extension into subarachnoid and intraventricular spaces with mild mass effect (253minutes)✶	CT brain: 4.7x3.5 x 2.5cm inferior right lobe intraparenchymal bleed with mild mass effect (70minutes)✶	CT brain: bilateral multifocal sutural haematomas of 4-5mm on each side with small subarachnoid bleed (11minutes)✶
At presentation laboratory results:	Hb 118. Plat 153, eGFR 56, INR 1.6, APTT 31, Fibrinogen 4.0	Hb 123, Plat 172, eGFR 47, INR 1.6, APTT 29, Fibrinogen 3.9	Hb 115, Plat 204, eGFR 75, INR 1.2, APTT 31, Fibrinogen 4.4	Hb 104, Plat 211, eGFR 85, INR 3.2, APTT 32, Fibrinogen 3.0
Drug level pre Andexanet: ✢	Rivaroxaban level 138.9 ng/ml	Apixaban level 368 ng/ml	Apixaban level 192.7 ng/ml	Rivaroxaban level 570ng/ml
Timing to drug level: ✢	collected at 90minutes, formal result at 270minutes ❊	collected at 70minutes, formal result at 433minutes❊	collected at 85minutes, resulted at 114minutes❊	collected at 36minutes resulted at 94minutes❊
Administeration of other blood products and time:	No	No	No	No
Time of administration of Andexanet ✢	Issued at 160minutes. Administered: 400mcg at 210minutes and 480mg at 225minutes	Issued at 375minutes , Administered: 400mcg at 461minutes and 480mcg at 479 minutes	Issued at 122 minutes, Administered: 400mcg at 383minutes and 480mcg at 397minutes	Issued at 167 minutes Administered: 400mcg at 336minutes and 480mcg at 356minutes
Imaging up to 12hrs post Andexanet:	Repeat 2 hrs post first scan: expansion of bleed by >35%. (scan at 23 hrs haematoma slightly reduced compared to second scan)	CT brain at 10hrs (minor haematoma growth of less than 10%)	Repeat at 2.5hrs CT brain: stable with no haematoma expansion	CT at 10.5 hrs: marked progression of haematoma of >35% with midline shift and inter ventricular progression.
Clinical changes up to 12hrs post Andexanet:	GCS drop required Bilateral External Ventricular drainage in OT within hrs of presentation.	No	Admitted to ICU on day 2 for ventilatory support due to LRTI.	Further GCS deterioration, febrile illness.
Restart of anticoagulation at d30:	No	No	No	No
Bleeding/thrombosis within 30day:	No	No	No	No
30 days mortality:	No	No	No	Yes (on day 11)
Functional Outcome (Modified Rankin score)	Significant functional disability (score 4-5)	Significant functional disability (score 4-5)	Mild functional disability (score 1-2)	Dead (score 6)

Table 1

✶ Time the imaging performed.
❊Verbal result often available average 1-2 hrs before formal validated result.
✢ Time calculated from presentation.

TO002

Platelet TREM-Like Transcript-1 (TLT-1) is elevated in patients with thrombocytopenia and levels are regulated by A disintegrin and metalloprotease 17 (ADAM17) on activated platelets

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Aim: Engagement of platelet glycoprotein (GP) VI by collagen or fibrin initiates intracellular signalling, platelet activation, and metalloproteinase-mediated receptor shedding from platelets. Triggering Receptor Expressed on Myeloid (TREM)-like transcript-1 (TLT-1) is a second platelet-specific protein that is released in sepsis and inflammation. Like GPVI, the shed fragment of TLT-1 is released into plasma and can be measured by ELISA. The mechanism of TLT-1 regulation on platelets is undefined.

We aim to evaluate TLT-1 levels and production of soluble (s) TLT-1 on resting and activated platelets and to assess sTLT-1 levels in patients with thrombocytopenia.
Methods: TLT-1 levels on resting and activated human washed platelets and patients' whole blood were assessed by flow cytometry. TLT-1 cytoplasmic domain-associated proteins were assessed by immunoprecipitation and immunoblot. sTLT-1 was quantified by ELISA. Temporal loss and extent of metalloproteolysis were compared with metalloproteolysis of GPVI.

Results: TLT-1 levels increased 4-fold on activated platelets and treatment with GPVI agonists convulxin or collagen-related peptide (CRP) triggered release of a 10-17 kDa ectodomain fragment of TLT-1 detectable by immunoblot. Release was inhibited 90% by 0.25 mM broad-spectrum metalloproteinase inhibitors or 80% with 5 μM of a specific inhibitor of A Disintegrin and Metalloproteinase (ADAM) 17. A calmodulin binding sequence within the TLT-1 cytoplasmic tail was identified however no association with calmodulin could be demonstrated by coimmunoprecipitation. However, treatment of platelets with calmodulin inhibitor W7 or thrombin triggered the release of TLT-1. Surface TLT-1 was enhanced ($p<0.0001$) and sTLT-1 ($p=0.0037$) was significantly elevated in plasma from patients with platelet counts below 100 x 10^9/L ($n=80$) compared with healthy donors.

Conclusion: Unlike GPVI, TLT-1 levels are increased on activated platelets, shed in response to thrombin, and regulated by ADAM17 metalloproteinases. Platelet TLT-1 and plasma sTLT-1 are increased in patients with thrombocytopenia. Heightened platelet activation may underpin thrombocytopenia.

TO003

Ribosome biogenesis inhibition aids in the differentiation of stem cells towards the MK/platelet lineage

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Aim: CX-5461, a ribosomal biogenesis inhibitor and candidate anti-cancer therapeutic has completed phase I/II clinical trials and received fast-track designation. Preclinical studies have shown that CX-5461 treatment increases circulating platelet numbers in both mice and humans through an undefined mechanism. We explored the mechanism(s) underpinning CX-5461-mediated thrombopoiesis.

Method: C57BL/6 mice received CX-5461 (35 mg/kg) or vehicle thrice weekly. Blood samples were collected across 42 days and blood cells were enumerated. Flow cytometry was used to quantify platelet lifespan, receptor levels, platelet function and bone marrow (BM) megakaryocyte (MK) numbers, ploidy, and haematopoietic subpopulations. Serum cytokines and plasma thrombopoietin (TPO) were quantified by ELISA, while liver TPO transcripts were measured via RT-qPCR. MK colony-forming unit (CFU) assays were performed using the whole BM.

Results: A single-dose of CX-5461 increased platelet counts (up to 34%) in 9/16 haematological malignancy patients. CX-5461-treated mice showed rapid, reversible 1.7-fold platelet increases at d7, while all other blood cells remained unchanged (leukocytes) or decreased (erythrocytes). Platelet glycoprotein (GP) Ibα, CD41 and GPVI were normal. A 2.3-fold increase in reticulated platelets, but normal platelet lifespan was measured. Among 23 cytokines measured, WT CX-5461-treated mice showed only a decrease in serum chemokine ligand 5 (CCL5) (*$p<0.05$) and an increase in CCL11 (*$p<0.05$). A >2-fold increase in MK numbers and increased $Sca1^{+}$MK (**$p<0.01$), platelet/MK-biased multipotent progenitor-2 (LSK $CD135^{-}CD48^{+}CD150^{+}$) (****$p<0.0005$). CX-5461 treatment led to a >3-fold increase in MK-CFU. CX-5461-induced platelet production was independent of TPO, as plasma TPO and liver TPO transcripts did not change with treatment, and CX-5461-treatment of $c\text{-}mpl^{-/-}$ mice resulted in a 5-fold increase in platelets (***$p<0.0005$, d28).

Conclusion: CX-5461 treatment increased circulating platelet levels by invoking a platelet/MK-biased haematopoietic pathway independent TPO signalling and cytokine upregulation. Ribosomal biogenesis inhibitors offer a novel avenue to treat thrombocytopenia and a tool to further our understanding of thrombopoiesis.

TO004

Retrospective review of thromboprophylaxis in patients undergoing urological surgery

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Aim: To evaluate local practice of thromboprophylaxis in urological surgery.

Method: Observational, retrospective study of a convenience sample of patients identified by ICD-10 coding as having undergone a urological procedure between May2022-April 2023 at a quaternary referral centre. Patients with a length of stay (LOS) <24hours, age <18 years, procedure abandoned, or absent documentation were excluded. Electronic medical records were reviewed with data collected on demographics, surgery type, risk factors for venous thromboembolism (VTE), thromboprophylaxis prescription, and clinical outcomes (VTE, bleeding). Primary outcome was adherence with local guidelines. Follow-up duration was 30 days after hospital discharge. Data were analysed descriptively. Chi-squared test was performed for subgroup analyses; p-value <0.05 considered statistically significant.

Results: Of 243 patients included, 81.5% were male, median age was 66.4 years (IQR 54.8-76.3) and 79% had at least one VTE risk factor. The majority of surgeries were elective (n=169, 69.5%) and the median LOS was 2.4 days (IQR 1.4-4.2). VTE risk profiles according to surgical and patient-related factors are displayed in Table 1. Contraindications to pharmacological prophylaxis were present in 116 (47.8%) patients, most commonly active bleeding. Overall, 61.3% of patients received VTE prophylaxis with 118 (48.6%) prescribed pharmacological thromboprophylaxis. This was initiated within 24 hours post-operatively in 90 (76.3%), at a median 9.9 hours. Mechanical thromboprophylaxis was utilised in 62 (25.5%) patients. Complete adherence to guidelines was assessed at 25.5% (95% CI 20.2, 31.5), which differed significantly between low- and high-risk patients (55.3% vs. 20%, p=0.005). Rate of bleeding was 9.5% (n=23) and there was one VTE (0.5%).

Conclusion: Local adherence to VTE prophylaxis guidelines following urological surgery is poor, likely driven by lack of mechanical thromboprophylaxis in patients with high VTE risk and concurrent bleeding. Although VTE incidence was minimal, ongoing vigilance on thromboprophylaxis practice in this cohort, balancing under- versus over-prescription, is warranted.

Table 1: VTE risk profiles

Category	**n=243**
Surgical risk, n (%)	
Low	117 (48.1)
Intermediate	62 (25.5)
High	64 (26.3)
Patient risk, n (%)	
Low	38 (15.6)
High	205 (84.4)

TO005

Multimodal cardiovascular risk prediction model in diabetes – incorporation of global coagulation assays outperforms HbA1c and Framingham Risk Score

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Aim: Cardiovascular disease (CVD) is the most prevalent cause of mortality in diabetes, however, current CVD risk prediction scores are inadequate. Global coagulation assays can provide a more comprehensive coagulation assessment, a key arm of thrombosis. We aim to create a multimodal CVD risk assessment score which includes GCAs, to predict arterial thrombosis for patients with diabetes.

Method: This prospective observational study recruited adult patients with diabetes from outpatients at Northern Health, Victoria. Exclusion criteria included end stage chronic kidney disease and anticoagulation. A baseline assessment was performed with routine laboratory testing and three GCAs; thromboelastography (TEG), calibrated automated thrombogram (CAT) and overall haemostatic potential (OHP). The primary outcome was arterial thromboembolism including myocardial infarction, stroke/transient ischaemic attack or critical limb ischaemia. Time-to-event analysis was performed with mortality as a competing event.

Results: 154 patients were recruited with median age 63 years old (IQR 50-72), 55.8% (n=86) males and median follow-up of 3.7 years (IQR 1.8-4.2). The median HbA1c was 7.5% (IQR 6.6-8.5). Fifteen (9.7%, 3.2/100-person-years) arterial thromboembolic events were captured with median time-to-event of 1.8 years. Patients with events were more likely to have hypercoagulable GCA markers compared to those who did not. The overall mortality was 13.0% (n=20), with no mortality due to arterial thromboembolic events. A multimodal risk score incorporating key GCA parameters outperformed HbA1c alone and the Framingham Risk Score in predicting arterial thromboembolic events (Harrell's C score 0.907 vs 0.675 vs 0.574 respectively) (Table 1).

Conclusion: While larger validation studies are required to confirm these findings, this pilot study suggests a multimodal CVD risk assessment approach incorporating GCA parameters may be practice changing and can improve individual prediction of arterial thrombosis in patients with diabetes.

	Subhazard ratio	**Harell's C score (95% CI)**
***HbA1c* alone**	1.37	0.673 (0.524-0.822)
Framingham Risk Score	1.69	0.574 (0.456-0.693)
Multimodal Score:		0.907 (0.861-0.954)
Maximum amplitude on TEG >66.5mm	14.87	
V*elocity index on CAT >55.19nM/min*	3.02	
OHP on OHP >14.75 units	8.50	
M*ale sex*	4.65	
HbA1c >7.45%	6.06	

TO006

Association between tissue factor pathway inhibitor (TFPI) and atherothrombotic events in patients with cardiovascular risk factors

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Aim: Tissue factor pathway inhibitor (TFPI) is a natural anticoagulant and the principal inhibitor of tissue factor induced coagulation. We aim to explore the association between TFPI and atherothrombotic events in patients with cardiovascular risk factors.

Method: A prospective observational study recruiting adults with existing cardiovascular risk factors was performed at Northern Health, Victoria. Patients on therapeutic anticoagulation were excluded. The primary outcome was arterial thromboembolism including myocardial infarction, stroke/transient ischaemic attack or critical limb ischaemia. Time-to-event analysis was performed with mortality as a competing event. Two high risk subcohorts were also analysed; chronic kidney disease (CKD) (defined as eGFR <30ml/min/1.73m^2) and diabetics (excluding eGFR <30ml/min/1.73m^2).

Results: 306 patients were recruited with median age 65 years (IQR 56, 74), 55.6% males (n=170) and median follow-up time 3.35 years. There were 77 patients in the CKD group and 143 in the diabetes group, with comparable median TFPI values between both subgroups (36.4 vs 35.4ng/mL, p=0.44). There was minimal correlation seen between TFPI and creatinine (Spearman coefficient =0.09) or HbA1c (0.21). A total of 49 (16.0%) atherothrombotic events were captured including 34 (25.2%) in the CKD group and 12 (8.4%) in the diabetes group (p<0.001). While higher TFPI was associated with atherothrombotic events in the overall cohort (p=0.012) and CKD group (p<0.001) this was not significant in the diabetes group (Table 1). An optimal TFPI cutoff to predict atherothrombotic events was created for each group based on Youden index and ROC curve. The overall cutoff was TFPI>42.0ng/mL (subhazard ratio (sHR) 2.28, 95%CI 1.30-4.00) while it was >61.4ng/mL in the CKD group (sHR 3.23, 95%CI 1.59-6.57).

Conclusion: This pilot data suggests that elevated TFPI may be predictive of atherothrombotic events in CKD patients but not patients with diabetes. Further studies are required to validate these findings and explore the mechanisms behind this association.

	Overall	**No event**	**Atherothrombotic event**	**sHR (95% CI)**	**p-value**
All Patients	N=306	N=257	N=49		
TFPI	33.4 (18.6, 53.3)	31.0 (17.7, 50.2)	45.5 (25.9, 75.3)		**0.012**
TFPI >42.0ng/mL	112 (36.6%)	85 (33.1%)	27 (55.1%)	**2.28 (1.30-4.00)**	**0.004**
CKD (eGFR<30)	N=77	N=43	N=34		
TFPI	36.4 (21.4, 64.5)	35.6 (19.7, 54.7)	49.1 (21.4, 79.4)		**<0.001**
TFPI>61.4ng/mL	22 (28.6%)	7 (16.3%)	15 (44.1%)	**3.23 (1.59-6.57)**	**0.001**
Diabetes	N=143	N=131	N=12		
TFPI	35.4 (20.6, 57.3)	34.4 (20.3, 57.2)	40.1 (30.2, 75.3)		0.35
TFPI >29.5ng/mL	85 (59.4%)	75 (57.3%)	10 (83.3%)	3.55 (0.77-16.28)	0.10

TO007

Adults with immune thrombocytopenia (ITP) who discontinued or switched thrombopoietin receptor agonist (TPO-RA): Outcomes from an Australian tertiary hospital

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Aim: 1. Evaluate outcomes in patients with ITP who discontinued TPO-RA after achieving stable complete response (CR). 2. To determine the reasons and outcomes in patients with ITP who switched TPO-RA agents.

Method: Retrospective cohort study of adult patients with ITP on TPO-RA: romiplostim, eltrombopag or avatrombopag. Patient selection criteria for discontinuing TPO-RA were based on national guidelines(1). Measured outcomes as per previously published (1,2); sustained CR off therapy (SCROT) = platelet ≥ 100 × 10^9/L.

Results: We evaluated a total of 50 patients with median TPO-RA treatment duration of 22.5 months, patient characteristics are shown in Table 1. Fourteen patients were identified in which TPO-RA was weaned, median platelet count prior to TPO-RA wean was 333 x 10^9/L. Of these, 8 patients were on romiplostim (median dose 2mcg/kg/week) and 6 on eltrombopag (dose 50mg daily). Median duration of TPO-RA wean was 2 months. Seven of 14 patients (50%) demonstrated SCROT at 6 and 12 months (Figure 1). No bleeding or rescue therapy were required in the 7 patents who failed weaning. Of these, 4 of 7 recommenced the same TPO-RA, while 2 of 7 switched TPO-RA, all 7 regained CR. We also identified 13 patients who switched from one TPO-RA to another, 5 of 13 (38%) for convenience and 8 of 13 (62%) due to ineffective TPO-RA response. Median duration of TPO-RA prior to switch was 3 months. All patients that switched due to convenience maintained platelet response, while 6 of 8 patients who switched due to ineffective TPO-RA response achieved CR, median platelet count increase is shown in Figure 2.

Conclusion: Our findings provide evidence that TPO-RA discontinuation or switching in patients with ITP can be achieved safely, and in most patients leading to sustained platelet responses.

Table 1: Patient characteristics

Characteristic	Total Cohort (n= 50)
Gender	
Female n(%)	25 (50)
Age commencing TPO-RA	
Mean (SD)	55 (21)
Ethnicity n (%)	
Caucasian	42(84)
Asian	6(12)
Arabic	0(0)
Other/Unknown	2(4)
Primary ITP n (%)	23(46)
Secondary ITP n (%)	27(54)
Median No. different previous ITP therapies (IQR)	2 (1-3)
Most common previous ITP therapies n (%)	
Splenectomy	18(36)
Corticosteroids	50 (100)
IVIG	50 (100)
Rituximab	17(34)
ITP duration at TPO-RA initiation	
Acute n (%)	5(10)
Persistent n (%)	6(12)
Chronic n (%)	39(78)
TPO-RA class n (%)	
Eltrombopag	(51)
Romiplostim	(50)
Avatrombopag	(29)
ITP response to TPO-RA n (%)	
CR	33 (66)
OR	12 (24)
NR	5 (10)
TPO-RA duration, months (IQR)	22.5 (7.5 – 45)
VTE during TPO-RA n (%)	10 (20)
TPO-RA duration at VTE, months (IQR)	7 (2 - 10)
Duration of follow up	59 (30 – 92)

Figure 1: Proportion of patients in SCROT after TPO-RA Discontinuation

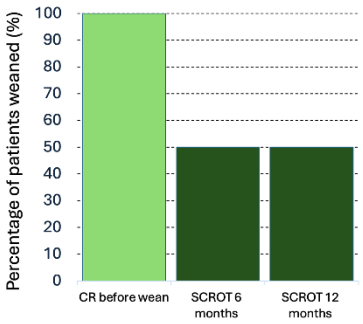
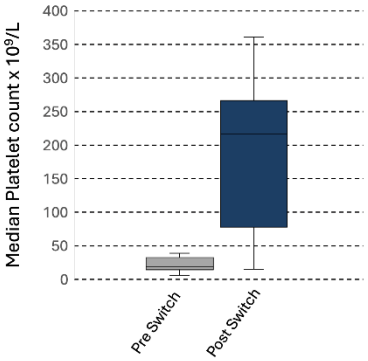


Figure 2: Median platelet count before and after TPO-RA Switch due to Ineffectiveness



1.Choi PYI, et al. Consensus guidelines for the management of adult immune thrombocytopenia in Australia and New Zealand. *Medical Journal of Australia* 2022, 216(1),43-52.

2. Guillet S, et al. Prolonged response after TPO-RA discontinuation in primary ITP: results of a prospective multicenter study. Blood. 2023 Jun 8;141(23):2867-2877

TO008

A study to compare two methods to measure VWF:FVIII binding capacity as screening tests for von Willebrand disease type 2N.

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Aim: Von Willebrand disease (VWD) type 2N is defined by impaired capacity of von Willebrand factor (VWF) to bind to Factor VIII (FVIII) and having recessive inheritance. It is important to measure VWF:FVIII Binding (VWF:FVIIIB) to correctly classify patients with low FVIII e.g. suspected VWD and Haemophilia A. This study compares a potential new method, the Stago Asserachrom VWF:FVIIIB Capacity ELISA (VWF:FVIIIB-S), to an established in-house ELISA (VWF:FVIIIB-IH).

Method: For the in-house ELISA, VWF:FVIIIB was read from a calibration line and reported as the ratio to VWF:antigen (VWF:FVIIIB-IH % ratio, normal range 60-160%). In the new ELISA the samples were tested after pre-dilution to 10 IU/dL VWF:Antigen and reported directly as VWF:FVIIIB-S % Binding Capacity (normal range 80-145%).

Results: Seventy-six patients from various categories were tested and there was acceptable correlation between the methods (Passing-Bablock $y = 0.89x-2.7$ and $R^2 = 0.70$). Results for 31/76 were normal by both methods and 25/76 were below the normal threshold by both. However 20/76 showed discrepancies in interpretation with 15/20 giving results below the method-specific normal cutoff by VWF:FVIIIB-S.

Eight patients had genetic or family confirmation as homozygous 2N or compound heterozygous: 8/8 had results <20% by VWF:FVIIIB-S and 5/8 by VWF:FVIIIB-IH. A further nine patients with no genetic information had VWF:FVIIIB-S <20%, with 6/9 <20% by the in-house method. In four known heterozygous 2N patients VWF:FVIIIB-S results were below normal (46-62%) whereas VWF:FVIIIB-IH results overlapped with normal (56-81%). Conversely, 7/24 patients with haemophilia A had VWF:FVIIIB-S below normal (51-79%) and only one of these was low by VWF:FVIIIB-IH (55%).

Conclusion: When screening for VWD 2N (homozygous or compound heterozygous) we found improved detection using the commercial ELISA compared to the in-house method. However results in the range for heterozygous 2N were not highly specific. All patients with reduced results would benefit from confirmation by genetic analysis.

TO009

Implementation of a novel Anticoagulation Stewardship program in an Australian Intensive Care Unit.

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Aim: Anticoagulants are a high risk medication in the Intensive Care Unit (ICU) due to multiple interacting patient risk factors for both bleeding and thromboembolism. These adverse events occur frequently and are often preventable. Antimicrobial Stewardship has been successfully implemented globally, and in the Australian ICU setting, and reduces preventable adverse events. We implemented an Anticoagulation Stewardship (ACS) program to determine feasibility and effectiveness of the intervention on anticoagulation prescribing in the ICU.

Method: The program consisted of once weekly multidisciplinary anticoagulation meetings between the facility's Haemostasis and Thrombosis team (Haematologist, Haematology registrar/s and VTE/Anticoagulation Stewardship pharmacist) and ICU team (Intensivist, ICU registrar/s and ICU pharmacist). All patients admitted in the ICU at a single metropolitan hospital in Sydney, NSW, at the time of the weekly ACS round, between February to April 2024 were included. Data was collected prospectively and summary statistics generated.

Results: Sixty-two patients were reviewed across eight meetings totalling 80 anticoagulation reviews. The largest proportion of reviews were conducted for patients with respiratory illnesses (19%, n=15). Mean meeting duration was 21.5 minutes and mean number of personnel present was 5. The median age of patients was 76 years with median ICU length of stay 4.4 days. Changes in prescription or recommendations occurred in 42.5% (34/80) of reviews, of which advice was accepted in 73.5% (25/34). Advice was generally accepted for complex bleeding and thrombosis and charting missing VTE prophylaxis. Advice which was not accepted was for recommendations to change, or dose adjust VTE prophylaxis (n= 6) and where changes were not required due to patient recovery (n=3). Eight continuing haematology consults resulted.

Conclusion: Anticoagulation stewardship is feasible to run in the ICU setting, promoting multidisciplinary collegiality resulting in management changes in a large proportion of patients. Further study is required to determine the impact on patient outcomes.

TO010

Platelet Biogenesis in Human health and disease.

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Aim: One hundred billion platelets (10^{11}) are produced in humans to maintain a platelet count of 150-400x10^9/L. How this process occurs in humans remains unresolved. Experiments in mice have visualised proplatelet formation, membrane budding and megakaryocyte fragmentation as potential mechanisms. We therefore aim to understand how platelets are produced in humans by quantifying the cellular and cytoskeletal processes of megakaryocytes, proplatelets, membrane buds, and platelets in archival human bone marrow trephine sections.

Method: FFPE bone marrow trephine sections at 10μm thickness were obtained from the Royal Melbourne Hospital research unit. These were staging bone marrow biopsies, devoid of any underlying haematological disorder with normal peripheral blood parameters. Sections underwent antigen retrieval and deparaffinisation. Primary and secondary antibodies to GP1bα, α-tubulin, and thrombopospondin-1 were applied. Immunofluorescence imaging was performed on confocal microscopy with data analysis using ImageJ. One-way ANOVA performed using R statistics on 100 megakaryocytes and 100 platelets from 5 separate human samples (n=20x5) showed no statistical difference ($p>0.05$) for megakaryocyte and platelet size indicating they can be used as a collective baseline comparative analysis with disease samples.

Results: Out of 100 megakaryocytes analysed across 5 human samples, 43% were budding megakaryocytes (Figure 1a), 19% formed proplatelet including beads of string appearance (transitional/early, Figure 1b and c) and 38% were non-budding or non-proplatelet-forming megakaryocytes (Figure 1d).

Conclusion: This study demonstrates how platelets are produced in humans. It shows that membrane budding occurs. Future research in the primary mechanism for platelet production in disease samples of Essential Thrombocythaemia (ET) and Immune Thrombocytopenic Purpura (ITP) is being undertaken to identify the primary mechanism of platelet production in human health and disease.

Figure 1a Proplatelet

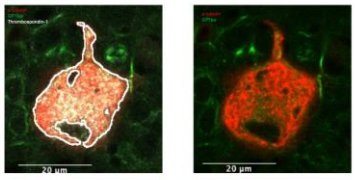


Figure 1c Budding megakaryocyte

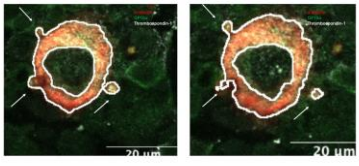


Figure 1b Transitional or early proplatelet

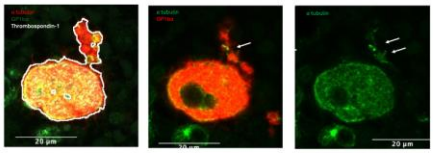
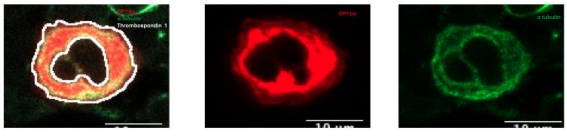


Figure 1d Non budding megakaryocyte



TO011

Plasma proteome profiling of patients with Vaccine Induced Immune Thrombotic Thrombocytopenia (VITT) reveals alterations in complement and platelet signalling pathways.

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Aim: VITT is a rare life-threatening complication associated with adenovirus vector-based COVID-19 vaccines, characterised by thrombosis, thrombocytopenia, elevated D-dimer and anti-platelet factor 4 antibodies. We investigated the proteomic changes in plasma from patients with VITT using two different platforms.

Method: Plasma from 10 VITT patients and 14 asymptomatic volunteers post-vaccination were analysed using targeted Proximity Extension Assay (PEA) technology (Inflammation and Cardiovascular III Target panels (Olink Proteomics) and unbiased (non-targeted) Mass Spectrometry (MS) proteomics (data-independent acquisition, library-free; timsTOFpro (Bruker)). The MS analysis included an additional 7 VITT samples and 14 controls. 10 patients with thrombosis post-vaccination but without VITT (VTE-noVITT) were also subjected to PEA analysis. Differential protein abundance between the groups was performed using, optimized pipelines for protein QC, reproducibility, imputation (MS-only) and statistics (*t*-test), as well as a separate, direct statistical evaluation (ANOVA) of proteins identified in the two methods (n=23).

Results: Targeted (PEA) and untargeted (MS) plasma proteomics provided complementary results. When evaluating each method independently, 47 proteins with a primary difference in the VITT group were identified using PEA (44 upregulated, 3 downregulated). MS identified 53 significant protein differences between VITT vs control. Trend-analyses of differentially abundant proteins in MS highlighted significant Reactome terms in complement cascade, platelet activation, signalling and platelet aggregation in VITT samples.

When both were evaluated in their respective statistical pipelines, 4 proteins of 181 in the PEA dataset were also identified in the 336 plasma proteins in MS which met the standard cut-offs for QC and reproducibility.

Conclusion: VITT is characterised by both unique and shared proteomic changes compared to VTE-noVITT and control samples. MS technology enabled identification of the reactome pathways involved in VITT while PEA technology facilitated a sensitive evaluation of specific protein changes within these pathways. Further analyses are underway to identify additional biochemical pathways modulated in patients with VITT.

TO012

The role of Endoplasmic Reticulum stress in Platelet production

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Aim: Platelet production from megakaryocytes is a highly regulated process and involves megakaryocyte maturation and proplatelet formation. Thiol isomerases (such as ERp57 and ERp5) fold proteins in the megakaryocyte endoplasmic reticulum (ER) and regulate the ER stress response. The response to ER stress is a physiological adaptive process by which the cell senses and fine tunes protein production in response to external stimuli. Although this process has been suggested to mediate platelet production in cell models, its role in thrombopoiesis *in vivo* is incompletely understood. The aim of this study is to understand the role of ER stress in thrombopoiesis with a focus on ERp5 and ERp57.

Method: We utilized mice with megakaryocytes deficient in ER proteins ERp5 and ERp57 (conditional knockout, CKO). Platelet production was measured by flow cytometry following platelet depletion assays with injection of R300 (anti-GPIbα) antibody. We measured proplatelet formation by culture of bone marrow explants. We investigated for ER stress by immunofluorescence staining of megakaryocytes for stress markers. We measured calcium mobilization using calcium dyes (Fura-2 and Cal-520-AM).

Results: Megakaryocytes deficient in either ERp5 or ERp57 show defects in proplatelet formation (**Figure 1**). ERp57 deficient megakaryocytes had shortened proplatelet extensions whereas ERp5 deficient megakaryocytes have decreased proplatelet formation. Platelet recovery occurred more rapidly after depletion in ERp5 and ERp57 CKO animals. ERp5 deficient megakaryocytes had evidence of activation of the Inositol-requiring enzyme type 1 (IRE1) ER stress pathway. Both ERp5 and ERp57 deficient platelets showed increased calcium mobilization in response to chemical induction of ER stress.

Conclusion: Our results suggest that ER proteins ERp5 and ERp57 play a role in thrombopoiesis by controlling ER stress responses of maturing megakaryocytes. Further studies are required to determine whether ERp57 and ERp5 inhibitors may have a role in decreasing excess platelet production in myeloproliferative disorders.

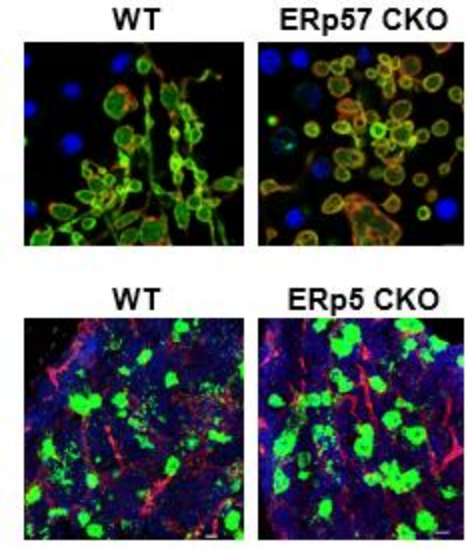

Figure 1. Shortened proplatelet extensions in ERp57 deficient megakaryocytes (ERp57 CKO) compared to wildtype (upper panels). GP1bα highlighted in green, SiR-tubulin in red; nuclei in blue. Decreased number of megakaryocyte fragments in the bone marrow of mice with ERp5 deficient megakaryocytes (ERp5 CKO) (bottom panels); GP1bα highlighted in green, laminin in red, nuclei in blue.

TO013

Final analysis of the Prospective Cohort Study on patients with a Haematological malignancy on Anticoagulants who develop Thrombocytopaenia (HAT Study).

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[1]Fiona Stanley Hospital, [2]Sir Charles Gairdner Hospital, [3]Royal Perth Hospital, [4]Pathwest

Background: Anticoagulation medications pose an increased bleeding risk in patients with thrombocytopenia in the setting of haematological malignancies which is balanced against an increased risk of venous thromboembolism.

Aim: To determine the rate of bleeding and thrombosis that occurs with an anticoagulant dose adjustment protocol based on thrombocytopaenia.

Method: An observational prospective cohort study of the ISTH risk stratified anticoagulation adjustment protocol for thrombocytopaenia and the European Society of Cardiology guidelines for the management of Atrial Fibrillation (Figure 1.). The inclusion criteria were age >18 with a haematological malignancy on anticoagulation for Venous Thromboembolism (VTE) or Atrial Fibrillation (AF) with thrombocytopaenia <100 $x10^9$/L.

Results: Analysis of 41 patients enrolled during the initial period (June 2022 until June 2024) with 52 instances of thrombocytopaenia. The protocol was followed in 31 instances (59.6%)

At 30 days there were one episode of arterial thromboemboli in all patients. There was one episode of venous thromboemboli (VTE) (3%), two episodes of major bleeding (6%) and two episodes of clinically relevant non-major bleeding (CRNMB) (6%) in the group that followed the protocol compared to one episodes of VTE (5%), two instances of major bleeding (10%) and three instances of CRNMB (14%) in those with protocol deviation. All four instances of major bleeding that occurred were considered not attributable to anticoagulation.

The median platelet transfusion amongst all patients was 0 (0, 3) with no difference amongst variation and protocol compliant groups. The median red cell transfusions amongst all patients was 0 (0, 3) equal across variation and protocol compliant groups.

Conclusion: Our ISTH/ESC guideline-based risk stratified protocol for anticoagulation management in thrombocytopaenic patients showed low rates of bleeding and clotting supporting the use of this protocol in this high-risk group of patients.

Figure 1. Hospital Anticoagulation Thrombocytopaenia Protocol

Atrial Fibrillation	Platelet count <50	Stop anticoagulation
	Platelet count 50-100	Prophylactic dose anticoagulation
	Platelet count >100	Treatment (full) dose anticoagulation
High Risk VTE during 1st Month	Platelet count <50	Transfuse platelets to keep count over 50 and continue treatment dose anticoagulation
	Platelet count >50	Treatment dose anticoagulation
Low Risk VTE or High risk after 1st Month	Platelet count <25	Stop anticoagulation
	Platelet count 25-50	Prophylactic dose anticoagulation

	Platelet count >50	Treatment (full) dose anticoagulation
Prophylactic Dose Anticoagulation	40mg/d enoxaparin	
	2.5mg bd apixaban	
	10mg/d rivaroxaban	
Treatment Dose Anticoagulation	1mg/kg bd or 1.5 mg/kg enoxaparin	
	5mg bd apixaban	
	20mg/d rivaroxaban	
***High Risk VTE: Symptomatic segmental PE, Large proximal DVT, presence of known concurrent thrombophilia (Protein C, S, Antithrombin deficiency, homozygous Factor V Leiden or prothrombin gene mutation)/ antiphospholipid syndrome, recurrent/ progressive thrombosis**		
***Low Risk VTE: Below knee DVT, asymptomatic segmental PE, subsegmental PE, central venous access line associated VTE**		

TO014

Successful cardiac surgery in 3 patients with Haemophilia A on Emicizumab

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Over the last two decades there has been significant advances in the care and treatment of persons with haemophilia (PWH). With life expectancy now matching persons without haemophilia in developed countries. PWH are now developing age related complications such as cardiovascular disease requiring intervention. Emicizumab is a monoclonal bispecific antibody that mimics the function of Factor VIII and represents one of the major advances in the management of PWH. The introduction of emicizumab however has presented several laboratory challenges due to its interferences with coagulation assays.

Emicizumab interferes with active partial thromboplastin time (aPTT) by falsely shortening it, and there are conflicting reports in the literature as to how much emicizumab interferes with ACT measurement. In cardiac surgery, ACT monitoring to guide heparin dosing and protamine reversal is the current standard of care. Given the interferences due to emicizumab with standard monitoring used in cardiac surgery, our centre utilised Anti-Xa monitoring of heparin, similar to what is used for patients with antiphospholipid antibody syndrome undergoing cardiac surgery.

We describe three patients with Hemophilia A on emicizumab prophylaxis who have undergone successful cardiac surgery with factor VIII replacement without any bleeding or thrombotic complications with the use of Anti-Xa monitoring of heparin and bovine chromogenic monitoring of FVIII levels. Two patients underwent off-pump coronary artery bypass graft surgery (OPCABG) and one patient a PEARS (personalized eternal aortic root support) surgery. Meticulous care coordination between the haemophilia treatment centre, cardiothoracic surgeons, anaesthetists, intensivists, transfusion nurses, the coagulation laboratory and pharmacy staff is necessary to undertake surgery of this nature in this subgroup of haemophilia patients.

To our knowledge this is the first case series of patients with haemophilia A on emicizumab who have successfully undergone cardiac surgery.
No conflicts of interest to disclose.

TO015

Heparin-induced Thrombocytopenia (HIT) immune complexes induce Endothelial Thromboinflammation

Qiyu S[1], Subah Z[1], Fenwick J[1], Dupuy A[1], Passam F[1], Perdomo J[1]
[1]Charles Perkins Centre, University of Sydney

Aim: Immunothrombosis in heparin-induced thrombocytopenia (HIT) is initiated by anti-platelet factor 4 (PF4) antibodies that form immune complexes with endogenous PF4 and heparin. The HIT immune complex activates platelets and neutrophils via Fc receptor interaction, resulting in thrombocytopenia, venous and arterial thrombosis and a hypercoagulable state. However, the role of HIT immune complexes in endothelial activation is yet to fully described. Here we aimed to investigate the direct effect of HIT immune complex on endothelial cells and its significance in thrombus formation in endothelialised biochips (Endo-chips) mirroring physiological conditions.

Method: Association of HIT immune complexes with HUVECs was assessed by confocal microscopy using labelled HIT antibody and PF4. Endo-chips were prepared by coating polydimethlysiloxane chip microchannels with human umbilical vein endothelial cells (HUVEC). Resting or activated (10 ng/ml TNF-α) HUVECs were incubated with HIT immune complexes (HIT antibody, PF4 and heparin at 37^{o}C, 60 min. N=4). HIT immune complex-primed Endo-chips were washed to remove free complexes and perfused at a venous shear rate of 100 s^{-1} with recalcified anti-CD9-reactive donors' blood (labelled with fluorescent antibodies to detect platelets, neutrophils and fibrin). Thrombus formation was imaged for 15 min by confocal microscopy and quantitated using ImageJ software. Statistics: one-way ANOVA with Dunnett's multiple comparison test.

Results: HIT immune complexes interact with endothelial cells. Stimulation of Endo-chips with HIT immune complexes resulted in marked increases in fibrin deposition, platelet accumulation and neutrophil adhesion in TNF-α primed cells upon perfusion of healthy blood. This level of thrombosis was not observed in Endo-chips stimulated with normal IgG in the presence of PF4 and heparin (Figure 1).

Conclusion: Our Endo-chip model demonstrates the capacity of HIT immune complexes to directly interact and activate endothelial cells and promote a pro-thrombotic environment. This model allows for detailed characterization of endothelial involvement in the immunothrombotic process of HIT and the assessment of new interventions.

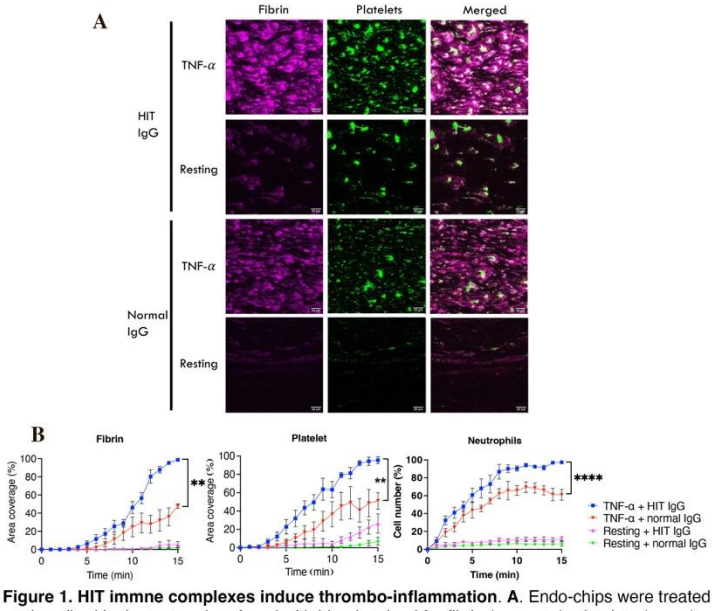

Figure 1. HIT immne complexes induce thrombo-inflammation. **A**. Endo-chips were treated as described in the text and perfused with blood stained for fibrin (magenta), platelets (green) and neutrophils. Confocal images of fibrin and platelets are shown. Scale bar: 20 um. **B**. Normalised fibrin, platelet and neutrophil accumulation over HUVECs with or without TNF-a stimulation, pefused 15 min with healthy blood. Mean ± SD. **P<0.01; ***P<0.001

TO016

Utility of panel-based genetic sequencing in von Willebrand disease

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Aim: Von Willebrand disease (vWD) is the most prevalent inherited bleeding disorder with Alfred Health (AH) overseeing care of over 400 patients with VWD. Next-generation sequencing (NGS) is a useful modality in the diagnosis of this condition as it allows analysis of the entirety of the large *VWF* gene. This aids subtyping and allows concomitant assessment of other genes to differentiate genocopies. Genetic sequencing for bleeding disorders has been performed at AH since 2020 using whole-exome sequencing (WES) with analysis restricted to a relevant 93-gene panel.

Method: We conducted a single-centre retrospective descriptive study of patients with vWD who had panel-based WES performed at AH. Patients were tested at clinician discretion, focusing on type 2 VWD. Data collected on *VWF* variants, concomitant variants in other genes on the panel and laboratory testing for vWD including antigenic and functional measures, platelet count, FVIII activity and blood group. Clinical impact from the sequencing result was undertaken.

Results: We identified 13 adult patients (10 kindreds) who had panel-based WES for vWD. In 10/13 (77%) patients, the sequencing results impacted clinical management (Table 1). Notably, two patients were changed from a type 2A to a type 2B subtype, which affects ddAVP use. A female of child-bearing age initially suspected of type 2N was a carrier for both a *F8* mutation and a quantitative vWD mutation, necessitating genetic counselling. Kindred ‘k’ had a complex genotype with three different *VWF* mutations in various combinations resulting in compound heterozygous severe type 1 vWD in two siblings (k-1 and k-2), a mild low vWF phenotype in the mother (k-3) and a combined type 2B with a significant quantitative vWF reduction in the father (k-4).

Conclusion: Panel-based sequencing for vWD in a well-selected cohort is highly clinically relevant in differentiating genocopies, subtyping and informing genetic counselling.

TO017

Management of bleeding disorders in pregnant women: A single tertiary-centre experience

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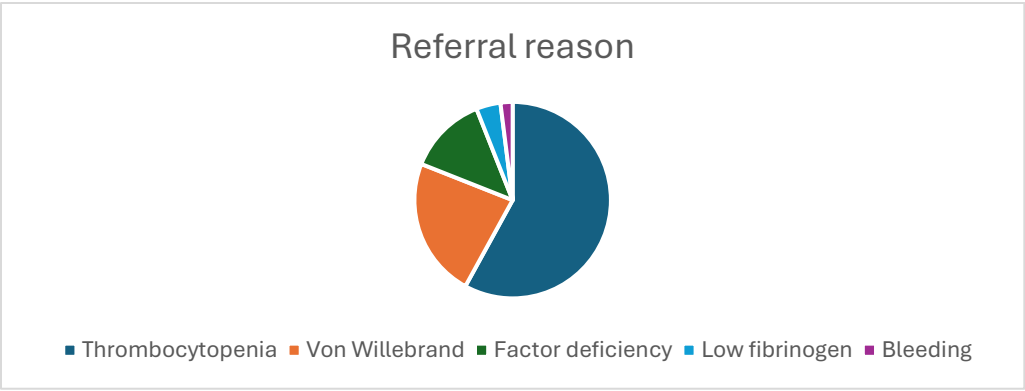
Background: Women with bleeding disorders face significant haemostatic challenges during pregnancy and childbirth. Management of such patients is not well-characterized, with little high-quality data in the literature reporting outcomes and management.

Aim: Identify bleeding outcomes and facilitation of birth preferences in management of patients with bleeding disorders in pregnancy.
Methods: Single-centre audit of consecutive referrals of pregnant or peri-partum women with bleeding, thrombocytopenia, or bleeding disorder, identified March 2023-March 2024.

Results: 53 women were referred. Referral reason included thrombocytopenia 58% (9% congenital), Von Willebrand 23%, factor deficiencies 13%, low fibrinogen 4% and bleeding 2%. 5/53 referrals were post-partum and 48/53 antenatally. Median gestation at initial haematology consultation 30 weeks (range 6-39), 19% ≥36 weeks. 23% required haemostatic optimization with steroids, immunoglobulin (IVIG), tranexamic acid (TXA), biostate, FactorXI and/or fibrinogen.
So far 45/53 have delivered with 26 normal vaginal delivery (NVD), 10 required induction and 12 caesarean section (CS) (5 emergency). Overall, 66% women were able to have neuraxial anaesthesia.

10/45 primary post-partum haemorrhage (PPH), 80% obstetric-related and 20% thrombocytopenia-related despite support. 1 PPH was post CS, 9 post NVD with median blood loss 750mls (range 600-1800mls) and average haemoglobin drop 15g/dL. No secondary PPH or other bleeding occurred.

Paired antenatal birth preferences and outcomes showed 62% had their birth preference facilitated, with 36% requiring support to achieve this. Of those without birth preferences facilitated, 47% were due to obstetric indications (including 5 emergency CS, 3 supported), 33% of patients who wanted epidural were not facilitated (40% for haematological contraindication).
Conclusion: PPH due to obstetric complications remains a significant risk despite optimisation of bleeding disorders. Bleeding risk is an important consideration for inherited and acquired bleeding disorders in the peripartum. Early referral supports planning for intervention. Birth preferences should be facilitated where possible and is often achievable with intervention if required.



TO018

Updating the algorithm: Evolution of Lupus Anticoagulant diagnosis in the days of the DOAC.

Stanton T[1], Coleman R[1], Adams R[1], Keng T[1], Vanderham A[1]
[1]Sullivan Nicolaides Pathology

The introduction of direct oral anticoagulants (DOACs) has complicated laboratory testing for thrombosis risk assessment. Clinicians are particularly aware of their interference in the diagnosis of Lupus Anticoagulant and would like to proceed with testing without having to pause DOAC therapy.

At the 2019 Blood conference, Anneke Vanderham discussed the hurdles DOAC's add to Lupus Anticoagulant diagnosis, and outlined a study done in the laboratory in order to assess their impact. A tentative strategy was presented to navigate these hurdles to provide appropriate investigation of potential Lupus Anticogulant patients(1). This update comes five years after our initial presentation, outlining the laboratory's experiences, the challenges overcome, and our current Lupus Anticoagulant diagnostic algorithm.

This update will examine our laboratory analysis and validation of DOAC Stop. This includes DOAC Stop's impact on commonly used anticoagulants. A range of routine and special haemostasis assays were assessed pre and post-DOAC Stop treatment.

The findings of this formed the basis for the laboratory's updated testing algorithm for Lupus Anticoagulant. The new process, which includes a new reporting format, is easy for staff to follow and delivers accurate identification of patients with Lupus Anticoagulant who are receiving DOAC therapy. It is the hope that with this update, clincians and laboratories alike will benefit from our experiences navigating Lupus Anticoagulant testing where DOACs have become the anticoagulant of choice.

References:

1. Vanderham A, Coleman R. Viper venom and algorithms: Lupus Anticoagulant Diagnosis in the days of the DOAC. [abstract]. In: BLOOD 2019 Abstract Book 2019 Scientific Meeting. Blood 2019: 20-23 October 2019; Perth, Western Australia. Available from: https://www.hsanz.org.au/resources/Documents/Blood%20Abstract%20Supplement/Blood%202019%20abstract%20supplement.pdf

TO019

Single Dilution one stage factor levels with Reflex Multi-dilution testing – Feasibility, diagnostic accuracy, and cost-effectiveness of a change in Coagulation Testing Paradigm

McKeague S[1], Stanton T[1], Coleman R[1], Adams R[1], Harvey Y[1], Keng T[1]
[1]Sullivan Nicolaides Pathology

Aim: One stage coagulation factor assays are traditionally performed using multi dilution analysis (MDA) to assess for the presence of non-parallelism (NP). Despite being widely accepted, the clinical benefit and cost effectiveness of this approach is unknown.
This study aimed to:

(i) Determine the frequency, causes and clinical impact of NP in routine MDA
(ii) Determine frequency of NP in presence of known lupus anticoagulant (LAC) or rivaroxaban use and assess relationship to LAC strength and rivaroxaban level
(iii) Develop a model of single dilution testing with reflex multi-dilution testing that maximises diagnostic accuracy and financial efficiency.

Method: Routine factor levels performed with 3 level MDA over a period of 56 days in a single laboratory were retrospectively reviewed. NP was defined by >20% difference between first (1/10) and third (1/40) dilution. Samples with known lupus anticoagulant (LAC) positivity or rivaroxaban use were prospectively collected and tested for APTT based factor levels (VIII, IX, XI, XII). An optimal pathway for reflex MDA was developed by examining different thresholds for MDA and their effect on diagnostic accuracy and cost saving.

Results: Amongst 1324 factor levels, NP is rare (5.3%), occurring most frequently in in Factor XI assays (11%) and least frequently in Factor IX assays (0.7%). When relying only on clinical information and routine ancillary testing, the cause is mostly not identifiable (43%). The most common identifiable causes are direct-acting oral anticoagulant (DOAC) use (33%) and LAC (8.5%). The degree of non-parallelism is strongly related to rivaroxaban concentration measured with Anti-Xa (Pearson R^2 0.8703, $p = 0.000$) but not to measures of LAC strength. A model that only performs MDA on levels outside of 0.6-1.8 IU/dL retains diagnostic accuracy, reduces the proportion of samples requiring MDA to 20.9% and is estimated to save~$23,000 AUD annually.

Conclusion: Single dilution factor levels with reflex multi-dilution testing represents a feasible, accurate and cost-effective alternative to the traditional paradigm of universal MDA.

TO020

Metabolomic Signatures as Predictors of Bleeding in Anticoagulant Therapy

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Aim: Anticoagulation is commonly prescribed for people with thromboembolic diseases, including venous thromboembolism and atrial fibrillation. However, 1 in 5 people will develop a bleeding event from anticoagulation. Models, such as the HAS-BLED score, have been developed to predict for in bleeding risk but these models have limitations in their predictive accuracy, and do not account for individual metabolic variations. New technologies such as metabolomics offers a promising avenue to identify specific biomarkers associated with bleeding risk in people taking anticoagulants.

Method: We performed a cohort study, utilising the UK Biobank (UKB), a population-based dataset containing health data from approximately 500 000 individuals. The UKB has data linkage to hospital inpatient data (ICD-10 codes), medication prescribing, and death registry. We evaluated all patients who were prescribed an anticoagulant (rivaroxaban, apixaban or warfarin) from January 2013 – July 2023, and assessed for bleeding events within 3 months of anticoagulant prescription. We then analysed metabolomic data, and used multivariable logistic regression for the outcome of bleeding. We report odds ratios (OR) with 95% confidence intervals (CI).

Results: Overall, 4870 patients were included in the analysis. The demographic data is shown in Table 1. After adjusting for demographic factors, including age, sex, race, body mass index, medical comorbidities and lipid-lowering medications, we found that several metabolites were associated with anticoagulant-bleeding, including LDL-cholesterol (OR 0.51, 95% CI 0.41 – 0.64) and sphingomyelins (OR 0.50, 95% CI 0.4 – 0.64). Both these metabolites showed an inverse correlation with bleeding.

Conclusion: After adjustment for known risk factors for bleeding, several metabolites remain significantly associated with anticoagulant-related bleeding. This study provides new insights into how an altered metabolome contributes to risk of bleeding, and can be used to improve current strategies to predict bleeding risk.

Table 1: Clinical Characteristics of Study Participants

	Bleeding events n = 1019	**No bleeding events n = 3851**
Age (+/- SD)	68.2 (6.3)	67.7 (+/- 6.6)
Gender, (%)		
Female	391 (38.4)	1314 (34.1)
Male	628 (61.6)	2537 (65.9)
BMI (+/- SD)	30.2 (6.0)	29.1 (5.1)
Anticoagulation, (%)		
Warfarin,	812 (79.7)	2902 (75.4)
Rivaroxaban	129 (12.7)	594 (15.4)
Apixaban	78 (7.6)	355 (9.2)
Medical history (%)		
Hypertension	557 (54.7)	1685 (43.7)
Cardiovascular disease	252 (24.7)	569 (14.7)
Stroke	83 (8.1)	226 (5.9)
Diabetes	140 (13.7)	371 (9.6)

TO021

Antiphospholipid Syndrome-related Ischaemic Stroke is associated with Complement Activation and Platelet Hyperreactivity

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[1]Concord Repatriation General Hospital, [2]ANZAC Research Institute, University of Sydney, [3]University College London, [4]2nd Propedeutic Department of Internal Medicine, Hippokration Hospital, [5]University College London Hospitals NHS Foundation Trust

Aim: Antiphospholipid syndrome (APS)-related stroke has high rates of recurrent thrombosis despite treatment. This study aimed to assess complement activation in APS-related stroke to guide research into improving outcomes.

Method: Patients with APS and imaging-proven brain ischemia were recruited (n=71), with control cohorts of ischemic stroke patients without antiphospholipid antibodies (n=40) and healthy donors (n=40). C3a-desArg (C3a), C5a-desArg (C5a), sC5b-9 and Bb fragment were measured as common and alternative complement pathway activation markers. Complement-induced cell death was measured by the modified Ham (mHam) test: patient serum was added to PIGA-null TF-1 cells (paroxysmal nocturnal haemoglobinuria cell line) lacking cell surface complement regulators; ≥20% cell-death is considered positive. Patient plasma was added to healthy donor whole blood with procoagulant platelet (annexin-V+/P-selectin+) response measured (flow cytometry), assessing the absolute change in proportion of thrombin-stimulated (2U/mL) platelets compared to autologous plasma.

Results: Healthy controls were younger (median 36 years) than the patient cohorts (median >50 years), however, there was no correlation between age and levels of complement activation. C3a, sC5b-9 and Bb fragment were significantly increased in APS patients compared to stroke and healthy controls. C3a was most prominent (Figure 1A). The mHam test was positive more frequently with higher-risk APS (triple antibody positivity/recurrent thrombosis, n=30): 60%, compared to other, lower-risk, APS patients: 37% (n=41), stroke (13%) and healthy controls (18%, $p<0.0001$). C3a levels correlated weakly with complement-induced cell death ($r=0.22$, $p=0.01$). Plasma samples from APS patients (n=14) induced formation of far more procoagulant platelets in thrombin-stimulated healthy donor whole blood compared to healthy control cohort plasma (n=6): median 24.2% (interquartile range, IQR, 7.6-38.5%), and 0% (IQR -6.8-5%, $p=0.002$)(Figure 1B). C3a significantly (positively) correlated with the degree of platelet reactivity; $r=0.64$ ($p=0.002$)(Figure 1C).

Conclusion: Increased complement activation, particularly C3a, is evident in APS-related ischemic stroke, correlating with APS-plasma induced platelet hyperreactivity.

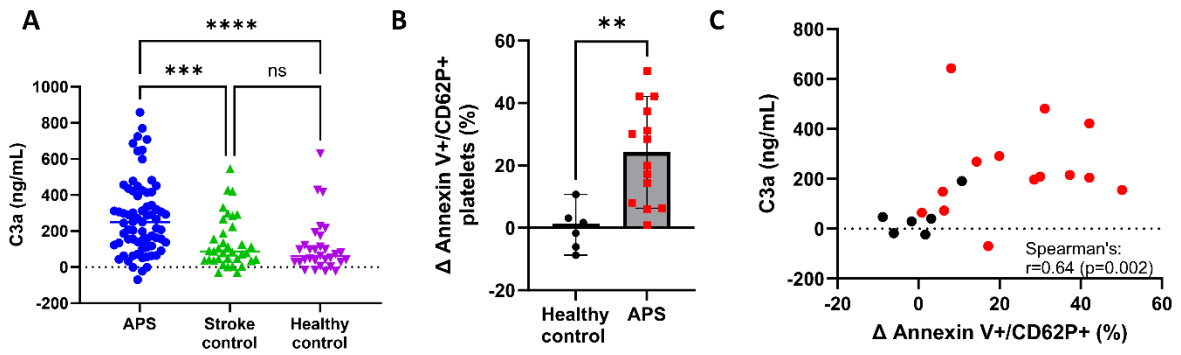

Figure 1. Complement activation is evident in antiphospholipid syndrome (APS)-related stroke and correlates with platelet hyperreactivity. (A) Complement marker C3a-desArg (C3a) measured by commercial ELISA (MicroVue, Quidel) in EDTA plasma from APS patients (n=71) and controls (n=40 each). (B) Procoagulant platelet (annexin V+/P-selectin+) response was measured by flow cytometry after addition of APS (n=14) or healthy control (n=6) plasma and thrombin 2U/mL to healthy donor whole blood. Absolute change in procoagulant platelet proportion compared to addition of autologous plasma is shown. Median and 95% confidence interval shown. Comparison of platelet flow cytometry results and C3a results; red denotes APS patients, black: healthy controls. **p<0.01, ***p<0.001, ****p<0.0001, ns – not significant

TO022

RNA Sequencing identifies differential Transcriptomic Signatures in Platelet subpopulations and the proximal role of large GTPase dynamin in Procoagulant Platelet Formation

Tohidi-Esfahani I[1,2], Whittaker S[2], Lee C[2], Liang H[2], Kaur A[5], Lai K[2], Kockx M[2], Kritharides L[2,3], Gardiner E[5], Larance M[4], Chen V[1,2]

[1]Haematology Department, Concord Repatriation General Hospital, [2]ANZAC Research Institute, University of Sydney, [3]Cardiology Department, Concord Repatriation General Hospital, [4]Charles Perkins Centre, University of Sydney, [5]John Curtin School of Medical Research, Division of Genome Science and Cancer, The Australian National University

Aim: The procoagulant platelet subpopulation (PRO) is more prominent in pathological thrombosis than haemostasis. To identify specific targets for PRO, this study evaluated unique pathways through RNA-sequencing that drive platelets to become procoagulant following activation.

Method: Healthy donor (n=6) platelets were separated into PRO ($GSAO^+$/P-$selectin^+$) and activated non-procoagulant (ANP, $GSAO^-$/P-$selectin^+$) subpopulations (Hua, *Blood* 2015), after thrombin 2U/mL plus crosslinked collagen-related peptide 4µg/mL stimulation, using flow cytometry cell sorting. RNA was extracted, sequenced, with differentially expressed (DE, fold-change >/=2, false discovery rate/FDR <0.05) genes input into Ingenuity Pathway Analysis (IPA). qPCR and functional validation were performed for candidate gene, dynamin 1. Procoagulant platelet markers were assessed by flow cytometry and confocal microscopy with inhibitors MiTMAB and dynasore.

Results: 1024 DE genes in PRO were identified (Figure 1A). IPA identified integrin signalling, endocytosis and actin cytoskeleton-related pathways as highly enriched. Dynamin 1, involved in both endocytosis and actin rearrangement, was 4.9-fold increased (FDR<0.05), confirmed by qPCR (3.4-fold increased, p<0.01, n=10). Dynamin inhibition by MiTMAB dose-dependently reduced agonist-induced PRO formation by flow cytometry, while >97% of platelets remained activated (P-$selectin^+$)(Figure 1B). By confocal microscopy, activation-induced procoagulant "balloon" formation in platelets was also inhibited by MiTMAB (vehicle 21.6±0.7%, MiTMAB 1.7±0.3%, p=0.0003). Alternative dynamin inhibitor, dynasore, confirmed dose-dependent reduction in procoagulant platelet formation (n=6, p<0.0001). Dynamin appeared proximal to key processes in PRO formation. MiTMAB resulted in reduction in platelets with thrombin-induced supramaximal calcium levels (Fluo-$5N^+$, vehicle 8.5±1.3%, MiTMAB 1.2±1.0%, p=0.004) and mitochondrial membrane potential loss ($TMRE^-$, vehicle 20.8±2.2%, MiTMAB 4.7±3.1%, p<0.01).

Conclusion: Transcriptional profiling of PRO reveals a distinct subpopulation and identifies dynamin I as an important driver in their formation. Complete inhibition of PRO with relative preservation of platelet activation with dynamin inhibition suggests transcriptional differences are involved in determination of functionally distinct activated platelet subpopulations, highlighting ways for targeting specific subpopulations.

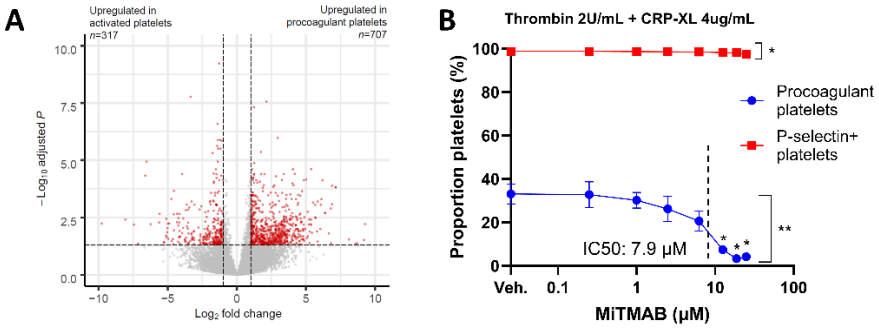

Figure 1. The procoagulant platelet subpopulation has a distinct transcriptome, functionally validated by dynamin inhibition with MiTMAB. (A) Volcano plot of differential gene expression analysis (DESeq2) of the procoagulant platelet subpopulation and activated, non-procoagulant platelets RNA from healthy donors (n=6). Vertical dotted lines represent $\log_2$ fold change of -1 and 1, horizontal dotted line: Benjamini-Hochberg adjusted p-value (false discovery rate) of 0.05. (B) Stimulated healthy donor washed platelets were treated with increasing concentrations of dynamin inhibitor, MiTMAB (n=3, repeated measures ANOVA). CRP-XL - crosslinked collagen-related peptide, *p<0.05, **p<0.01

NURSING Oral Presentations

NO001

A tissue typing dilemma

Cryer J[1]
[1]St George Hospital

Aim: To ensure match sibling donor transplant

Method: Many haematological diseases require Allogenic stem cell transplant as a curative treatment.

In an institution where allogenic transplant is not performed, referral and ongoing open communication with the transplant centre, Lifeblood Redcross and the Australian bone marrow donor register is essential.

At diagnosis allogeneic transplant is indicated and information is required. This begins with tissue typing of siblings.

In an ethnically diverse community finding a donor can be challenging especially when the sibling may live overseas.

This presentation will describe a case study of a gentleman diagnosed with Acute myeloid leukaemia who migrated to Australia who is originally from Myanmar, where his only sibling lives.

This presentation will describe how tissue typing samples were gained from a country under Military rule where freedom communication and travel is almost impossible. A country where contact with developed nations for example Australia is treated with suspicion.
When his sister is identified as a match the dilemma then becomes how will he receive his siblings stem cells.

Results: successful collection of sibling donor

Conclusion: Positive outcome from allogenic stem cell transplant

NO002

Elevating nursing practice: integrating a clinical nurse specialist within a specialist nursing model of care in the myeloma and autograft service

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Introduction: The Myeloma and Autograft Service at the Peter MacCallum Cancer Centre provides comprehensive care for patients diagnosed with multiple myeloma (MM) and plasma cell dyscrasias. To meet the demands of increasing patient needs and consumer expectations a Clinical Nurse Specialist (CNS) role was incorporated into an existing specialist nursing model of care (MoC).

Aim: This paper describes the integration of a CNS role within the specialist nursing MoC in clinical haematology.

Method: In collaboration with the Advanced Nursing Practice Committee, the scope of practice for the CNS was examined. Following an evaluation process, a decision was made to embed the CNS role within the specialist nursing MoC, where the CNS works under the supervision of the Clinical Nurse Consultant (CNC). The evaluation of this role integration will include established quality improvement projects for the service, patients enrolled in the Myeloma and Related Disease Registry (MRDR), and patients enrolled in the nurse-led MM survivorship clinic.

Outcome: The CNS has achieved significant outcomes including the establishment of standardised documentation for the home-based self-administration of subcutaneous treatments program, enhancing clinical documentation and reducing clinical risk. Additionally, the CNS has assisted in increasing data input to the MRDR, bringing the total number of patients enrolled in the registry to 400. Moreover, the CNS role has been integral in assisting the CNCs in establishing a novel nurse-led MM survivorship clinic, delivering with over 40 survivorship care plans.

Conclusion: After 12 months of implementation, the CNS role has proven to be a valuable addition to the specialist nursing MoC in the myeloma and autograft service. The integration of CNS creates capacity to implement new services and embark on quality improvement projects to optimise patient experience. This role should be incorporated into other specialist nursing MoC, establishing a novel CNS that elevates the standard of care.

NO003

Home-Based monitoring of patients following consolidation chemotherapy for Acute Leukaemia using wearable technology

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Aim: To assess the safety of an at-home based model of care for patients receiving chemotherapy for acute leukaemia using wearable technology.

The primary outcome measure is the composite endpoint of the proportion of consolidation cycles whereby a patient develops severe sepsis at initial presentation with fever, requires intensive care admission or dies within 30 days of commencing consolidation chemotherapy.

The secondary outcome measures, days spent per patient as an outpatient per cycle of chemotherapy; time from development of fever to delivery of IV antibiotics; patient satisfaction.

Method: This is a prospective, single-arm cohort design of patients undergoing consolidation chemotherapy for acute leukaemia.

Patients will undergo chemotherapy consolidation as per standard of care for the treatment of acute leukaemia. Consented patients meeting all inclusion and none of the exclusion criteria will commence participation in this study from the time of developing a peripheral blood neutrophil count of less than 0.5x10^9/L. From this point in time, the home-based monitoring program will commence using wearable technology called the Biobeat.

Results: The home-based neutropenic monitoring program for patients with Acute Leukaemia was found to be safe, feasible, effective, and highly satisfactory. A median of five bed days were saved per monitoring cycle, with 50 bed days saved in total. No participants experienced adverse outcomes or near miss events whilst being monitored at home. All participants reported high levels of satisfaction in the home monitoring program, particularly regarding the ability to have care delivered in the home setting which improved patient experience compared to ward-based management.

Conclusion: Demonstration that a home-based neutropenic monitoring program for patients undergoing chemotherapy for acute leukaemia is safe, feasible, and is associated with high levels of patient satisfaction and is able to reduce the frequency of inpatient hospitalisation.

NO004

Kikuchi-Fujimoto disease in a young African patient with Sickle Cell disease

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Kikuchi-Fujimoto disease (KFD), a necrotising histiocytic lymphadenitis is a rare, benign condition, characterised by lymphadenopathy and fever. Symptoms are suspicious for lymphoma and diagnosis is usually made after extensive workup.[1,2,3]

Case study: We present a case of a young African woman with Sickle cell disease presenting with a prolonged course of unexplained fever complicated by anaemia and reticulocytopenia.

Patient X, presents with a one-week history of lethargy, fever and anaemia in the context of a recent increase in Hydroxyurea dose to improve HbF induction. Initial bloods revealed Hb 61, Plts 92, WCC 5.6, Neuts 3.9 with normal haematinics and mildly increased LDH, Ferritin & CRP. Differential diagnoses include aplastic crisis, myelosuppression or infection.[1,2]

Over the following six weeks blood tests show a fluctuating picture of inflammation with ongoing fevers (>38°C - 40°C). Screening for extended respiratory panel, blood cultures, virology, Parvovirus and TB were all negative. Bone marrow biopsy demonstrated adequate trilineage haemopoiesis. After four weeks a palpable cervical lymph node was identified and subsequent PET showed diffuse lymphadenopathy. Lymph node biopsy revealed partial nodal replacement by a necrotising, histiocyte-rich infiltrate, with no evidence of background B- or T-cell lymphoma consistent with KFD[3].

Due to cytopenias Hydroxyurea was ceased and 4 weekly erythrocytapheresis commenced. KFD is traditionally managed with high dose steroids however as Patient X had started to improve clinically they were not required. Two months from onset of symptoms fevers have settled and the patient has resumed Hydroxyurea therapy with resolution of baseline haematological parameters.

Conclusion: Whilst the ultimate outcome of a diagnosis of KFD is that of a benign condition which is self-resolving the time to diagnosis is typically lengthy to exclude infective and malignant causes.[1,2] In the patient with sickle cell disease, the diagnosis was further confounded by the underlying disease and management with Hydroxyurea.

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NO005

Risk of secondary malignancy is real after Allogeneic stem cell transplant

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Background: Survivors of allogeneic stem cell transplant (AlloSCT) are increasing in number and are projected to increase fivefold by 2030 [2]. Survivors at a considerable risk of developing late effects in the years post AlloSCT. One of the potentially life changing effects among this group of patients is secondary malignancy, which can have substantial impact on quality of life [1].

Aims: 1. To examine the incidence of secondary malignancy in patients post AlloSCT attending a dedicated long term follow up (LTFU) clinic from Nov 2014 to Sept 2023.
2. To identify the common secondary malignancy, and the risk factors for developing secondary malignancy.

Method: Using the Allogeneic bone marrow transplant LTFU service database from Nov 2014 to Sept 2023, we conducted a retrospective analysis of 652 survivors who were >2 years post AlloSCT at first review in LTFU clinic. We used the data to examine the incidence and identify the common secondary malignancy among long term survivors of AlloSCT. We also examined the risk factors such as exposure to radiotherapy and chronic graft versus host disease (GvHD) in developing secondary malignancy.

Results: 652 AlloSCT survivors were referred to the LTFU service. 623 attended their first LTFU review and 28 did not attend. Of those who attended, 100 individuals have been identified to have developed secondary malignancy at first visit to LTFU clinic. Skin cancer (both non melanomatous and melanomatous) is the most common secondary malignancy identified. Other secondary cancers include breast, thyroid, lung, renal and haematological malignancy. More than 40% of individuals had radiotherapy exposure and 70% have or had chronic GvHD.

Conclusion: The findings from the retrospective analysis provide future directives on (1) the importance of cancer screening adherence from clinicians and patients, (2) regular review of cancer screening guidelines based on national and international recommendations and (3) healthy lifestyle counselling and education to promote better patient outcome.

References:

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NO006

Developing and Implementing Evidence-Based Vascular Access Device Guidelines

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Aim: Clinicians find little utility in research, guidelines, position statements and recommendations for patient management unless they can be seamlessly and efficiently incorporated into clinical practice. The Cancer Nurses Society of Australia (CNSA) Occlusion Prevention and Management Guidelines align with the revised, evidenced-based eviQ and eviQ Education central venous access device procedures, education, and resources launched in July 2021. All documents use a common language and provide an evidence-based, peer-reviewed, and standardised approach located on open-source webpages. This project reviewed and evaluated the impact of the CNSA Occlusion Prevention and Management Guidelines and recommendations.

Method: Website analytics - webpages accesses by unique users - from 1 July 2021 to 30 January 2024 were requested from eviQ. CNSA Sosido questions and CNSA Congress 2022 and 2023 abstracts pertaining to vascular access devices were collated and analysed descriptively.

Results: The CNSA Guidelines have been accessed 1,857 times and the Patency Algorithm 6,553 times via the eviQ web-based platform. The top 3 Sosido questions were: (i) preventing and managing occlusion; (ii) implementing and sharing guidelines; and (iii) annual competency. Two CNSA abstracts presented the implementation of the Guidelines into clinical practice.

Conclusion: This project highlights the Guidelines are informing clinical practice and generating professional conversations to inform patient safety.

NO007

Pregnancy and Delivery Management of women who carry the Haemophilia Gene in Queensland.

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Aim: To provide an overview of the Queensland Haemophilia Centre (QHC) management of haemophilia carriers in pregnancy and delivery, to evaluate our management compared to international and national guidelines.

To evaluate the neonatal outcomes of babies born with haemophilia.

Method: A 5-year retrospective review of pregnancy data and delivery outcomes in Queensland of women with inherited bleeding disorders, managed by the QHC.

Literature review of national and international management guidelines and how this pertains to Queensland and how this influenced the QLD model of care.

Results: 48 known pregnant carriers of haemophilia were managed by QHC.

2 women had postpartum haemorrhages, 1 was readmitted 12 days postpartum with return to theatre, the other was managed conservatively. Some women were lost to follow up.

Location of delivery included Metro North, Cairns, Townsville, Toowoomba, GCUH, SCUH, Bundaberg and private hospitals.

21 females, 13 unaffected males and 15 affected males were born: 3 severe, 7 moderate and 5 mild Haemophilia.

3 male babies had adverse events post birth: 1 moderate suffered a grade 1 intraventricular haemorrhage detected via ultrasound on day four post birth. 1 moderate had a subgaleal haemorrhage confirmed on day three; 1 baby with severe was treated for a mild cephalhematoma day 1 post birth. Coincidentally 1 baby with an unknown family history had a grade 2 bilateral intraventricular haemorrhage and consequently diagnosed with severe haemophilia A.

All babies had cord testing performed.

All babies born with severe haemophilia had cranial ultrasounds performed prior to discharge as per the guidelines.

Conclusion: QHC management of women who carry the haemophilia gene follows current national and international guidelines. QHC guidelines of management of labour and delivery were followed. The 3 adverse events were identified.

“QHC comprise the Royal Brisbane and Women’s Hospital adult haemophilia centre and the Queensland Children’s hospital haemophilia centre.

NO008

Oral Mucositis Management in Haematopoietic Stem Cell Transplantation in Australia and New Zealand (CAN EAT SURVEY)

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Aim: The Multinational Association of Supportive Care in Cancer (MASCC) has published evidence-based international guidelines on the management of oral mucositis (OM). However, the adherence to the guidelines has never been evaluated. This survey assessed management of OM in haematopoietic stem cell transplantation (HSCT) centres in Australia and New Zealand.

Method: Specialist nurses in 41 hospitals were invited to participate in the survey. Survey questions included general unit information, oral assessment (tools, assessors, frequency), prevention strategies (guidelines, the use of oral care, cryotherapy, photobiomodulation, palifermin and the barriers if not using) and treatment strategies (pain management and nutrition supplements). Collected data was analysed descriptively.

Results: In total, 23 hospitals completed the survey (56%). Oral assessment was predominantly conducted by nurses (100%) and doctors (78%), and the WHO grading tool (43%) and pain score (39%) were the most utilised. EviQ (Australian online cancer resource) guidelines (65%), which do not include palifermin and photobiomodulation, dominated practice, followed by institutional (26%), then MASCC guidelines (17%). The top 3 basic oral care interventions were sodium bicarbonate (96%) and normal saline (43%) mouth rinses, and patient education (57%). Cryotherapy was commonly used with melphalan (96%) and the use of photobiomodulation in only one facility. Palifermin was used in 3 centres with total body irradiation and the barriers to use were cost and access. All 23 units administered as required opioids for mucositis pain, 12 of which utilised patient-controlled analgesia and 11 used concurrent topical anaesthetics. When OM affects oral intake, enteral nutrition (43%) and parenteral nutrition (35%) were used.

Conclusion: In Australia and New Zealand, HSCT centres use inconsistent OM assessment tools, pain management and nutrition supplementation. Most centres use oral care and cryotherapy as prevention. Photobiomodulation and palifermin are rarely used due to cost and access, and EviQ guidelines do not recommend these.

NO009

SCIg patient story prompts codesign of consumer travel checklist

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Aim: Overseas travel with Subcutaneous Immunoglobulin (SCIg) can be an unfamiliar and complex process for staff and consumers. A consumer-friendly checklist could guide patients and their SCIg Nurses when planning to travel overseas with SCIg.

Method: Plan: A SCIg Program in a Local Hospital District in NSW co-designed a checklist with a SCIg consumer, SCIg Program Coordinator, and Patient Information Officer.

Do: They reviewed existing Australian resources available and adapted them by applying plain language principles and incorporating the consumer's experience.

Study: Checklist was tested by consumers and qualitative feedback was obtained via patient stories from consumers on return from travel.

Act: Feedback was considered, and checklist was refined and published on district's intranet Patient Information Portal.

Results: Consumers provided practical feedback on the timing of their SCIg doses prior to departure and on return to save space in luggage; making smart consumable choices – what must be packed, and what can be sourced at their destination; navigating airport security and hotels.

Consumers who travelled overseas with SCIg experienced feelings of excitement; reconnection with family and friends; independence and empowerment to take more control of their own healthcare and travel plans.

Conclusion: *Overseas Travel Checklist for Subcutaneous Immunoglobulin (SCIg) Patients* was published on the district's Intranet Patient Information Portal in December 2023. It has been successfully used by subsequent SCIg patients and their SCIg Nurses to plan for their trip. The SCIg Program continues to seek feedback from consumers via patient story to inform further revisions. The consumer who co-designed the checklist enjoyed the collaboration with the health district and has now also joined the district's Blood Management Committee as a Consumer Representative.

NO010

Driving health equity. A safe and effective shared model of care initiative following allogeneic stem cell transplantation: An Alfred Health (AH) and Northern Health (NH) collaboration

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[1]Alfred Health, [2]Northern Health

Aim: The Victorian Cancer Plan 2021-2024[1] recognises the importance of health equity for Victorians as a key objective, so they are not disadvantaged by residence location. The complexity of care required for individuals following allogeneic stem cell transplantation (alloSCT) highlights the need for novel approaches to achieve this objective. Alfred Health (AH) and Northern Health (NH) have developed a shared-care model providing alloSCT recipients equal access to tertiary advice and care without travelling the distance to do so.

Method: In 2023, a formal program of coordinated patient centred care for alloSCT recipients referred from NH began, led by AH transplant physicians, the NH haematology team, the NH haematology nurse practitioner candidate (HNPC) and AH bone marrow transplant (BMT) nurse practitioner (NP). Post alloSCT transplant admission, patients are clinically reviewed twice weekly in the ambulatory setting. The clinical decision to share care between NH and AH were decided on a case by case basis by the primary transplant physician. Patient reviews and updates were carried out weekly by the NH HNPC with weekly updates to AH transplant physician and BMT NP. In addition, NH commenced a fortnightly BMT clinic with a visiting AH transplant physician providing additional support and access to specialist knowledge and care.

Results:
Demographics of alloSCT recipients referred to NH for post-transplant management

Characteristics of AH alloSCT recipients seen at NH between February 2023 to January 2024 (n = 6)	
Median age (range)	44.5 (34-60)
Gender (male/female)	4/2 (67%/33%)
Disease • Acute Myeloid Leukamia • Acute Lymphoblastic Leukaemia • Myelodysplastic syndrome	 1 (17%) 4 (67%) 1 (17%)
Median day post alloSCT at first NH visit	62 (30-94)
Episodes of care managed at NH • Outpatient review (specialist clinic) • Review by NH HNPC • Blood product support • Central access line care	 32 88 20 42
Non GvHD / GvHD cohort	4/2 (67%/33%)
Re-presentations to hospital • Alfred Health • Northern Health	 0 5 (100%)
Adverse events documented	0

Conclusion: The development of a novel, collaborative metro–tertiary specialist care program post alloSCT for a complex procedure has demonstrated improvements in small, but growing numbers, expanding the delivery of quality specialist care to NH alloSCT recipients, thus reducing the financial, emotional and transport stressors compounding care. Furthermore, this model has provided immediate access to specialist knowledge and decision making in a peer mentoring capacity as well as supported clinic consult access for NH patients following transplantation. Improvements are demonstrated in the ability to manage safe and equitable episodes of specialist post alloSCT patient care at a non alloSCT health service.

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BMTSAA Oral Presentations

BO001

Correlation of post-thaw vCD34 and vCD3 reporting between the Westmead Blood Transplant and Cell Therapies Laboratory and other Australian Blood and Marrow Transplant Laboratories.

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The Westmead Blood Transplant and Cell Therapies (BTCT) laboratory actively participates in the RCPA Quality Assurance program (QAP) for haematology and immunophenotyping covering CD34 and CD3 counts for fresh blood samples. Participation in external quality programs ensures laboratory results are within analytical specifications and conform to peer group. However, no program is currently active covering viable CD34 and CD3 counts post-cryovial thaw testing, although the RCPA is currently developing such a program in conjunction with Australian BMT laboratories.

During the COVID pandemic, the large drop in fresh harvest transports due to issues with logistics and border closures resulted in cryopreservation of harvests prior to transport to off-site/interstate transplant centres. In this period, the Westmead BTCT laboratory transported and received cryopreserved HPC to/from transplant/collection centres, performing confirmatory pilot vial testing on all products. This review compares Westmead data against data obtained from local cryopreservation/transplant centres to determine if viable post-thaw counts were comparable between Australian interstate laboratories.

Data from 19 HPC harvests collected, cryopreserved and transported frozen between January 2021 and September 2022 was reviewed and post-thaw counts performed by Westmead and interstate laboratories were compared. Of these, 5 harvests were cryopreserved at Westmead before transport to interstate transplant centres, and 14 harvests were cryopreserved interstate before transport to Westmead. The interstate transplant centres involved were Royal Melbourne Hospital (VIC), Royal Brisbane and Women's Hospital (QLD), Royal Adelaide Hospital (RAH) and Fiona Stanley Hospital (WA).

Post-thaw viable CD34 and CD3 counts from confirmatory testing of these transported cryopreserved products showed comparability between laboratories. (Average %difference ±SD: vCD34 = 12.3 ±8.0% (n=17, R^2=0.96); vCD3 = 0.88 ±0.64% (n=9, R^2=0.74)). While additional data would further support the observed correlation, analysis of currently available data indicates that viable correlation would be expected between Australian laboratories participating in a viable CD34 and CD3 program.

BO002

Meditation and medication - How we circumvent HPC (A) product clumping in a processing laboratory

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Background & Aim: Product clumping during an HPC (A) collection seldom escapes the vigilant surveillance of an apheresis operator. It is uncommon that a stem cell processing laboratory receives an HPC (A) product with clumps. We aim to present a laboratory troubleshooting procedure to salvage an autologous HPC (A) product with significant clumping.

Method: A patient on Plerixafor rescue underwent the second day of stem cell harvest. A 370mL product was received into the processing laboratory and found to have significant small clumps. The addition of 10% v/v ACD-A (37mL) and product filtration with a non-leukodepletion filter was adopted before processing commenced. A product sample was taken before the addition of ACD-A, and again after product filtration. Total nucleated cells, platelets, and viable CD34+ cells of the product from before and after manipulation were compared.

Results: The total nucleated cell (TNC) loss and viable CD34 loss were 6.7% and 4%, respectively. Almost 70% of the platelets in the product were removed after product filtration. No further clumping has occurred downstream of the processing procedure. No clumping was observed during the pilot thaw of the product. The TNC and viable CD34 recoveries of the product post-thaw were within laboratory-acceptable limits. No clumping has occurred during product thaw for reinfusion.

Conclusion: The addition of ACD-A equivalent to 10% of product volume has prevented further clumping during processing. The extra ACD-A likely halts the platelet activation cascade which causes clump formation. Reduction in TNC and CD34 in the product due to clumping &/or product filtration is unavoidable. Extra ACD-A in the product also prevented clumping during product reinfusion. This troubleshooting procedure pre-processing presented herein has been implemented in our SOP.

BO003

Stopping the stem cell collection marathon - Optimising Plerixafor use in GRIFFIN-treated patients, a single centre experience

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Background & Aim: The negative impact of the GRIFFIN protocol on haematopoietic progenitor cell (HPC) mobilisation in myeloma patients is well-recognised. Plerixafor (PXF) administration is often a salvage measure for poor mobilisers especially when the pre-harvest CD34 count dropped from the previous day. This study evaluates the use of PXF (pre-emptive vs contingency) in GRIFFIN-treated patients in our institution.

Method: Eighty- three HPC harvests from 53 patients treated by the GRIFFIN protocol at our institution from October 2020 to May 2024 were included. Patients requiring PXF for stem cell mobilisation were divided into two groups (i) G-CSF+ PXF given overnight as in-patients (pre-emptive PXF), (ii) G-CSF+ PXF given within 2 hours of apheresis at the bedside (contingency PXF). The collection efficiency and the apheresis yield between the two groups were compared.

Result: 39/83 (47.5%) of all collections required administration of PXF. The median collection efficiency of apheresis involving the use of pre-emptive PXF (28/39) and contingency PXF (11/39) was 49.5% and 164%, respectively. 72% (8/11) of collections using the contingency PXF achieved the target stem cell dose in one apheresis session. The three patients requiring a second collection had achieved >50% of the target after a single apheresis.

Conclusion: We have shown that our contingency use of Plerixafor maximised stem cell yield and reduced the need for further apheresis sessions. Bedside administration of PXF eases the pressure on in-patient bed shortage. This approach also caters to the unexpected drop in CD34 count on the planned harvest day.

BO004

Long-distance transport of HPC followed by cryopreservation does not adversely impact post-thaw viable CD34 recoveries and patient outcomes.

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During the COVID pandemic, haematopoietic stem cells (HPC) harvested from matched unrelated donors were cryopreserved at the overseas collection centres, followed by transport of the frozen cell bags to Australian transplant centres, due to issues with logistics and border closures. Patient conditioning treatment was commenced only once cryopreserved cell bags were safely received and confirmatory testing completed. In 2023, Westmead Hospital and The Children's Hospital at Westmead began transitioning to transport of fresh cells to Westmead, followed by cryopreservation of the cells on receipt, prior to starting patient conditioning. This data review aims to determine the impact of long-distance transport in addition to cryopreservation of HPC on cell dose, viability and subsequent patient engraftment post-infusion of the thawed cells.

Data from February 2023 to May 2024 was analysed (HPC(A), n=41), including 4 two-day harvests and 5 harvests that were transported fresh, CD34 positive selection performed and resultant fractions cryopreserved prior to infusion (Values presented as Average ±SD). Confirmatory viable CD34 counts of the fresh product was performed on receipt of the harvest and were found to correlate highly to reported collection centre counts (Average %difference ±SD = 10.8 ±9.3%; R^2=0.98). Post-thaw viable CD34 recoveries were ≥50% (vCD34 %recovery: 76.5 ±13.6%; CD34 viability%: 83.1 ±12.9%) in all except two cases (36% and 47%, no evident cause identified). Time from collection to cryopreservation showed no correlation to post-thaw viable CD34 recovery (42.1 ±11.26hrs; Range: 23.0-68.4hrs; R^2=0.06).

Transplanted vCD34 cell doses were satisfactory (n=34, Dose: 5.3 ±1.88 x10^6/kg, Range: 2.3-10.8 x10^6/kg) and engraftment occurred within an expected timeframe (Neutrophils >0.5x10^9/L: 16.6 ±3.3 days; Platelets >20x10^9/L: 23.1 ±10.3 days) except in one patient who did not achieve platelet engraftment. Based on the data reviewed, cryopreservation of HPC following long-distance travel did not negatively impact the cell dose, viability and engraftment.

HSANZ Poster Presentations

Acute Leuk

HP001

B-Acute Lymphoblastic Leukaemia with Burkitt-like morphology in patients

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Aim: We report three cases of patient present with Burkitt-like cells on peripheral blood who were subsequently diagnosed with B-acute lymphoblastic leukaemia with hypodiploidy.

Method: Patient 1: 57M presents with three months history of cough, myalgia, worsening shortness of breath and B symptoms for 3-4 months with 12kg weight loss. Hb 104, neutrophils 0.41, platelets 26, peripheral blast 4%, LDH 436.

Patient 2: 70F presented with four days of lower back pain and chest pain with elevated troponins (1439) treated as a myocardial infarction. Admission bloods showed abnormal lymphocytes with Burkitt like morphology. Hb 122, neutrophils 3.02, platelets 115, peripheral blasts 3%, LDH 1380.
Patient 3: 58F representation for recurrent infections and severe headache. Hb 99, platelets 154, neutrophils 0.79, peripheral blasts 7%, LDH 644.

Results: All three patients demonstrated large abnormal lymphocytes with deeply basophilic cytoplasm and prominent vacuolation suggestive of Burkitt-like cells. However, subsequent flow cytometry confirmed the diagnosis of B-ALL. All three patient demonstrated hypodiploidy on SNP microarray testing on bone marrow aspiration.

Patient 1:
- Flow: positive CD19, CD20, CD22, CD38, CD58, CD66, CD79A, CD81, CD123, HLA-DR, TdT
- SNP: Monosomy 3, 7, 15, 16, 17
- Patient received R-HyperCVAD

Patient 2:
- Flow: positive CD10, CD19, CD20, CD22, CD34, CD38, CD58, CD79A, CD81, HLA-DR, TdT
- SNP: Monosomy X, 2, 3, 4, 7, 12, 13, 15, 16, 17
- Patient received POMP

Patient 3:
- Flow: positive CD19, CD22, CD33, CD34, CD38, CD58, CD66C, CD79A, CD81, CD123, HLA-DR, Tdt.
- SNP: Monosomy 3, 7, 8, 13, 14, 15, 16, 17, 20.
- Patient received hyperCVAD

Conclusion: Burkitt-like morphology in patients with B-ALL with hypodiploidy has not been previously reported in this B-ALL subtype and warrants further investigation as to whether this may be a pathognomonic feature.

HP002

The interaction of frailty, genetics and treatment selection in older patients with newly diagnosed acute myeloid leukaemia.

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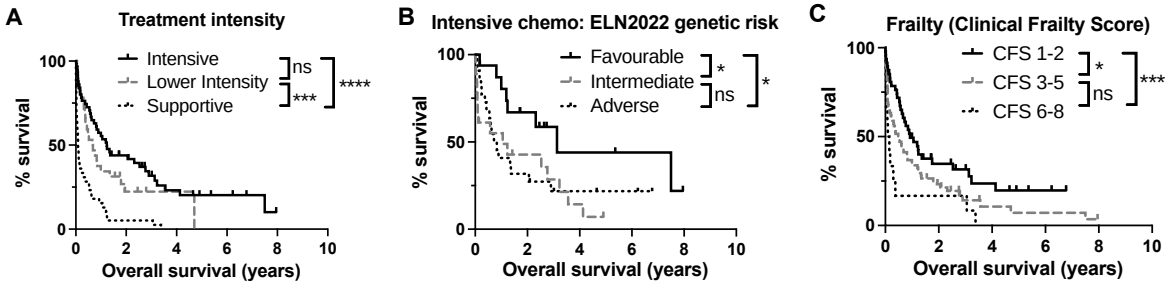
Aim: To assess the correlation between frailty, genetic risk and treatment intensity with survival outcomes in older patients (≥60 years) with AML.

Methods: Retrospective audit of patients with newly diagnosed AML, aged ≥60 years, January 2019 - December 2023 identified from the Princess Alexandra Hospital bone marrow database. Frailty was determined by Clinical Frailty Score (CFS) (Rockwood) at presentation; if not documented, it was retrospectively assessed based on chart reviews. Treatment regimens included: intensive chemotherapy (IC) (7+3/Hidac, Vyxeos), lower intensity regimens (LI) (venetoclax / azacitidine or venetoclax / low-dose cytarabine (LDAC)) or best supportive care (BSC) (single agent azacitidine, LDAC or no AML-directed therapy).

Results: 128 patients were identified (median age 71 (range 61 – 93), 79 (61%) were male). Fifty-six (39%), 32 (25%) and 40 (31.25%) patients received IC, LI and BSC treatments, respectively. Median CFS was 2 ('Well') for IC and 3 ('Managing well') for LI and BSC. Fifteen patients received an allogeneic bone marrow transplant post IC (median age 64.5, CFS 2). Patients who received IC or LI had improved OS compared to BSC ($p<0.0001$ and $p=0.0002$, respectively) but no difference between IC and LI ($p=0.14$) (Figure A). In patients receiving IC, ELN2022 genetic risk stratification identified a relatively favourable risk subgroup, but did not separate intermediate and adverse risk (Figure B). CFS also showed significant ability to stratify survival (Figure C). Patients with CFS 3 who appear 'fit' had similar survival to those with CFS 4-5 ('Vulnerable'-'Mildly frail').

Conclusion: IC did not show survival benefits over LI, although patients with favourable ELN2022 risk appeared to preferentially benefit from IC. Higher frailty is associated with worse OS. Patients with CFS ≥3 may benefit from more comprehensive frailty assessment to identify those at higher risk of treatment mortality. Prospective studies should integrate quality of life and patient- and carer-reported outcomes to enhance interpretation of this data.



HP003

Immunophenotypic changes in patients with acute myeloid leukaemia treated with azacytidine and venetoclax

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Background : Multiparametric flow cytometry (MFC) monitoring in patients with acute myeloid leukaemia (AML) treated with azacytidine/venetoclax (aza/ven) is not well characterised. By comparison, MFC measurable residual disease (MRD) in intensively treated patients is prognostic and may lead to therapeutic interventions in clinical trials.

Aim: We examined the phenotype of progenitor populations across the treatment course of patients with AML treated with aza/ven.

Methods: Bone marrow MFC files were retrospectively analysed for patients with AML treated with aza/ven.

Results: Ten patients were included. All were male, median age was 75 years (range 67-88). The median number of bone marrow samples/patient was 5 (range 4-6).

Blast populations showed phenotypic drift in all patients, the most common being weakening of CD117. Varying HLA-DR, CD13 and CD33 intensity were also observed. No clear relationship between immunophenotypic changes and G-CSF use or infection was identified.

Blast phenotype was tracked through the disease course with changes significant enough to be considered a different population emerging in over half of the patients.

A recurring population of 0.05-2.8% (mean 0.68%) with the phenotype: CD117+++,CD33++,CD13weak,CD15-,CD34-,HLA-DR-, CD45moderate with variable side scatter was frequently noted. This population equivalent was further characterized prospectively with a view to interrogating for normal variant populations with strong CD117 e.g. mast cells/precursors, early erythroid precursors as well as abnormal plasma cells.

Two patients had molecular MRD assays available. In one case NPM1 MRD loosely correlated with abnormal progenitor populations detected by MFC. In the second, an abnormal blast population by MFC (0.1%) was seen in a sample with discordant NPM1 (undetectable) and FLT3-ITD (50.87%) MRD. This was followed, 4 weeks later, by morphologic relapse.

Conclusion: Immunophenotypic changes are common in patients with AML treated with aza/ven. New blast populations are frequently observed during follow up and their implications for prognosis and therapy requires further study.

HP004

Examination of tetrandrine as a potential treatment of acute myeloid leukemia

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Aim: Tetrandrine is a calcium channel blocker with anti-cancer effects in solid tumours, however research into its effects in acute myeloid leukemia (AML) is limited. Clinical trials of tetrandrine in AML has shown variable outcomes, likely due to a lack of predictive biomarker for response. Potential biomarkers may include dysregulated pathways like the inflammasome, focusing on NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3)-inflammasome and Sirtuin 1 (SIRT1) overexpression, and the calcium signalling pathways, through calcium–calmodulin-stimulated protein kinase II (CaMKII) phosphorylation. The aim of this study was to determine if CaMKII, NLRP3, and/or SIRT1 are biomarkers for treatment response by correlating expression and/or phosphorylation with cell survival after tetrandrine, or tetrandrine/hypomethylating agent (HMA) combination, treatment.

Method: Resazurin assays were used to measure the viability of 3 AML cell lines after exposure to tetrandrine, HMA, and tetrandrine/HMA combination. Dose-response curves and IC50 values were generated using non-linear regression and synergy combination assays were performed using the highest single-agent (HSA) model. Sub-lethal synergistic combinations were used for immunoblotting to examine SIRT1 and NLRP3 protein expression and CaMKII phosphorylation compared to untreated control. Protein expression comparison was analysed using a one-way ANOVA and Bonferroni post-test. Correlation between protein expression/phosphorylation and cell survival was analysed using Pearson's correlation coefficient.

Results: Tetrandrine, but not HMA, IC50 values were statistically different between THP-1/Kasumi-1 and MV4-11 cell lines (7.664/6.884μM vs 3.052μM). Synergy between HMA and tetrandrine combination was highest at low dosages of tetrandrine (0.078-0.3125μM). Correlation analysis revealed CaMKII, NLRP3, and/or SIRT1 expression/phosphorylation showed positive trends but did not significantly correlate to treatment response.

Conclusion: Although all three cell lines demonstrated synergistic effects between tetrandrine and HMA, none of the proteins examined directly predicted for sensitivity to tetrandrine. Further research into additional cell lines and protein expression is required to discover a biomarker for tetrandrine treatment.

HP005

Azacitidine-Venetoclax: How "Non-Intensive" is it?

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Background: Since the availability of venetoclax on the PBS from Dec 2021, azacitidine + venetoclax (Aza-Ven) is now widely used for the management of older, unfit patients with Acute Myeloid Leukaemia (AML).

Aim: To describe the incidence of adverse events associated with Aza-Ven during AML induction and to identify associated risk factors.

Method: A retrospective audit of all patients treated with upfront Aza-Ven at our institution between December 2021 and February 2024 was undertaken. Baseline disease and patient demographics were described and correlated with adverse events and treatment outcomes.

Results: Of the 35 patients identified, 66% (23/35) were discharged for outpatient neutropenic monitoring after initial inpatient admission for venetoclax ramp-up. 19 patients (83%) required re-admission after a median duration of 10 days (1-17). 71% of all patients had an episode of febrile neutropenia with 46% (16/35) found to have a microbiologically confirmed infection. 44% (15/35) had grade 4 neutropenia >28 days and the rates of microbiologically diagnosed infection in this group was 73% (11/15). Patients with a higher bone marrow blast burden (>50%) at diagnosis had longer duration of neutropenia (median 27 days vs 9 days). Patients with longer durations of grade 4 neutropenia (>14 days) had lower median neutrophil count at diagnosis (0.5 x 10^9/L vs 4.5 x 10^9/L). 9% (3/35) required an ICU admission. The 30-day treatment-related mortality was 6% (2/35), both related to sepsis.

Conclusion: Aza-Ven is associated with a high burden of prolonged neutropenia and infectious complications. Based on this we will undertake a detailed analysis of patient factors to help identify a low-risk patient group most suited to an ambulatory model of care.

HP006

Outcomes in Elderly Patients with Acute Myeloid Leukaemia Between Different Front-Line Treatment Modalities and the Effect of Comorbidities on Treatment Choice (a single centre study)

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Aim: Whilst the incidence of acute myeloid leukaemia (AML) increases with age, the five year survival rate declines sharply in older patients[1]. There is limited data comparing outcomes between treatment options in older AML patients. This study aims to evaluate the influence of patient comorbidities, using the Charlson Comorbidity Index (CCI) on treatment choice in this population and to evaluate outcomes between three different treatment groups – Group A: supportive care; Group B: non-curative treatment (including single agent Azacitidine, Cytarabine or combinations with Venetoclax); Group C: Intensive anthracycline based induction chemotherapy.

Method: Retrospective analysis of 101 patients aged ≥70, who presented to St George Hospital with newly diagnosed AML between the 1/2/2012 until the 30/6/2022. A two-tailed T test was used to compare mean CCI between treatment groups. Cox regression analysis was used to evaluate OS between the treatment groups.

Results: There was a significant difference in OS between patients who received any treatment compared to those who received supportive care alone (p value <0.001). There was no significant difference in OS between group B and group C (p value = 0.895), even when controlling for age, CCI and previous malignancy.

There was no significant difference in mean CCI between group A and group B (p = 0.190). There was a significant difference in mean CCI between group A and group C (p = 0.000) and between group B and group C (p = 0.003).

Conclusion: Our study revealed that receiving treatment regardless of intensity improves survival, however patients individual comorbidities did effect treatment choice. Our study did not find a significant difference in survival between those treated with intensive chemotherapy compared to non-curative treatment, however larger studies are needed to investigate this further. Future directions for research should investigate the impact of different treatment modalities on quality of life in this patient cohort.

References:

1. “Cancer Data in Australia.” n.d. Australian Institute of Health and Welfare. Accessed February 17, 2023. https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancersurvival-data-visualisation.

HP007

The role of synchronised 48-hour cell cultures and MECOM and KMT2A FISH in the investigation of AML where overnight cultures demonstrate a normal karyotype

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Aim: Rapid availability of conventional cytogenetics (CGEN) and fluorescence *in situ* hybridisation (FISH) are critical to the accurate classification and risk stratification of acute myeloid leukaemia (AML). Routinely in our centre, when the initial analysis from an overnight (ON; 15-24 hr) culture does not identify clonal aberrations (normal karyotype; NK), a prolonged/synchronised culture (SYNC; 48hr) is assessed. In addition, FISH to identify cytogenetically cryptic *MECOM* (3q26) or *KMT2A* (11q23) gene rearrangements is routine when both cultures demonstrate NK. The aim of this study is to review the incidence of clonal aberrations where ON cultures show NK and incidence of cytogenetically cryptic *MECOM*r or *KMT2A*r.

Method: Our AML karyotype database was interrogated between 11/Nov/2022 to 18/Jan/2024, identifying a total of 487 new cases [446 (91.5%) successfully karyotyped; 41 (8.4%) no mitosis]. Second culture was not set up for 43 (8.8%) of cases (insufficient sample). During a similar timeframe (June ’23 – Apr ’24), we performed interphase FISH with *MECOM* and *KMT2A* break-apart probes in 137/146 cases where CGEN identified a NK on both ON and SYNC cultures (9 cases had insufficient sample). FISH results were interpreted according to in-house determined measurement of uncertainty values.

Results: Overnight cultures demonstrated NK in 174 cases (35.7%) while clonal aberrations were seen in 272 cases (55.8%). 3/158 (2%) synchronised culture showed low-level clonal aberrations (Table 1). No cases were re-classified according to the ELN criteria. *MECOM* or *KMT2A* rearrangement was not identified in any case by FISH testing where CGEN demonstrated a NK. During the same timeframe (June ’23 – Apr ’24), *MECOM* and *KMT2A* rearranged AML were identified in 10/363 (3%) and 8/363 (2%) of cases by CGEN, respectively.

Conclusion: The additional benefit of examining synchronised cultures in cases with NK on ON cultures is questionable. Our data demonstrates that cytogenetically cryptic *MECOM* and *KMT2A* rearranged disease is exceedingly rare.

Table 1: Clonal karyotypes detected by synchronised culture where overnight culture was normal.

Patient	Karyotype	ELN Risk Category
85yo, M	45,X,-Y,del(13)(q?12q31-33)[3]/46,XY[57]	Intermediate
92yo, F	45,X,-Y[3]/46,XY[27]	Intermediate
65yo, F	47,XX,+8[3]/46,XX[55]	Intermediate

HP008

Streamlining the detection of FLT3-ITD (FLT3 Internal Tandem Duplication) using an the GeneXpert® Automated Cartridge-based qPCR System

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Aim: The targeted therapies for AML demands fast and reliable diagnostic tests. FLT3-ITD is the most common targetable mutation in AML (~25%). Current diagnosis of FLT3-ITD by PCR involves numerous, laborious, and time-consuming steps for whole blood processing, DNA isolation, plate-based PCR and subsequent fragment analysis by capillary electrophoresis (CE). The objective of this study was to develop an automated FLT3-ITD diagnostic prototype that is faster, requires less hands-on time and can detect all clinically relevant ITD lengths.

Method: A FLT3-ITD prototype assay using an automated cartridge platform for FLT3-ITD detection has been developed to streamline the process using less than 30 minutes off-board time. The cartridge performs automated DNA isolation, purification, and qPCR. Quantitative fragment analysis can easily be performed on the PCR product using CE for allelic ratio (AR) callout. Additionally, the PCR product can be analyzed on a bioanalyzer or standard Agarose Gel-Electrophoresis.

Result: The developed automated FLT3-ITD diagnostic prototype demonstrated significant improvements over the existing methodologies with substantially reduced time to result and simplicity in use. We observed sensitivity and linearity down to 0.01-0.02 AR by CE for the ITDs tested (3, 21, 30, and 75 bp). Importantly, the prototype detected all lengths of ITD mutations with inserts from 3bp to 300 bp using plasmid test materials.

Conclusion: We have successfully developed a novel FLT3-ITD diagnostic prototype that is sensitive to detect down to 0.01-0.02 AR and has several major advantages over existing methodologies. The prototype detects all lengths of ITD mutations with inserts from 3bp to 300 bp and significantly reduces the time and hands-on effort required for analysis, streamlining the diagnostic process for same day results, demonstrating the potential to improve future diagnostic therapeutic interventions in the clinic for AML.

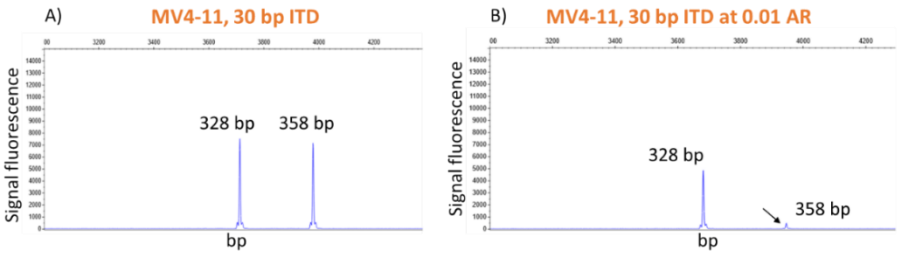

Figure 1. A) Capillary electrophoresis (CE) spectrogram of MV4-11 cell line DNA. 328 bp represents the wildtype peak, while 358 bp is the detected 30 bp ITD at an allelic ratio of 1. B) depicts accurate detection of a 0.01 AR sample.

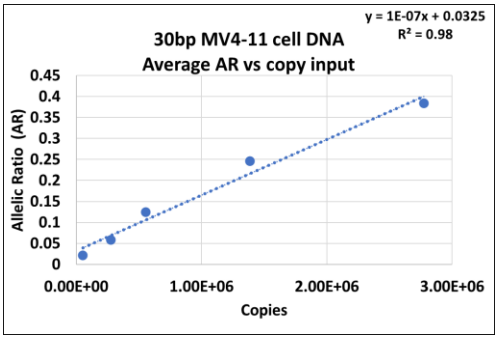

Figure 2. Analytical Linearity of MV4-11 DNA spiked into negative EDTA blood. Samples were run using the FLT3-ITD prototype and quantitative AR was analyzed using capillary electrophoresis (CE). AR dynamic range 0.01-0.4 with a linearity R-squared coefficient of >0.98. N = 4 replicates per copy level.

HP009

Development of an IDH1&2 Mutation Prototype Assay, an Automated and Standardized cartridge-based qPCR Assay to Detect 17 IDH1 and IDH2 Mutations in AML Patients

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[1]Oncology, R&D, Cepheid

Aim: Mutations in IDH1 or IDH2 are associated with disease relapse and reduced survival in AML. Detecting IDH1 & IDH2 mutations with required sensitivity is critical for early cancer detection and efficient selection of targeted inhibitors for AML patients. Here, we describe the effort to develop a rapid and user-friendly cartridge-based qPCR assay that can detect 7 IDH1 and 10 IDH2 major mutations directly from peripheral blood with required sensitivity and specificity.

Method: The assay linearity was evaluated using serial dilutions of plasmids carrying four major IDH1&2 mutations (R132C, R132H, R140Q, and R172K) or using R132H human cell line DNA in EDTA whole blood lysate (WB), targeting ~64% to ~0.0625%. The assay sensitivity was evaluated using plasmid (13 mutations) and mutant cell line DNA (14 mutations) to spike into WB, targeting the assay limit of detection (LoD) (~1%). The assay specificity was assessed by testing WB from 20 individual donors in quadruplicate.

Results: The linearity analysis of the prototype IDH1&2 assay demonstrated a dynamic range from ~64% to ~0.0625% with a LoD at 1% in four mutations for both plasmid DNA (Figure 1 in red) and human cell line DNA (Figure 1 in blue). The remaining 10 mutations in human cell line DNA perform similarly to plasmid DNA, demonstrating equivalency between the two test materials. The assay LoD is also evaluated at ~1% in plasmid DNA for the remaining 13 mutations with less than 2 Ct differences observed across all mutations.

Conclusion: We have successfully developed a prototype18-plex IDH1&2 assay to detect 7 IDH1 and 10 IDH2 mutations and call out its corresponding codon in EDTA whole blood samples using a single cartridge at the assay LoD of 1%, meeting the sensitivity required for managing the AML patients carrying mutation in IDH1 or IDH2.

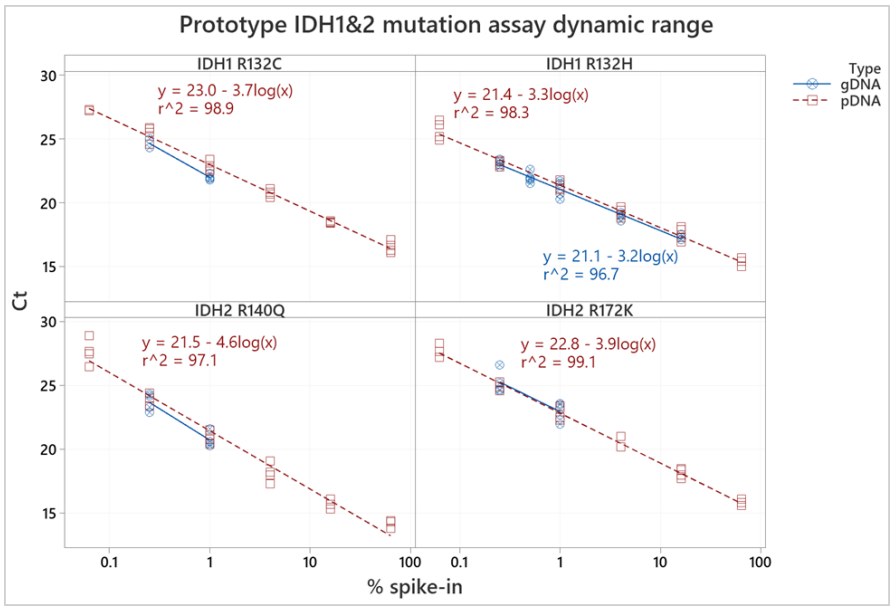

Figure 1: The Cts of the prototype IDH1/IDH2 mutation assay across the assay dynamic range for the most prevalent mutations. Two types of test materials, genomic DNA in blue, and plasmid DNA in red, are shown with their corresponding linear regression equations and r-squared values. % spike-in is calculated as mutation copies over 5 million WT copies (based on average white blood cell count) per cartridge.

HP010

Development of a PML-RARa Assay, an Automated and Standardized Cartridge-based Assay with Required Performance Characteristics for Quantitative Measurement of PML-RARa Fusion Transcript for Acute Promyelocytic Leukemia (APL)

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Aim: APL is an acute form of blood cancer with significant increase of malignant promyelocytes. Although APL is highly curable with current therapies, it is still linked to >30% of early death in part because of sub-optimal diagnostic methods. The PML-RARa fusion transcripts are expressed in more than 95% of APL patients. Therefore, RT-PCR assay that can rapidly and reliably diagnose PML-RARa could help save APL patients' life. Here, we describe the performance evaluation of a PML-RARa assay (Assay), an automated and standardized test for quantifying PML-RARa fusion transcripts (isoforms; bcr1/bcr2/bcr3) relative to ABL1.

Method: Assay's linearity and sensitivity (LoD,/LoQ/LoB) were evaluated using serial dilutions of the three PML-RARa IVT-RNA isoforms in whole blood lysate (WB). Assay's specificity was determined by testing WB of 50 healthy donors. Additionally, the three IVT-RNA isoforms were contrived near LoD in WB for comparison testing between Assay and a commercially available molecular test (Comparator) used as standard of care for APL. Furthermore, 105 samples were tested at a collaboration site on Assay and Comparator.

Result: Assay's linearity is within 0.012–835%. Bounded by the software upper limit, the reportable dynamic range is 0.012–500%. The LoD/LoQ was determined at 0.012% as the highest % reporting among the LoD/LoQ study results (Table 1&2) and the lowest linearity determined above. Assay's LoB is 0% and specificity is 100%. In house comparison study for all three isoforms showed 100% detection on Assay near LoD, while <50% detection on Comparator (Table 3). External evaluation showed 99% PPA and 91% NPA with 98% accuracy between Assay and Comparator (Table 4), including 3 atypical diagnosis bcr2 samples significantly under-quantified by Comparator.

Conclusion: Assay is highly sensitive with performance better than Comparator, indicating that Assay may be suitable for quantitative measurement of PML-RARa to provide fast and reliable information for diagnosis and prognosis of APL.

Table 1. Limit of Detection, Limit of Quantitation and, and Limit of Blank (LoD, LoQ, and LoB) of the PML-RARa assay [% PML-RARa/ABL]

Subtype	LoD [%PML-RARa/ABL]	LoQ [%PML-RARa/ABL]	LoB [%PML-RARa/ABL]
bcr1	0.0052%	0.011%	0.00%
bcr2	0.0110%		
bcr3	0.0082%		

Table 2. Summary of the linearity and dynamic range analysis of the PML-RARa assay [% PML-RARa/ABL]

Subtype	Linear Range	Intercept	Slope	R^2
bcr1	**0.0064-862%**	0.1189	0.9994	0.9964
bcr2	**0.0099-835%**	0.0529	0.9603	0.9984
bcr3	**0.0124-1750%**	0.0177	0.9694	0.9990

Table 3. Summary of the sensitivity at ~1x LoD on the PML-RARa assay (Assay) vs. Comparator

Hit Rate for 20 Replicates at ~1x LoD (0.012% PML-RARa/ABL) per Assay		
	Assay	**Comparator**
bcr1	100%	35%
bcr2	100%	45%
bcr3	100%	40%

Table 4. Two-by-Two Table: the PML-RARa assay (Assay) vs. Comparator

		Comparator		
		PML-RARa POS	**PML-RARa NEG**	**Total**
Assay	**PML-RARa POS**	93	1	94
	PML-RARa NEG	1	10	11
	Total	94	11	105
PPA		**99%**		
NPA		**91%**		
Accuracy		**98%**		

HP011

Clinical Evaluation of a BCR-ABL p190 Test, an Automated and Standardized Multiplex Assay for Quantitative Measurement of BCR::ABL p190 in ALL and CML Patients During Monitoring of Treatment

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[1]Peter MacCallum Cancer Center, [2]NSW Health Pathology, [3]Oncology, R&D, Cepheid

Aim: RT-PCR assay with high sensitivity and accuracy that can reliably detect BCR::ABL p210 and p190 transcript levels is recommended as standard of care in managing ALL and CML patients during therapy. By comparing to three comparator methods that are currently used in standard of care, we demonstrated that the BCR-ABL p190 test (Test) can be used for quantitative measurement of BCR::ABL1 p190 transcript level relative to ABL1 for monitoring ALL and CML patients during treatment.

Method: Test was first evaluated clinically by comparing to a commercially available molecular test (Comparator-I) at three institutions in the U.S. as part of a multi-site clinical study in 31 ALL or CML patient EDTA whole blood specimens (WB). Two additional studies were conducted in Australia in 21 ALL or CML patients (N=70 WB) who were monitored by a molecular test (Comparator-II or -III) as standard of care, including one that is commercially available. At least three timepoints were tested per patient. The regression analysis was performed to evaluate the correlation and concordance between Test and Comparator (II or III). Acceptance criteria: Intercept: -0.3 and +0.3 and Slope: -0.8 and +1.2.

Result: In the multi-site clinical study**,** Test showed good correlation (Pearson Correlation Coefficient r=0.904) and acceptable concordance (Slope=0.94 and Intercept=-0.25) with Comparator-I in a Deming regression analysis with a low bias of 0.01 (Figure 1). In the monitoring during the treatment study, the regression analysis showed good correlation (R^2=0.90) and acceptable concordance (Slope=1.15 and Intercept=0.22) between Test and the respective Comparator results (II or III) (Figure 2).

Conclusion: The clinical performance evaluation studies demonstrated that Test's results are well-correlated and highly concordant with the results from current standard of care testing for BCR::ABL1 p190 positive ALL or CML patients undergoing monitoring of treatment, thereby supporting the intended use of the test for the monitoring application.

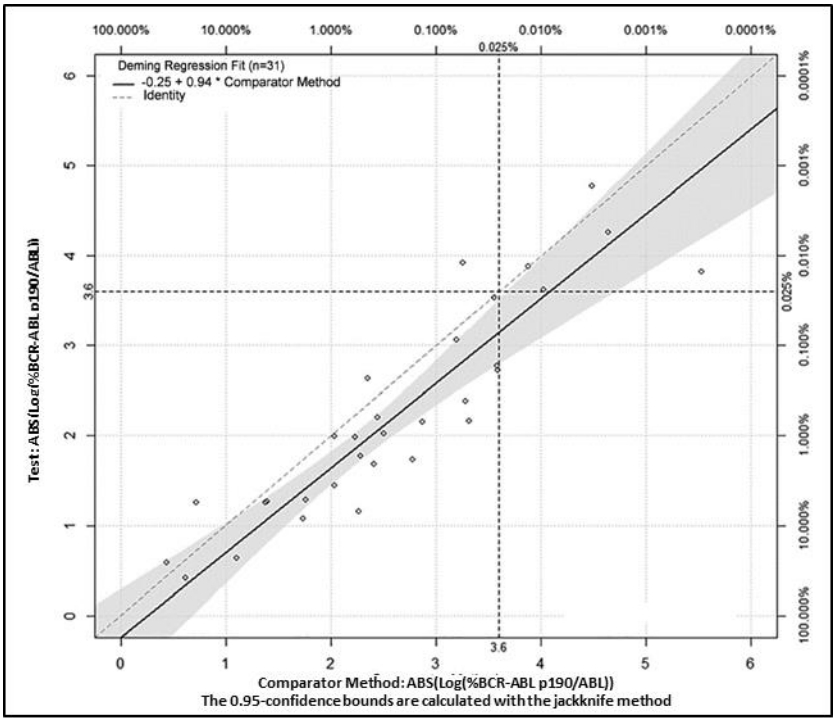

Figure 1. Deming regression plots of the correlation analysis for the BCR-ABL p190 test (Test) vs. Comparator-I for 31 CML or ALL patient specimens. High correlation and concordance observed between Test and Comparator-I method. The Deming regression has a slope of 0.94 and an intercept of -0.25, meeting the acceptance criteria for the intercept and slope. The overall correlation (Pearson Correlation Coefficient) r=0.904 was high.

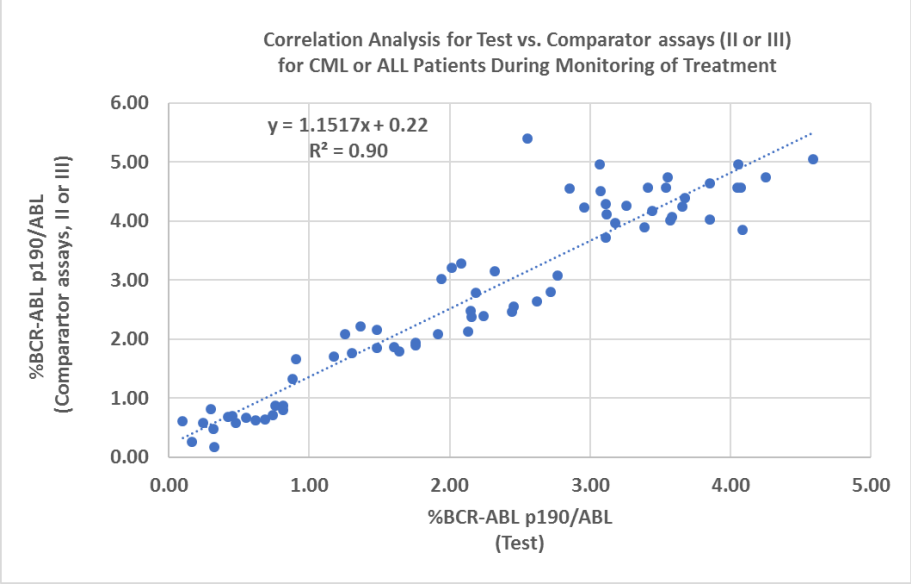

Figure 2. Regression plots of the correlation analysis for the BCR-ABL p190 test (Test) vs. Comparator-II or III for 70 specimens collected from 21 CML or ALL patients during monitoring of treatment. High correlation and concordance observed between Test and Comparator-II or III methods. The regression has a slope of 1.15 and an intercept of +0.22, meeting the acceptance criteria for the intercept and slope. The overall correlation (Pearson) R^2=0.90 was high.

HP012

Detection of 17 IDH1&2 Mutations from Acute Myeloid Leukemia Peripheral Blood Using a Cartridge-based Multiplex Real-time qPCR System

Kadiyala V[1], Tan L[1], Baculi E[1], Nguyen B[1], Huynh N[1], Song T[1], Yuan L[1], Day G[1], Wei H[1]
[1]Oncology, R&D, Cepheid

Aim: Mutations in IDH1 or IDH2 are associated with disease relapse and reduced survival in AML. Detecting IDH1 & IDH2 mutations with required sensitivity is critical for early cancer detection and efficient selection of targeted inhibitors for AML patients. Here, we describe the effort to develop a multiplex PCR assay that can detect 17 major IDH1 & IDH2 mutations directly from peripheral blood with high sensitivity and specificity.

Method: 17 IDH1 & IDH2 mutant plasmid DNA templates and 14 CRISPR-engineered IDH1 & IDH2 mutant cell lines were synthesized. There are four technical aspects contributing to this high sensitivity and specificity qPCR assay: **1.** Special primer designs, including SuperSelect (SS) and amplification-refractory mutation system (ARMS), help detect different mutations within the same codon. **2.** A two-step nested PCR to reduce non-specific amplification due to non-specific binding of primer to unwanted binding sites. **3.** A short (20-25nt) blocking oligonucleotide (wild-type blocker, WTB) to reduce SS and ARMS primers binding at the WT codon site. **4.** Four probes carrying different fluorescence reporters were used to detect the four IDH1 & IDH2 mutation codons. The designed SS and ARMS primer were screened with $5x10^4$ cps/test of mutant template in a whole blood background.

Result: All 17 IDH1 & IDH2 mutations can be detected at the LoD level (1%) (Figure 1, red). Adding WTB improved the specificity with a reduced background signal. Importantly, genomic DNA of the 14 IDH1 & IDH2 mutant cell lines can be detected when spiked into whole blood lysate at the LoD level (1%) with performance similar to plasmid DNA (Figure 1, blue).

Conclusion: A prototype IDH1&2 assay has been developed in an automated cartridge system that can detect 17 mutations of IDH1 & IDH2 directly in peripheral whole blood with required sensitivity and specificity to help manage AML patient therapy.

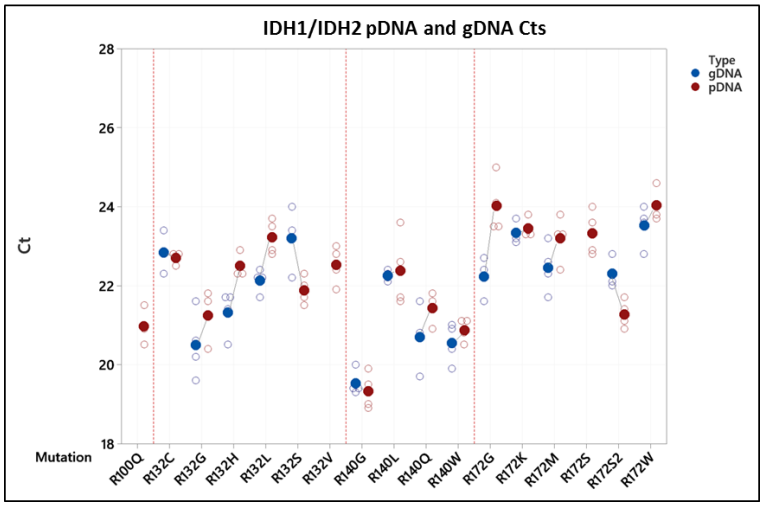

Figure 1: All 17 IDH1 & IDH2 mutations can be detected at the LoD level (1%) by the IDH1/2 Mutation assay. The cycle threshold (Ct) of 17 mutations was presented and grouped by codons. The mutation template (genomic DNA, gDNA or Plasmid DNA, pDNA) was spiked into EDTA whole blood lysate at 5x10^4 cps/test. No template spike-in gave a Ct >30 in one replicate and completely negative in the other seven replicates (data not shown). Gray lines connect average Cts of gDNA and pDNA templates with the same mutation.

HP013

Development of a NPM1 Mutation Test, an Automated and Standardized Cartridge-based Assay with Required Performance Characteristics for Quantitative Measurement of NPM1 Mutations

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[1]Oncology, R&D, Cepheid

Aim: AML is the most common acute leukemia in adults. NPM1 is one of the most common genetic abnormalities in AML (30%-35%). RT-PCR assay with high sensitivity and accuracy has become standard of care to determine the NPM1 mutation status for diagnosis, prognosis, and monitoring of AML. Here, we describe the analytical performance evaluation of the NPM1 Mutation test (Test), an automated and standardized test for quantifying mutant NPM1 mRNA transcripts (subtypes A, B, and D) relative to ABL1 as % NPM1 Mutation/ABL.

Method: Test's linearity and sensitivity (LoD, LoQ and LoB) were evaluated using serial dilutions of cell lysate in whole blood lysate for each of the three NPM1 mutant subtypes (A, B and D) and compared to a commercially available molecular test that is routinely used as standard of care (Comparator) clinically. Test's specificity was determined by testing 25 healthy donors. Test's reproducibility and precision were evaluated with general principles according to CLSI EP05-A3.

Result: Test's LoB was determined at 0.0085%. Test's highest LoD/LoQ was determined among the three subtypes at 0.030% (A/0.025%, B/0.023%, and D/0.030%), comparable to Comparator's sensitivity determined internally (Table 1A, B, and C). The Test demonstrated linearity within 0.014% – 2020%. Bounded by the LoQ and the software upper limit, the reportable dynamic range is 0.030–500% and showed high correlation with Comparator in a regression analysis (Slope =1.01, Intercept = 0.034, R^2 = 98.6%) (Figure 1). The Test has an analytical specificity of 100%. Test showed good reproducibility and precision at two input concentrations with acceptable total CV (~5%: 21.74-26.23; ~0.2%: 20.68-79.22).

Conclusion: The analytical performance evaluation demonstrated that the Test is highly sensitive and well-correlated with a commercially available molecular test that is routinely used as a standard of care testing for quantitative measurement of NPM1 mutation for monitoring AML during treatment.

Table 1. Analytical sensitivity evaluation of the NPM1 Mutation assay (Test)

1A. Limit of Detection, Limit of Quantitation and, and Limit of Blank (LoD, LoQ and LoB) of the NPM1 Mutation test [% NPM1 Mutation/ABL]

Subtype	LoD [%NPM1 Mutation/ABL]	LoQ [%NPM1 Mutation/ABL]	LoB [%NPM1 Mutation/ABL]
mutA	0.025%	0.025%	0.0085%
mutB	0.023%	0.023%	
mutD	0.030%	0.030%	

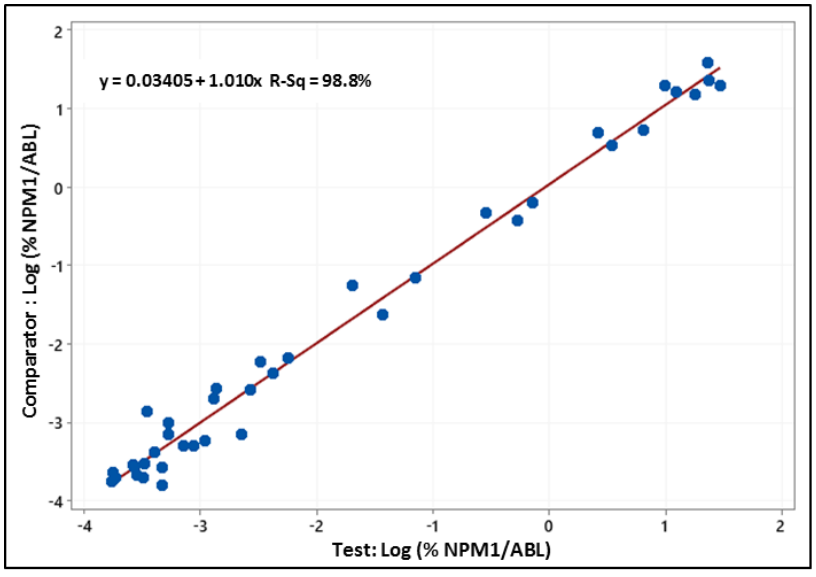
1B. Sensitivity comparison between the NPM1 Mutation assay (Test) and the Comparator assay at the % NPM1 Mutation/ABL near the assay LoD level for the three NPM1 mutation subtypes

Subtype	Test		Comparator	
	% Report	Pos rate	% Report	Pos rate
A	0.018%	20/20	0.020%	12/20
B	0.018%	20/20	0.023%	18/20
D	0.017%	20/20	0.018%	14/20

1C. Sensitivity comparison among the NPM1 Mutation assay (Test), the Comparator assay and an in-house ddPCR NPM1 mutation assay at the % NPM1 Mutation/ABL near the assay LoD level for the NPM1 mutation subtype B

NPM1 Mutation Subtype B	Test	Comparator		In-house ddPCR	
# of Cell/mL	% NPM1 Mutation/ABL	% NPM1 Mutation/ABL	Fold difference (Xpert/Comparator)	% NPM1 Mutation/ABL	Fold difference (Xpert/ddPCR)
1-cell	0.009%	0.034%	0.3	0.015%	0.59
2-cell	0.013%	0.016%	0.9	0.014%	0.93
4-cell	0.047%	0.031%	1.5	0.024%	1.93
10-cell	0.152%	0.222%	0.7	0.114%	1.34

Figure 1. Regression analysis of the linearity comparison showed high correlation and high concordance between the NPM1 Mutation assay (Test) and the Comparator assay



HP014

Development of a BCR-ABL p190 Test, an Automated and Standardized Multiplex Test for Quantitative Measurement of BCR::ABL p190 in ALL and CML Patients During Monitoring of Treatment

Tran T[1], Liu Y[1], Nguyen P[1], Saini J[1], Aslam A[1], Kadiyala V[1], Tan L[1], Liu M[1], Wei H[1], Day G[1], Yuan L[1]
[1]Oncology, R&D, Cepheid

Aim: RT-PCR assay with high sensitivity and accuracy that can reliably detect BCR::ABL p210 and p190 transcript levels is recommended as standard of care in managing ALL and CML patients during therapy. Here, we demonstrated the analytical performance evaluation of an automated and standardized BCR-ABL p190 test (Test) for quantitative measurement of BCR::ABL1 p190 transcript level relative to ABL1 for monitoring ALL and CML patients during treatment.

Method: Test's linearity was evaluated using serial dilutions of total RNA isolated from ALL SUP-B15 cell line containing BCR::ABL p190 transcripts in whole blood lysate (WB). Test's sensitivity (LoD, LoQ and LoB) was evaluated using serial dilutions of ALL/BCR::ABL p190 positive clinical specimens in WB. Test's specificity was determined by testing whole blood specimens from 20 healthy donors. Test's performance was further evaluated by comparing to three RT-PCR tests, including two commercially available molecular tests that are used as standard of care (Comparator I and II) and an in-house developed ddPCR test.

Result: Test's LoB was determined at 0.00032%. Test's LoD/LoQ was determined as 0.0065%. Test's linearity was demonstrated within 0.001% – 25%. Bounded by the assay LoD/LoQ, the reportable dynamic range is 0.0065 – 25%. Test's specificity is 98.8%. Test showed high correlation with three comparator assays in a regression analysis (Test/Comparator I, R^2 = 99.06%; Test/Comparator II, R^2 = 98.1%; Test/ddPCR, R^2 = 98.46%) (Figure 1). Test has comparable or better assay sensitivity among 4 tests (Table 1).

Conclusion: The analytical performance evaluation studies demonstrated that Test is highly sensitive and accurate. In the comparison study, Test showed good correlation and has comparable or better assay sensitivity when compared to three assays, including two commercially available tests as standard of care for measuring BCR::ABL1 p190 transcript level, supporting the intended use of the Test for the monitoring application for the ALL and CML patients during treatment.

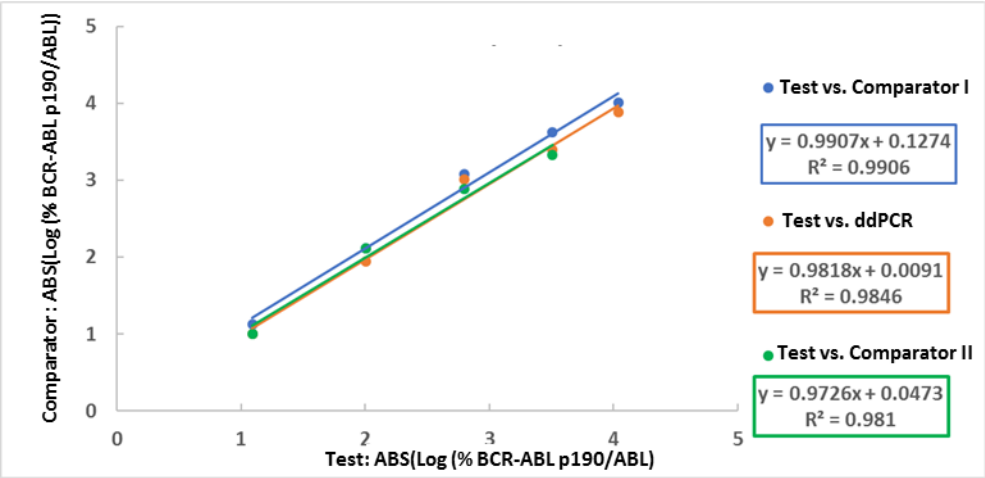


Figure 1. Regression plots of the correlation analysis for Test vs. three comparator assays (Comparator I, Comparator II and In-house ddPCR) for 42 BCR::ABL p190 positive samples.
High correlation observed between Test and Comparator methods (Test/Comparator I, R^2 = 99.06%; Test/Comparator II, R^2 = 98.1%; Test/ddPCR, R^2 = 98.46%).

Table 1. Sensitivity comparison for Test vs. three comparator assays

	Test	Comparator I	Comparator II	In-house ddPCR
Neg (3 negatives)	3 (-)	3 (-)	3 (-)	2 (-); 1**
0.005% – 0.01% (9 low positives)	9 (+)	8 (+); 1 (-)	8 (+); 1 (-)	7 (+); 2 (-)
0.03% – 25% (33 positives)	33 (+)	33 (+)	32 (+); 1 (-)	32 (+), 1**

**ddPCR abort due to loading error

HP015

Development of a FLT3-TKD Mutation Prototype Assay that is Fast and Quantitative using Lab in a Cartridge™ Technology

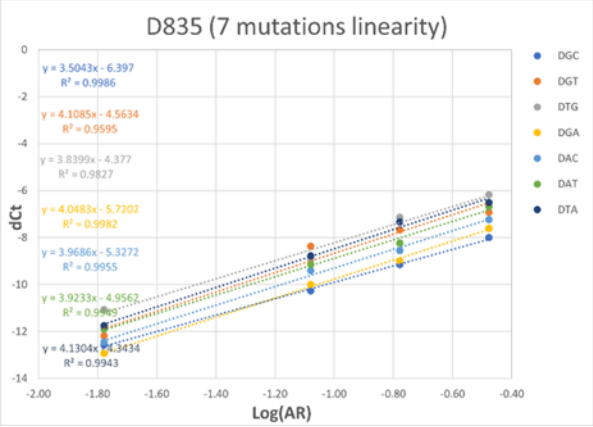
Saatian B[1], Calayag K[1], Das S[1], Xie G[1], Day G[1], Kushal S[1]
[1]Oncology, R&D, Cepheid

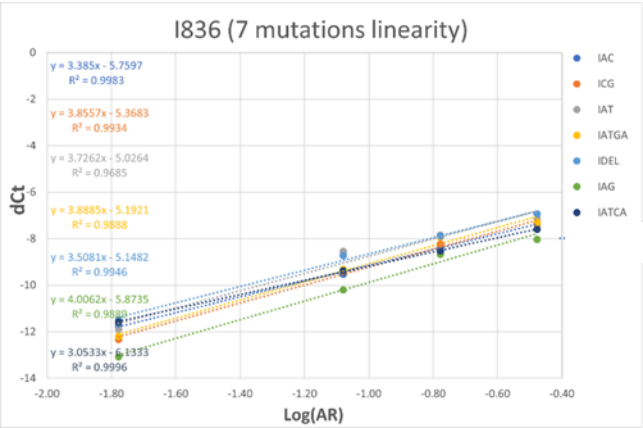
Aim: The targeted therapies for AML demands fast and reliable diagnostic tests. FLT3-TKD mutation is a common targetable mutation in AML (~7%). Current diagnosis of FLT3-TKD by PCR involves numerous, laborious, and time-consuming steps that includes whole blood (WB) processing, DNA isolation, plate-based PCR, enzyme digestion and subsequent fragment analysis by capillary electrophoresis. This study aimed to develop a faster, automated, and highly sensitive FLT3-TKD prototype that requires less hands-on time, no use of restriction enzymes or capillary electrophoresis and quantitatively detects 14 major clinically relevant FLT3-TKD mutations (7 in D835; 7 in I836) to support diagnosis and monitoring of AML patients.

Method: This assay uses the special chemistry, special design primers, and an optimized wild-type blocker to specifically detect SNPs and indels in FLT3-TKD mutated DNA, quantitatively. The dynamic range was evaluated using plasmid DNA with each of the 14 mutations spiked into the whole blood (WB), individually. The assay sensitivity was evaluated using serial dilutions of plasmid DNA of D835Y and CRISPR-CAS engineered cell line for the D835 G>A mutation in WB. Allelic ratio (AR) callout is calculated based on “Ratio of TKD mutation copies/ABL copies” in WB.

Result: The assay can detect and quantify all 14 FLT3-TKD mutations with an estimated LoD of AR 0.02 in WB. We observed good alignment of dCt-AR (deltaCt-Allelic ratio; dCt = ABL Ct – FLT3-TKD Ct) regression curve among all 14 mutations within the dynamic range tested (0.02-0.33). Using the mutant cell line (D835 G>A), and plasmid from most prevalent mutation D835Y G>T, the mutation was detected down to AR 0.008.

Conclusion: We have successfully developed an automated cartridge-based FLT3-TKD mutation prototype assay that can detect 14 major FLT3-TKD mutations in less than 3 hours in a dynamic range of 0.02–0.33 AR that can aid prognostic evaluation and monitoring of treatment in AML patients.





HP016

Illuminating the dark: systematic false negative FLT3-ITD detection by capillary electrophoresis in Australian testing

Du M[1], Tiong I[1], McBean M[1], Thompson E[1], Blombery P[1]
[1]Peter MacCallum Cancer Centre

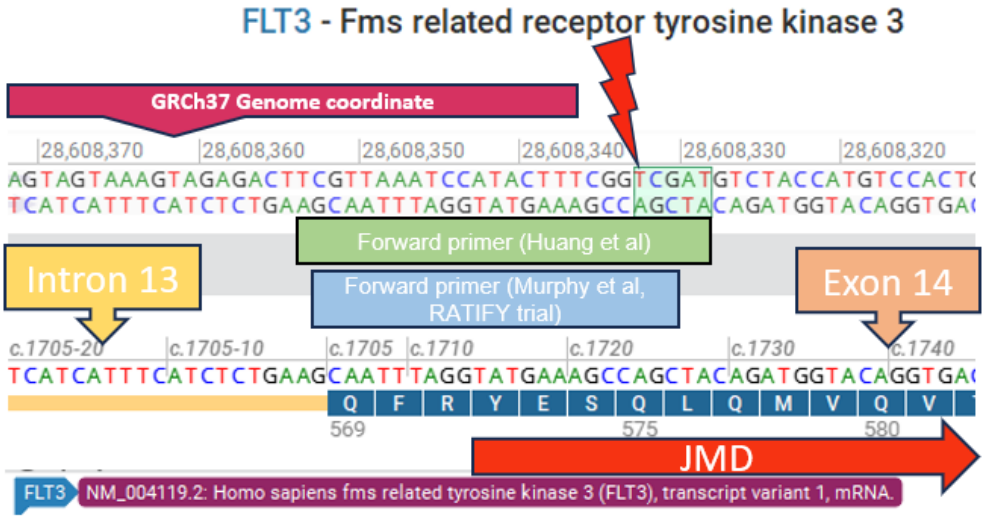
The rapid and accurate detection of internal tandem duplications (ITD) in the *FLT3* gene is critical for treatment decisions and prognostication in acute myeloid leukaemia (AML). Fragment length analysis by capillary electrophoresis (CE) is regarded as the gold standard assay for *FLT3*-ITD detection. Here, we present a case to highlight the risk of false negative results by CE and uncover likely systematic false-negatives in Australian CE testing.

A 74-year-old male was diagnosed with *NPM1*-mutated AML. *FLT3*-ITD was not detected by CE testing. Targeted next generation sequencing (NGS) unexpectedly revealed a 24-bp *FLT3*-ITD with a variant read frequency of 18% in the juxtamembrane domain (JMD) (NM_004119.2:c.1724_1727delinsTAGATGGTACAGGTGGTACAGGTGTACC).

Further investigation identified that the forward primer used for CE-PCR anneals within exon 14 and encompasses a small portion of the JMD (c.1714_1728). In this case, the *FLT3*-ITD occurred at the primer annealing site and was therefore not amplified or represented in the CE assay readout.

A survey of molecular diagnostic laboratories in Australia (n=7) revealed that one other laboratory currently uses the same primers for *FLT3*-ITD analysis (based on Huang et al, PMID:18477048) whereas six laboratories use primers first published by Murphy et al (PMID:12707374) and also used in the RATIFY trial (Stone et al, PMID: 28644114). Importantly, in both assays, the forward primer anneals to exon 14 and would not be expected to detect the above described *FLT3*-ITD or others located within this portion of the JMD (**Figure**).

Our findings highlight a limitation of the commonly used CE assays for *FLT3*-ITD detection in Australia, potentially leading to missed mutations and significantly impacting patient care. We aim to raise awareness among clinicians and laboratory professionals regarding this finding. We are currently designing new primers and retrospectively screening previously *FLT3*-ITD CE-negative AML cases to assess possible missed variants.



HP017

Auditing outpatient therapy and care coordination in adults with acute myeloid leukaemia

Nguyen R[1], Range H[3], Pitiyarachchi O[2], Descallar J[4], Nguyen J[1], McEwan A[1], Getta B[1], Dunlop L[1], Viiala N[1,2]
[1]Department Of Haematology, Liverpool Hospital, [2]UNSW Sydney, [3]Department of Pharmacy, Liverpool Hospital, [4]Ingham Institute for Applied Medical Research

Aim: Current treatment for fit patients with acute myeloid leukaemia (AML) is induction chemotherapy, with up to 4 cycles of high/intermediate dose cytarabine (H/IDAC) consolidation alone, as bridge to allograft or before maintenance therapy. Although patients require admission for induction chemotherapy, eligible patients in our centre can receive H/IDAC as an outpatient, with cytarabine delivered on days 1,3,5 via CADD pump; follow-up thrice weekly; and admission if required. To support safe delivery of outpatient H/IDAC, this audit assessed quality of care and adherence to haematology department guidelines to identify risks with this approach.

Method: Patients with AML eligible for intensive induction therapy at Liverpool Hospital (2015-20) were identified; cancer care coordinator (CC) involvement recorded; and suitability against key departmental outpatient H/IDAC eligibility (age<60; first H/IDAC as inpatient; age-specific dose; residing within 1hour of Liverpool Hospital; specific outpatient-based treatment consent) assessed. Descriptive statistics reported; time-to-event was calculated by Kaplan-Meier method.

Results: Of 109 patients identified, 62 patients received 131 cycles of H/IDAC. Median age of patients was 55y (range, 18-70); 31 (50%) males. 81 cycles commenced as an outpatient; 27 patients commenced all cycles as outpatients. 35 patients received their first H/IDAC as an inpatient; 39 met eligibility for age ≤60 years; 60 patients lived within 1 hour of Liverpool Hospital; 12 received cytarabine dose discordant from age-based recommendations, 3 receiving doses higher than recommended. Written consent was unable to be located for 11 pts; no consent forms specified outpatient chemotherapy delivery. 49/109 patients (45%) received care coordination; 3 were linked by prior diagnosis (secondary AML). Median time from diagnosis to CC review was 56 days (IQR 45-385).

Conclusion: This audit highlights the need for increased access to care coordination and improved adherence to agreed eligibility criteria, including consent process, patient suitability for outpatient chemotherapy, and aged-based cytarabine dosing.

Criteria	Compliance (N=62)
Age ≤ 60 years, n (%)	39 (63%)
Residence within 1 hour of Liverpool Hospital, n (%)	60 (97%)
Cytarabine dose concordant with age-based recommendation, n (%)	50 (81%)
Cytarabine dose at or below age-based recommendation, n (%)	59 (95%)
Received first consolidation cycle as inpatient, n (%)	35 (56%)
Written consent specified delivery of H/IDAC as outpatient, n (%)	0 (0%)

Table 1. Suitability of patients receiving outpatient H/IDAC consolidation assessed against departmental protocol eligibility criteria.

HP018

Utility of panel-based gene sequencing in the investigation and risk stratification of core binding factor Acute Myeloid Leukaemia

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Aim: Next generation sequencing (NGS) has become an invaluable tool in identifying mutations of clinical significance in acute myeloid leukaemia (AML). Currently, in Queensland, all newly diagnosed AML patients undergo testing using the commercial Archer Core Myeloid Gene Panel (CMGP). The results of core binding factor (CBF) AML patients have been analysed to assess impact on diagnosis, prognosis and treatment.

Method: A search was conducted on the Queensland Cancer Alliance QOOL database to identify patients with AML. These patients underwent NGS using a 37-gene Archer VariantPlex Core Myeloid Gene Panel to detect variants of clinical significance in myeloid neoplasms. Of these, we extracted the data of those with CBF-AML. We established their cytogenetic profile at time of diagnosis using the standard AML panel, and then again after CMGP testing. We classified each patient into favourable, intermediate or adverse risk, according to the 2022 ELN classification system, both pre- and post-CMGP.

Results: 509 AML patients had CMGP testing between October 2019 and May 2024. A total of 27 patients were CBF-AML (63% male, median age 47), defined by the presence of *RUNX1::RUNX1T1* or *CBFB::MYH11* gene fusion. CMGP identified additional variants of significance in 24 (89%) of these patients, including variants in the following genes; *KIT, FLT3, NRAS, TET2, ASXL1, WT1, KRAS, CBL, DNMT3A, PTPN11, RUNX1, SRSF2 and U2AF1*. In all patients, ELN risk was favourable both pre- and post-CMGP testing. Identification of variants did not influence the treatment plan.

Conclusion: As per the 2022 ELN classification by genetics at initial diagnosis, CBF-AML always results in favourable risk categorisation, regardless of additional variants detected. CMGP testing in this cohort, over and above the standard diagnostic testing, does not currently add any benefit to inform treatment decision making. Considering the constraints on NGS testing, patients with CBF-AML could be considered non-urgent.

HP019

Is shorter course of Azacitidine- Venetoclax for NPM1 mutated AML adequate to achieve durable remission?

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Background: NPM1 is now considered an AML-defining mutation in myeloid malignancies (1)(2). Combination of Azacitidine and venetoclax (Aza-Ven) is standard of care for induction-ineligible patients with AML, though it is not considered curative therapy and is used until progression or intolerance (3). NPM1 mutations appear to have significant sensitivity to venetoclax, with MRD-negative remissions reported (4). Here we report a durable, ongoing MRD-negative remission four years following only two cycles of Aza-Ven.

Case Presentation: A 62-year-old female presented with symptomatic anaemia on a background of hypertension, hypercholesterolaemia, obesity and generalised anxiety disorder. Bone marrow examination was hypercellular with multilineage dysplasia and 7% blasts and an NPM1 (Type Non-ABD, (NPM1 c.870_873delinsTATGGCAA; p.(Trp290Cysfs*10)) mutation was demonstrated. MDS with excess blasts-1 was diagnosed as per WHO 2016 classification. Repeat examination 4 months later demonstrated 11% blasts, in keeping with Acute Myeloid Leukaemia with NPM-1 mutation by modern classification. A myeloid next generation sequencing (NGS) panel demonstrated no other mutations, and the karyotype was normal. Aza-Ven was initiated, but was ceased after 2 cycles due to prolonged, severe cytopenias complicated by pseudomonas bacteraemia requiring intensive care. Repeat bone marrow biopsy demonstrated morphological and MRD-negative remission by NGS method. MRD remained negative on peripheral blood for >2 years, and the patient remains in CR at 4 years post therapy with normal blood counts.

Conclusion: NPM1-mutated AML is sensitive to venetoclax. This is the first report, to our knowledge, of potential cure from only two cycles of Aza-Ven. This is worthy of further exploration in MRD-adapted clinical trials.

Reference:

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HP020

The real-world experience of CPX-351 use in Australia: an analysis of the Vyxeos Managed Access Program

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[1]Austin Health, [2]Peter MacCallum Cancer Centre

Aim: CPX-351 (Vyxeos), a liposomal formulation of cytarabine and daunorubicin at a fixed 5:1 molar ratio, has previously been demonstrated in a pivotal phase III study to improve outcomes (compared to 7+3) in the treatment of high-risk or secondary acute myeloid leukaemia (AML), a heterogeneous condition for which highly effective therapies have been lacking. This present study evaluates the real-world Australian experience of patients receiving CPX-351 via the Vyxeos managed access program (MAP).

Method: In this multicentre retrospective review, data were collated from the 28 sites across Australia which had cumulatively treated over 80 high-risk or secondary AML patients aged ≥18 years with at least one dose of CPX-351, accessed through the MAP. Particular focus was placed on patients' baseline cytogenetic and molecular characteristics, in order to identify differences in outcomes between subgroups, acknowledging the significant disease heterogeneity and recent evolutions in AML classification. Survival estimates were calculated by the Kaplan-Meier method, and the log-rank test was used to compare patient groups. Prognostic factors impacting overall and event-free survival were analysed using Cox proportional hazards model.

Results: The Australian experience with Vyxeos demonstrates adoption of the MAP across public and private hospital settings. Survival and response outcomes were similar to observed outcomes in the pivotal phase III trial and the experience of other groups internationally. While trends towards differences in outcomes were observed with particular cytogenetic and molecular subgroups, further evaluation is warranted to determine whether CPX-351 particularly benefits those with specific underlying genomic aberrations.

Conclusion: The availability of CPX-351 in Australia through a MAP has enabled Australian haematologists to gain knowledge in the safe and effective use of a novel treatment option in a challenging patient population. These data contribute to the global experience of CPX-351. Further study of CPX-351's benefits to particular genomic subgroups is warranted.

HP021

Does It Ring True: A Case Report of The Development and Spontaneous Resolution of Monosomy 7 in Acute Myeloid Leukaemia in Remission Post-Cytotoxic Therapy

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[1]QML Pathology, [2]The University of Queensland

We present a case of a 64-year old man with Acute Myeloid Leukaemia with NPM1 mutation diagnosed in November 2020. The patient received intensive chemotherapy and ultimately achieved a MRD negative remission at the end of chemotherapy treatment.

In April 2022, the patient developed moderate thrombocytopenia (platelets 75 x 10^9/L). Bone marrow examination demonstrated ongoing morphological remission with mild dyserythropoiesis. Interestingly, conventional karyotype revealed the new development of a ring chromosome 7 in 7/20 metaphases was noted. This ring chromosome consisted of the centromere of chromosome 7 with minimal additional genetic material, resulting in a functional monosomy 7. Interphase FISH also confirmed deletion of the long arm of chromosome 7 (deletion 7q). Serial bone marrow examination six months later confirmed persistence of this ring chromosome 7, albeit at a lower burden of 2/20 metaphases.

On bone marrow examination 12 months later, the ring chromosome 7 was subsequently not detectable and remained absent in March 2024, ultimately not detected on conventional cytogenetics, FISH, or Microarray. Of note, morphological findings at any of these timepoints did not support a diagnosis of MNpCT and NPM1 MRD using RT-qPCR methods remained negative during this period.

Spontaneous clearance of monosomy 7 is rare but has been described. This is postulated to occur due to either a) immune reconstitution post-chemotherapy and/or b) the monosomy 7 in not providing sufficient proliferative advantage to the clone in isolation. In this case, the persistent MRD negativity may suggest a subclonal distribution of the monosomy 7, rather than reflecting true relapse of the leukaemic clone.

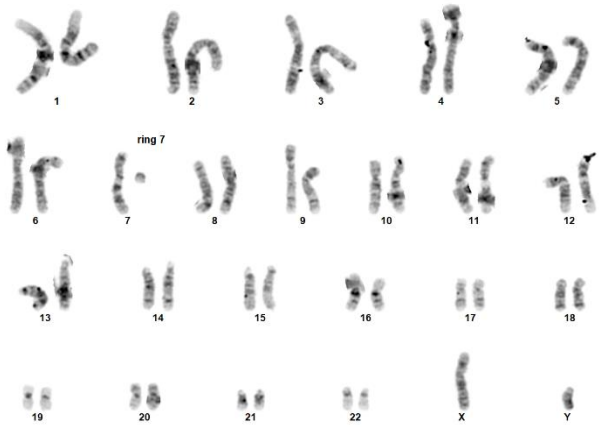

Figure 1. Giemsa-banded karyotype on the patient's bone marrow aspirate specimen in April 2022 displaying a ring chromosome 7 (labelled). This ring chromosome 7 consisted of the chromosome 7 centromere with minimal additional genetic material, resulting in a functional monosomy 7.

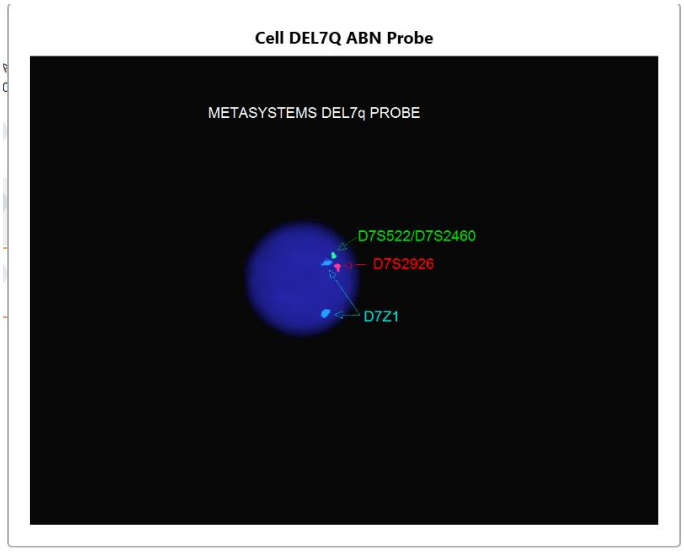

Figure 2. Fluorescent in-situ hybridisation with locus-specific probes for 7q22 and 7q31, confirming deletion of the long arm (q) of chromosome 7.

HP022

Difficulties in the Diagnosis and Management of Myelodysplasia with low blast count and NPM1 Mutation

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Aim and Method: The diagnostic definition of myelodysplasia (MDS) with low blast count and NPM1 mutation differs between the International Consensus Classification of Myeloid Neoplasms and Acute Leukemias (ICC)(1) and WHO 2022(2). The ICC mandates a blast count of ≥ 10% for the diagnosis of AML with NPM1 mutation. In contrast, the WHO classification has no blast count cutoff for AML with NPM1(1,2). Therefore, morphological MDS with < 10% blast and NPM1 mutation is classified as MDS by ICC or AML with NPM1 mutation by WHO.

We describe the clinical features and management outcome of 2 cases which fall into this category and were diagnosed prior to the new classification systems.

Results:

Case	1	2
Age	61	63
FBC at diagnosis	WCC 1.2 x10^9/L, Hb 117 g/L PLT 73 x10^9/L	WCC 2.9 x10^9/L, HB 92 g/L PLT 39 x10^9/L
Bone marrow (2016 WHO) Blast	MDS with MLD 1%	MDS-EB2 14%
ICC	MDS with multilineage dysplasia (MLD)	AML with NPM1 mutation
WHO	AML with NPM1 mutation	AML with NPM1 mutation
Cytogenetics	46,XY,t(5;60(q23.2;q23)c[20]	45,X,-Y[19]/46,XY[1]
Myeloid NGS	NPM1 c.860_863dup p.(Trp288Cysfs*12) 16.3% ETV6 c.775dup p.(Arg259Profs*41) 4.6% WT1 c.1159_1150insGCGG p.(Ala387Glyfs*4) 19.5%	NPM1 c.860_863dup p.(Trp288Cysfs*12) 32%
Treatment	Observation Progress marrow in 12 mths AML with NPM1 mutation. 70% blasts. 7+3 induction chemotherapy and matched sibling allogeneic stem cell transplant	Azacitidine x11, MUD allogenic stem cell transplantation
Survival from diagnosis	Alive, 15 mths	Alive 49 mths

Conclusion: The diagnosis of these cases varies between MDS-MLD and AML with NPM1 mutation depending on the classification system(1,2). The unifying feature is NPM1 mutation which is an AML defining variant(3,4) and is associated with transformation to AML(5). The standard treatment is contentious. Hypomethylating agent +/- allogeneic stem cell transplantation is a potential treatment with minimal residual disease monitoring.

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HP023

Real-world observation of poor deliverability of venetoclax and azacitidine in patients with acute myeloid leukaemia

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Aim: Venetoclax plus azacitidine (VEN-AZA) is the standard of care for patients with acute myeloid leukaemia (AML) unfit for intensive chemotherapy. Prolonged cytopenias and toxicities secondary to VEN-AZA limit treatment administration in certain patients leading to adverse outcomes, although exact characteristics are unclear. We describe our 'real-world' experience with VEN-AZA focusing on treatment deliverability.

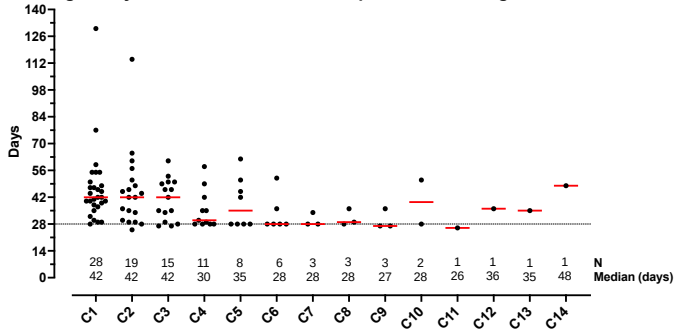
Method: Retrospective review of adult patients with AML treated with frontline VEN-AZA at Monash Health.

Results: 42 patients received VEN-AZA, 67% ELN2022 adverse risk and 46% secondary/therapy-related AML (sAML). Median age was 74 years (range 35-88). In Cycle 1 (C1), febrile neutropenia was observed in 57%, including 3 requiring ICU. 30-day mortality was 10%. 95% received VEN plus posaconazole for C1, median VEN duration 21 days (range 4-28). Median time to neutrophil≥1.0x10^9/L and platelet≥50x10^9/L (P50) in C1 were 33 (range 25-48) and 21 days (range 1-not recovered, 3 did not achieve P50), respectively.

Morphological remission was achieved in 67% (15 CR, 11 CRi, 2 MLFS). Median overall survival was 19.4 months. Median number of VEN-AZA cycles for patients achieving remission was 3 (range 1-15). We observed significant prolongation of cycle duration (Figure), with >50% commencing next cycle ≥42 days in C1-3. Only 10(36%) received >3 cycles, with 13(46%) ceasing therapy due to poor count recovery, 3(11%) for allotransplant and 2 deaths(7%) prior to Cycle 4. Factors associated with poor count recovery include sAML (7/11, 64%), prior azacitidine (3/3, 100%). Molecular correlates of count recovery were examined. Specifically, we observed cumulative prolongation of count recovery in 5(14%) patients with *DDX41* mutations (100% CR/CRi), with 100% VEN-AZA discontinuation by C3, 3/5(60%) due to prolonged G3/4 thrombocytopenia and 2/5(40%) to neutropenic sepsis.

Conclusion: We observed poor treatment deliverability of VEN-AZA in real-world patients, contrary to the median of 7 cycles reported in VIALE-A. Further multi-centre Australian data is needed for more robust analysis.

Figure. Cycle duration of VEN-AZA in patients achieving remission



HP024

Germline DICER1 mutation associated Acute Myeloid Leukemia.

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Aim: Cytopenias are a prevalent clinical presentation in hematology practice, with varied etilogies. Germline variants predisposing individuals to myeloid neoplasms (GVMN) constitute a relatively rare yet significant subset of inherited disorders frequently associated with cytopenia(s). This study aims to assess the utility of genetic testing through next-generation sequencing (NGS) in identifying (GVMN) as the cause of unexplained cytopenia(s).

Method: This retrospective study analysed 3-years of data from patients presenting with unexplained cytopenias. Initial investigations included comprehensive clinical evaluation, imaging studies, complete blood count, peripheral smear evaluation, and biochemical studies. Bone-marrow examination was performed to assess cellularity and morphology of all cell lineages. Other investigations included chromosomal breakage study and PNH testing. Cases of unexplained cytopenias were subjected to NGS. DNA extracted from peripheral blood was followed by NGS-library preparation and sequencing on Illumina® platforms. Standard bioinformatic pipelines were used to perform quality checks, read alignment, and pathogenicity testing, adhering to ACMG/AMP guidelines for variant reporting.

Results: Initially 88 patient's data was reviewed. 23 patients were excluded due to non-availability of adequate data. Sixty-five patients, aged 15-74 years, were analyzed, with a male-to-female ratio of 2.3:1. Pancytopenia was observed in 40 patients, while the remainder exhibited single lineage cytopenia (16) bicytopenia (9). Six (6/65, 9.2%) individuals exhibited at least one genetic variant, consistent with a GVMN. Identified heterozygous/ autosomal dominant variants included ANKRD26 (2), RUNX1 (2), DDX41 (1), and GATA2 (1). Point mutations were noted in all cases.

Conclusion: Individuals with GVMN progress to organ dysfunction and are predisposed to myeloid neoplasms. Failure to recognize this entity amidst cytopenia(s) may lead to misdiagnosis (e.g., ITP) and incorrect management. Screening family members is crucial to identify silent carriers, especially in sibling or related donor selection for hematopoietic stem cell transplantation. GVMN can explain the cause in ~10% patients with unexplained cytopenias.

HP025

Outcomes of AML allogeneic transplantation in Western Australia for Female donors to Male recipients

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Aim: To review patients receiving AML allografts from related donors in Western Australia from 1984-2024 and document the number of PBSCs vs BM, including in sibling Female to Male (FtoM) transplants. PBSCs have been linked to increased cGVHD[1,2], with a study showing non relapse mortality (NRM) and overall survival (OS) significantly worse at 2 years post allograft compared to bone marrow (BM) for FtoM (2-year OS, 76% vs 62%; P 5 .0084; 2-year NRM, 10% vs 21%; P 5 .0078)[1].

Method: We used existing databases and electronic medical records to obtain the data including donor type, recipient age, stem cell source, CD34 counts and outcomes including survival and GVHD.

Results: In Western Australia, 50 FtoM related donor transplants were performed in 49 patients over the past 40 years (One patient underwent a second allograft). The average age was 36 (range 3-68). One haploidentical related transplant was performed during this time. 23 patients (47%) are alive.

Since 2017, at Fiona Stanley Hospital, there were 19 FtoM allografts performed, all with PBSCs as the stem cell source (16 fresh, 3 cryopreserved) with average CD34 of 6.27 $x10^6$/kg (range 2.89-10.65). Recipient average age was 48 (range 17-68). 16 patients remain alive 84%, and 3 have died. Graft vs Host Disease and other information is to follow.

Conclusion: FtoM Allografts for AML performed at FSH have been associated with high survival rates and were performed on 19 patients from 2017-2024 with 50 procedures over the past 40 years.
PBSCs were used exclusively as the stem cell source, and this practice is being reconsidered in sibling FtoM AML cases, with GvHD rates being reviewed.

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HP026

Core-binding factor AML treated with non-intensive therapy in the MRD era – case report and literature review

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Aim: Core-binding factor acute myeloid leukaemia (CBF-AML) accounts for 15% of new AML cases. CBF-AML is categorised as favourable risk due to high remission rates with cytarabine-based chemotherapy and reasonable long-term survival. Measurable residual disease (MRD) monitoring by is predictive of survival and relapse risk in intensively-treated patients.

However, few data are published about the efficacy of non-intensive therapy in CBF-AML. The relevance of ELN prognostic classification and MRD assessment in this cohort is unclear.

We report a case of an elderly woman with CBF-AML treated with modified non-intensive therapy, and perform a literature review of non-intensive therapy in CBF-AML.

Method and Results: A 75-year-old woman presented April 2024 with fatigue and cytopenias. Bone marrow revealed acute monoblastic leukaemia with karyotype demonstrating inv(16)(p13.1;q22). *CBFB::MYH11* gene rearrangement was confirmed by FISH. Targeted DNA next generation sequencing demonstrated variants in *NRAS* and *WT1*.

She was unfit for intensive induction chemotherapy due to age and comorbidities. She commenced venetoclax azacitidine therapy for one cycle followed by intermediate-dose cytarabine consolidation for up to four cycles. Bone marrow MRD will be assessed at the end of each cycle. She is expected to have completed treatment by October 2024.

A literature review for evidence regarding non-intensive therapy in CBF-AML was undertaken. Patients with CBF-AML are often excluded from trials assessing non-intensive therapy, including VIALE-A. Evidence from small case series report overall response to venetoclax azacitidine therapy of 33 to 70%. In some series, patients are rescued or consolidated with cytarabine-based chemotherapy. Hypomethylating agents can convert low-level MRD to molecular remission in CBF-AML.

While MRD is predictive in other favourable-risk AML subtypes treated with non-intensive therapy, this evidence in lacking in CBF-AML.

Conclusion: The management of unfit patients with CBF-AML is an area of unmet need. We report an instructive case alongside the current evidence.

HP027

Safety and feasibility of outpatient venetoclax ramp-up in patients with acute myeloid leukemia

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Aim: Amidst the global healthcare crisis of hospital bed shortages, alternative strategies have been implemented in venetoclax-based regimens for acute myeloid leukemia (AML) patients at the Royal Brisbane and Women's Hospital. This involves ramp-up in the outpatient setting, following stringent criteria with close biochemical monitoring. We evaluate the safety and feasibility of venetoclax ramp-up in combination with low-dose chemotherapy for AML patients.

Method: We conducted a retrospective analysis evaluating all AML patients treated with venetoclax in combination with azacitidine or low-dose cytarabine (LDAC) between March 2021 and April 2024. Primary endpoint was incidence of tumour lysis syndrome (TLS) in outpatient cohort. Patients with molecular relapse but without morphological relapse were excluded. Patients were deemed suitable for outpatient venetoclax ramp-up if they met certain criteria based on WCC, LDH, renal function, ability to tolerate oral hydration and follow instructions (as per institutional guideline). TLS was defined by Cairo and Bishop criteria. Clinical and laboratory data were collected from electronic medical records.

Result: Thirty-eight AML patients (median age: 71 years; range: 21-84 years) received venetoclax/azacitidine or venetoclax/LDAC and were included in the study. Twenty-six (68%) patients met the criteria for outpatient venetoclax ramp-up (median age: 74 years; range: 21-81 years). Of these patients, fifteen (58%) had newly diagnosed AML and eleven (42%) morphological relapse. Three (12%) outpatients developed TLS (2 newly diagnosed; 1 relapse) and required admission for supportive care with no deaths or adverse events. Twelve (33%) patients were admitted for inpatient venetoclax ramp-up with two (17%) developing TLS. The most common reason for inpatient ramp-up included: renal impairment (n=5; 42%) and frailty (n=4; 33%).

Conclusion: Results demonstrate venetoclax ramp-up in the outpatient setting is safe and feasible in a carefully selected cohort of patients who meet low-risk criteria. Clear institutional guidelines are essential to avoid unnecessary hospital admissions while ensuring safety of all patients.

HP028

Molecular profiling of myeloid malignancies utilising a 37-gene next generation sequencing panel, incorporating diagnostic and prognostic reclassification via 2022 WHO, ICC and ELN guidelines

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Aim: To perform a retrospective audit of patients diagnosed with a myeloid malignancy and tested by the Archer Variant Core Myeloid next generation sequencing (NGS) panel across Queensland.

Method: The Archer NGS panel is a 37-gene DNA panel that covers 265 regions of interest clinically relevant to myeloid malignancies. Retrospective analysis was performed on 535 consecutive paediatric and adult patient specimens submitted for evaluation by the Archer NGS panel, from August 2019 to June 2022.

Results: The most frequently mutated genes in patients with acute myeloid leukaemia (AML, n=196), myelodysplastic syndrome (MDS, n=105), myeloproliferative neoplasm (MPN, n=100), MDS/MPN (n=46), and therapy-related myeloid neoplasms (n=36) were seen with frequencies similar to literature. 16 patients were newly identified with myeloid neoplasm with germline predisposition.

Of the AML-NOS and AML-MRC cohort (n=77, WHO 2017), there were 12 and 9 patients respectively that were reclassified as AML with defining genetic abnormalities via the 2022 WHO and ICC guidelines. A comparison of ELN 2017 versus 2022 diagnostic risk classification re-stratified 19% patients with AML into a worse prognostic category, and 3% into a better prognostic category.

Of the 105 patients with MDS (WHO 2017), there were 10 and 5 patients respectively that were reclassified as AML with defining genetic abnormalities via the 2022 WHO and ICC guidelines (due to *NPM1* and *MECOM* rearrangement). A further 9 were reclassified as MDS with biallelic/mutated *TP53*, and a further 13 and 12 respectively as MDS with *SF3B1* via 2022 WHO and ICC guidelines.

Conclusion: The Archer NGS panel covers all clinically actionable genes including those in recently updated classification and risk stratification guidelines, allowing seamless transition to adopting new consensus standards.

HP029

Patterns of Residual Clonal Haematopoiesis revealed by Whole Genome sequencing in AML in Morphologic remission

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Aim: The landscape of clonal haematopoiesis (CH) in acute myeloid leukaemia (AML) patients in morphologic remission has been predominantly studied with targeted sequencing to date and shown persistence of mutations in *DNMT3A*/*TET2*/*ASXL1*. We aimed to use an unbiased comprehensive whole genome sequencing (WGS) approach to understand the landscape of CH in AML remission samples.

Method: WGS was performed on 12 patients diagnosed with *de novo* or secondary AML. Bone marrow (BM) at diagnosis and in morphologic remission, alongside a matched germline (hair) sample, were assessed for somatic DNA alterations across all variant classes.

Results: CH was detectable in morphologic remission post-AML therapy in 8/12 patients. The median size of the compartment harbouring CH was 52% (range, 24-92%), with evidence of multiple distinct CH clones in 5 patients. Clonal relatedness to the original AML clone (i.e., preleukaemic CH) was demonstrated in 6/8 patients with CH. Emergent CH (i.e., no shared variants with AML clone) was detected in 7/8 patients.

The genomic complexity of CH in morphologic remission varied, with WGS showing a median of 637 single nucleotide variants (range, 209-1637) per patient. Chromosomal copy number variants persisted in morphologic remission in two patients. Mutations in canonical myeloid driver genes were detected in 8/13 CH compartments, while the remaining 5 compartments exhibited less established candidate drivers (*RIT1*^{S35T}, del20q) or no recognised drivers.

WGS revealed diverse clonal complexity in morphologic remission, with three broad phenotypes: (i) no/low-level non-complex CH in remission, (ii) compartment dominance by preleukaemic CH, (iii) complex compartment dominance by preleukaemic CH and emergent CH. Notably, 7 cases of AML, myelodysplasia-related exhibited all phenotypes, highlighting the heterogeneity of this entity.

Conclusion: WGS of patients in morphologic remission from AML showed a complex landscape of CH architecture. These results have significant implications for measurable residual disease detection, prognosis, and post-remission management.

HP030

Utility of Bone Marrow assessment during Consolidation Therapy in Acute Myeloid Leukaemia: too much of a good thing?

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Aim: Bone marrow aspirate and trephine (BMAT) is the primary method for assessing remission and MRD in AML, however it carries the risks of an invasive procedure. For all AML cases undergoing intensive induction/consolidation, ELN recommends bone marrow MRD assessment after 2 cycles of chemotherapy and end of treatment.[1] Institutional practices vary, with many undertaking more frequent BMAT assessment. The aim of this study was to assess the utility of BMATs performed outside recommended timepoints during consolidation, by detecting unexpected relapse in patients with reassuring peripheral counts.

Method: We conducted a retrospective analysis of all AML patients without a molecular MRD marker, undergoing consolidation chemotherapy at RBWH between January 2017 and May 2024. The primary endpoint was the number of BMATs performed outside ELN-specified timepoints and the rate of morphological or flow cytometry relapse on BMATs, in patients achieving at least CRh (neutrophils >0.5x10^9/L, platelets >50x10^9/L, absence of circulating blasts) on peripheral blood.

Results: Out of 142 patients undergoing consolidation chemotherapy over this period, 42 patients were identified for analysis. Median age was 57 years (19-69) with 62% male (n=26). After induction, 69% of patients (n=29) achieved remission and BMATs during consolidation were analysed. In total, 61 BMATs were performed, with 52% (n=32) outside ELN-specified timepoints. There were 5 patients (17%) who relapsed during consolidation; all failed to meet peripheral blood CRh at time of BMAT. Only one relapse was identified on BMAT performed outside of recommended timepoints. In patients with at least CRh on peripheral blood, no relapses were identified on BMAT.

Conclusion: Our cohort demonstrated a significant relapse rate during consolidation. However, performing BMATs outside ELN-specified timepoints in patients with at least CRh on peripheral blood, did not increase detection of relapse. These results support the ELN recommendations, and highlight the potential for judicious BMAT monitoring during AML treatment.

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HP031

Tetraploid AML – a distinct subgroup or part of the crowd?

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Aim: Tetraploidy/near tetraploidy (81-103 chromosomes) is a rare karyotype in AML. It is generally seen in older males, and morphologically associated with large blasts and dysplasia[1]. Due to its scarcity, clinical/prognostic data are limited, and it is unclear if it represents a distinct subgroup of AML.

Methods: We present a retrospective case series of tetraploidy in AML, from the central statewide cytogenetics laboratory (Pathology Queensland). Cases were reviewed to determine patient and disease characteristics including morphology, molecular/cytogenetic information, treatment, and outcomes.

Results: A total of 19 cases were identified, with key features in Table 1. In three cases (case 1-3), tetraploidy was stemline and not associated with a complex karyotype. In these cases, another abnormality fulfilling a WHO/ICC diagnosis was found – Trisomy 8 (Case 1), *RUNX1* and *SRSF2* variants (Case 2), and *SRSF2* and *EZH2* variants (Case 3). Most cases (n=13) were AML, myelodysplasia related, due to a complex karyotype, which incorporated tetraploidy as a component. Two cases had a favourable cytogenetic abnormality (case 16, 17), with outcomes consistent with the favourable classification. Excluding these cases, survival was poor, with 1 patient (case 2) surviving >18months.

Conclusion: Overall, this series does not separate tetraploidy as a distinct AML entity, with cases aligning with existing diagnoses incorporating recognised molecular/cytogenetic abnormalities. Tetraploidy presents challenges in karyotyping, and requires skilled interpretation in the presence of multiple clones and co-existent abnormalities. Additional cases are required to further define significance, and expanding NGS availability presents the opportunity to detect associated molecular signatures.

Table 1: Case descriptions for AML cases with tetraploid cytogenetics

	Sex	Age	WHO Classification (2022)	Tetraploid Classification	Therapy	OS (mo)
1	**M**	**71**	**AML, defined by differentiation**	**Stemline, not complex**	**Intensive**	**6**
2	**M**	**62**	**AML, myelodysplasia related**	**Stemline, not complex**	**Intensive**	**Survives**
3	**M**	**65**	**AML, myelodysplasia related; pCT**	**Stemline, not complex**	**Palliative**	**0**
4	M	78	AML, myelodysplasia related	Subclone, complex	Non-intensive	11
5	M	81	AML, myelodysplasia related	Subclone, complex	Non-intensive	1
6	M	57	AML, myelodysplasia related	Stemline, complex	Intensive	2
7	M	69	AML, myelodysplasia related	Stemline, complex	Palliative	1
8	M	8	AML, myelodysplasia related	Subclone, complex	Intensive	0
9	F	71	AML, myelodysplasia related	Stemline, complex	Intensive	16
10	M	85	AML, myelodysplasia related	Stemline, complex	Palliative	0
11	F	63	AML, myelodysplasia related	Subclone, complex	Intensive	2
12	M	86	AML, myelodysplasia related	Stemline, complex	Palliative	6
13	F	83	AML, myelodysplasia related	Stemline, complex	Palliative	13
14	M	75	AML, myelodysplasia related	Stemline, complex	Palliative	2

15	M	82	AML, myelodysplasia related	Subclone, complex	Non-intensive	1
16	M	58	AML, with RUNX1::RUNXT1 fusion	Subclone, complex	Intensive	Survives
17	F	54	APL with PML::RARA fusion	Stemline, complex	Intensive	Survives
18	F	30	Acute Undifferentiated Leukaemia	Stemline, complex	Intensive	0
19	M	73	MPN in blast phase (post ET-MF)	Subclone, complex	Non-intensive	2

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HP032

Outcomes following Azacitidine and Venetoclax for patients ineligible for standard induction therapy for Acute Myeloid Leukaemia in a regional centre

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Aim: To assess the efficacy of azacitidine and venetoclax in treating acute myeloid leukaemia (AML), focusing on survival, remission rates and adverse events.

Method: A retrospective single-centre observational cohort study was conducted between January 2021 and May 2024 of all patients with AML treated with azacitidine and venetoclax at The Tweed Hospital – Haematology Unit. Patient demographics and outcome data were extracted from electronic medical records.

Results: A total of 11 patients with AML were included. The median age was 74. Total azacitidine-venetoclax cycles ranged from 2 to 18. 63.6% of patients (7 of 11) had documented complete remission with incomplete haematological recovery after cycle 1. Median length of survival was significantly longer than the original VIALE-A study at 21.1 months compared to 9.6 months in the original study (p=0.049). Rates of grade 3 or higher anaemia, thrombocytopaenia, or neutropaenia were exceedingly high at 81.8%, 81.8% and 90.9% respectively. Notably, 81.8% of patients had at least one episode of febrile neutropaenia, of which 15.4% (2 of 13) required admission to ICU. The median cycle length was 36 days, indicating a median delay of 7 days from the recommended 28-day treatment cycle.

Conclusion: Remission rates following treatment with Azacitidine and Venetoclax remain largely favourable. Differences in survival likely represent the small population compared and the heterogeneity of the disease. High rates of adverse events, in particular infections and cytopaenias (mainly neutropenia) are challenging for the timely administration of the treatment. However, it is a feasible treatment protocol in regional centres with minimal or no options in the past.

HP033

Lenalidomide-associated B-lymphoblastic Leukaemia following Myeloma therapy: a single institution case series

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Adult-onset B-lymphoblastic leukaemia/lymphoma (B-ALL) is uncommon. There has been increasing recognition of secondary B-ALL occurring in patients with multiple myeloma, with lenalidomide therapy implicated as the cause. The management of these patients is complicated by their generally older age and more frequent co-morbidities. We reviewed cases of post-myeloma B-ALL in our pathology institution to examine characteristics of these patients, and relationship to lenalidomide therapy.

A total of six cases were identified between January 2021 and May 2024. Patient characteristics at time of B-ALL diagnosis are outlined in Table 1. Median age at B-ALL diagnosis was 67.5 years, at a median of 5.3 years following myeloma diagnosis. For five of the patients, their myeloma was in remission at time of presentation, occurring after their first-line therapy containing lenalidomide. Patient 4 had multi-relapsed myeloma with prior lenalidomide exposure, and had been on pomalidomide-containing therapy at time of B-ALL diagnosis. First-line induction therapy included Hyper-CVAD in four patients, and POMP alone in two patients. In our laboratory, B-ALL following myeloma therapy generally occurs in older adults with well-controlled myeloma at the time of B-ALL diagnosis. There was universal treatment with the immunomodulatory therapy lenalidomide prior to the B-ALL diagnosis.

Table 1. Demographics and disease characteristics of identified patients

ID	Age	Sex	Years Since Myeloma Diagnosis	Myeloma Status	Marrow Blasts	Cytogenetics	WHO Diagnosis
1	87	Female	5.9	sCR	95%	Complex including del(17p) B-ALL, NFC	B-ALL, not further classified
2	69	Female	4.1	sCR	91%	Failed. BCR::ABL1 negative	B-ALL, not further classified
3	61	Male	2	CR	12%	Complex, including -7	B-ALL, not further classified
4	75	Female	10.0	VGPR	77%	Hyperdiploid	B-ALL with hyperdiploidy
5	62	Male	4.7	sCR	33%	del(20q)	B-ALL, not further classified
6	66	Female	6.7	CR	Not available	Not available	B-ALL, not further classified

HP034

Very late relapsed Acute Myeloid Leukaemia Post Allogeneic stem cell transplant: a case of immune escape

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Background: Very late relapsed acute myeloid leukaemia (AML), defined as >5 years post complete response, is rare with an incidence of ~1-3%.(1) Unlike early relapse, the underlying mechanisms are complex and poorly understood including dysregulation of HLA expression, immune checkpoint alteration and remodelling of the tumour microenvironment.(2) Prognosis post very late relapse is universally poor with the optimal therapeutic approach unknown. Here we describe a case of relapsed AML, 10 years post allogeneic stem cell transplant (allo-SCT) which was successfully treated with a hypomethylating agent and novel BCL2 inhibitor followed by a second allo-SCT in complete remission 2 (CR2).

Case presentation: A 51yo male presented with pancytopenia and 12% circulating blasts 10 years post initial Fludarabine/Melphalan (FluMel) sex matched sibling allo-SCT for AML. Bone marrow biopsy was diagnostic of late relapse, with monoblastic morphology and 38% blasts. Flow cytometry demonstrated the original leukaemia-associated immunophenotype but new loss of HLA-DR. Cytogenetics of both initial and relapsed AML showed abnormalities in chromosomes 2p, 7 and 14. Molecular studies at relapse identified RUNX1, ASXL1, DNMT3A-non R882 and KIT variants. Chimerism studies demonstrated 66% myeloid and >95% CD3+ lymphoid to be of donor origin. Blueprint Genetics Comprehensive Hematology Panel, requested due to a history of spontaneously resolved childhood aplastic anaemia and young myeloid malignancy, identified no clinically significant mutations. The patient was treated with Azacitidine (75mg/m^2 d1-7) and Venetoclax (50mg with Posaconazole d1-14) achieving CR2 post cycle 1. He proceeded to a FluMel sex-mismatched sibling allo-SCT after 4 cycles. Day +33 chimerism demonstrated 100% myeloid and CD3+ lymphoid engraftment.

Conclusion: This case depicts immune evasion of the dormant leukaemic stem cell presumably through loss of HLA-DR and subsequent failure of graft vs leukaemic effect. Despite achieving 100% donor chimerism post second allo-SCT the durability of immune control and subsequently CR2 remains uncertain.

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HP035

Concordance of CEBPA mutational testing by high resolution fragment analysis (HRFA) and next generation sequencing (NGS) with a recommended testing approach to improve diagnostic yield and laboratory work flow efficiency

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Aim: This audit aimed to compare the concordance of CEBPA mutation status by HRFA and paired confirmatory sequencing; interrogate the reasons for discordant results and provide recommendations to inform test selection and in turn optimise laboratory work flow. Secondary aims were to detail the CEBPA mutational landscape, co-existing mutations and WHO 2022/ICC classification.

Method: Patients, of any age, who underwent bone marrow or peripheral blood CEBPA testing by HRFA at Pathology Queensland for acute myeloid leukaemia, myelodysplastic syndrome or blast phase myeloproliferative neoplasm between January 2020 and December 2023 were included. Paired sequencing was defined as sanger sequencing, whole exome sequencing or Core Myeloid Gene Panel within 7 days of HRFA. Descriptive statistics were primary used with sensitivity, specificity, positive predictive value and negative predictive value calculated.

Results: There were 677 instances of CEBPA testing by HRFA with 230 paired results. Six (2.6%) of the cases yielded a discordant result (n=2 HRFA false negative, n=2 NGS false negative, n=2 HRFA false positive). Sensitivity and specificity were similar between both testing modalities – HRFA 94.3%, 98.9% and CMGP/WES 92.9%, 100% respectively. Fifty-nine CEBPA variants were detected (n=26 N-terminal, n=25 C-terminal, n=9 Mid-region). Seventeen cases harbored a traditional CEBPA double mutation and 52% of the C-terminal variants were CEBPA bZIP in-frame. The most common co-occurring mutations were ASXL1 (11%), TET2 (11%), SRSF2 (9%) and STAG2 (9%).

Conclusion: HRFA offered marginally better sensitivity than CMGP/WES and improved the diagnostic yield by 0.8%. NGS was complementary detecting 2 cases missed by HRFA and provided variant sequencing, bZIP in-frame status and co-occurring mutations essential to the WHO 2022/ICC diagnostic hierarchy. Both methodologies are complementary and should be considered where detection of a CEBPA bZIP in-frame variant would alter therapeutic approach.

HP036

Karyotype takes the cake: a tricky B cell malignancy case

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A 39-year-old Caucasian male presented to our institution with a three week history of fatigue, night sweats, shortness of breath, left upper quadrant pain and gingival bleeding.

A peripheral Full Blood Count and film demonstrated mild anaemia (119g/L), neutropenia ($1.24x10^9$/L) and severe thrombocytopenia ($16x10^9$/L) with 50% of leukocytes comprising large immature nucleated cells concerning for blasts or high-grade lymphoid cells.

Immunophenotyping of the peripheral blood demonstrated a population of cells constituting 38% of all events with dim CD45 expression and increased side scatter. These cells expressed the B-lymphoid antigens CD19, CD10, intracellular CD79a and CD20, with indeterminate light chain expression. Markers of immaturity CD34, CD117 and CD1a were negative and intracellular TdT was indeterminate. Diminished or absent light chain expression along with the expression of CD10 can be associated with aggressive mature B-lymphoid neoplasms.

Trephine biopsy demonstrated almost complete effacement with a lymphoid infiltrate. Immunohistochemistry stains were also negative for CD34 and TdT. BCL2 was diffusely positive.

Subsequently, GTG banding of unstimulated blood revealed low-hypodiploidy in 45% of cells analysed. The remaining 55% of cells demonstrated a normal male karyotype.

A diagnosis of B Acute Lymphoblastic Leukaemia (B-ALL) was made in the setting of the low-hypodiploid state which was further supported by negative FISH studies for IGH translocations usually associated with mature B-cell neoplasms, including t(8;14). Following this, gene fusion panel identified the presence of an IKZF2::LOC fusion known to be highly recurrent in low hypodiploid B-ALL.

B-ALL with absent markers of immaturity including CD34 and TdT by immunophenotyping has been described in the literature[1,2]. The dual expression of CD10 and other B cell antigens with an absence of markers of immaturity in our patient suggested the possibility of an aggressive mature B- lymphoid neoplasm resulting in initial diagnostic uncertainty. Our case highlights the critical importance of karyotype analysis in the diagnosis of haematologic malignancies and in addition demonstrates the importance of supportive information provided by more modern molecular techniques.

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HP037

De novo AML in the setting of treatment naive CLL

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Acute Myeloid Leukaemia (AML) occurring in patients treated for Chronic Lymphocytic Leukaemia (CLL) is widely reported and attributed to prior cytotoxic therapy. AML developing in the setting of treatment naïve CLL is extremely rare with conflicting evidence for single cell of origin and unknown optimal treatment.[1-5]

A 76 year old female presented with 1 week of fatigue and bruising. The patient had an incidental diagnosis of CLL-type high count monoclonal B lymphocytosis (MBL) seven years earlier which progressed to CLL, that was asymptomatic and not requiring treatment. Automated full blood count (FBC) results demonstrated an increase in White Cell Count (WCC) to $175x10^9$/L on admission, from $19.6x10^9$/L over 9 months. Blood film examination and WCC differential demonstrated 40% blast cells and 50% small mature lymphocytes with smudge cells present.

A diagnosis of NPM1 mutated AML (WHO2022) was made following bone marrow biopsy and further molecular testing. Core myeloid gene panel of 37 genes identified a Type A NPM1 mutation at a variant allele frequency (VAF) of 23.89%, FLT3 ITD mutation at a VAF of 43.08% and two DNMT3A-non R882 variants at VAFs of 33.22% and 33.32%.

The patient was cytoreduced with hydroxyurea and subsequently treated with Venetoclax and Azacitadine. Treatment was complicated by grade 4 neutropenia and thrombocytopenia, and neutropenic fevers. The patient achieved morphological remission at day 21 of the first cycle, at which point, a monoclonal B cell population was also no longer detectable by conventional flow cytometry.

This case raises a number of interesting discussion points. Firstly, whether these malignancies arise from a single common progenitor cell population. Secondly, the treatment- phenotype interactions and overlapping efficacy/ toxicity of the drugs selected. Thirdly, there are important considerations in the long term about whether targeted approaches to co-existent mutations (e.g. FLT3-ITD) should be pursued.

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HP038

The role of FDG-PET/CT in Aggressive Systemic Mastocytosis: a novel case report and literature review

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Systemic mastocytosis (SM) is a clonal disorder characterised by mast cell activation and proliferation. The value of PET/CT in SM has limited evidence, mainly in SM with associated haematological non-mast cell lineage disease (SM-AHNMD). We report a novel case of aggressive SM with FDG-PET/CT changes.

An 81 year old woman presented with 35kg of unexplained weight loss, refractory diarrhea and large volume abdominal ascites. Initial bloods demonstrated mild macrocytosis with otherwise normal peripheral blood counts (Hb125g/L, MCV101gL, WCC4.4x10^9/L, neutrophils2.12x10^9/L, platelets433x10^9/L). FDG-PET/CT then showed heterogenous increased activity in the axial and proximal appendicular skeleton, as well as mild splenomegaly with increased uptake (SUVmax4.3) with moderate uptake in subcarinal lymph node (SUVmax4.1,12mm,Image1). Bone marrow biopsy demonstrated dense aggregates of mast cells with spindle-shape morphology, increased reticulin staining (MF-3) and dense mast cell aggregates(Image2). Aberrant CD2+/CD25+ mass cell expression was seen(Image3). There was no concurrent dysplasia or other haematological malignancy. cKIT D816V mutation was positive at 34.5% VAF by ddPCR. Serum tryptase was found to be >200ug/L. The patient was commenced on cladribine 0.14mg/kg by intravenous infusion which improved symptoms and reduced tryptase to 101ug/L most recently.

The value of FDG-PET/CT in SM is yet to be determined(1). A French group reported a case series of 19 adult patients with SM and FDG-PET/CT findings(2). No significant FDG uptake was seen in patients with smouldering or aggressive SM. Of those with SM-AHNDM, 6 of 10 had increased FDG bone marrow uptake, and 5 of whom also had increased FDG nodal uptake. No correlation was found between FDG avidity and serum tryptase, BM mast cell percentage and aberrant mast cell expression.
Conclusion: FDG-PET/CT can be considered in the investigation of SM-AHMDN, but as in our case, also in aggressive SM. Its role in assessing response to treatment is yet to be determined.

Image 1 FDG-PET/CT with heterogenous skeletal & splenic uptake with splenomegaly

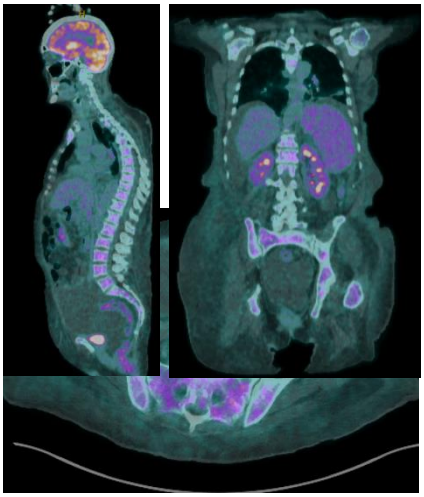


Image 2 Bone marrow: abnormal mast cell morphology (A), trephine H&E (B), CD117 IHC (C), reticulin stain (D)

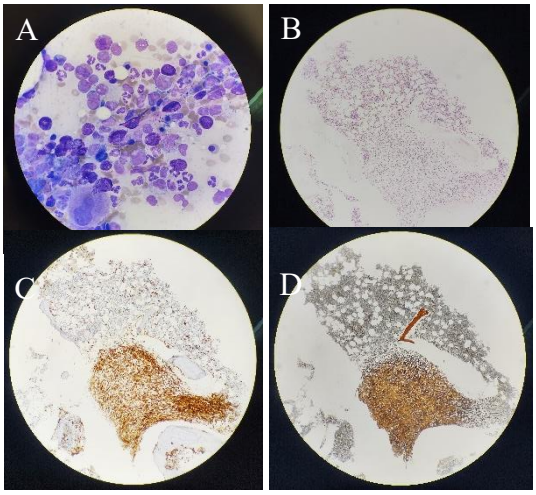
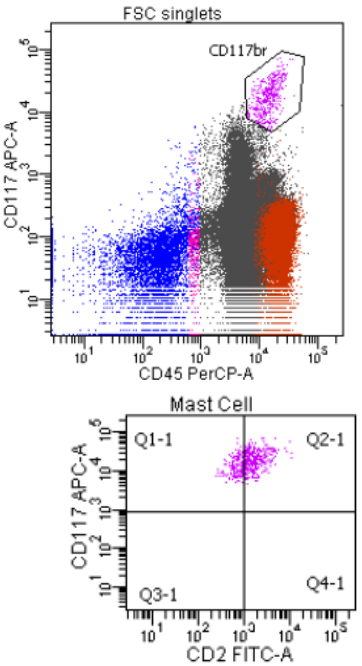


Image 3 Aberrant CD2 and CD25 expression on CD117 positive mast cells



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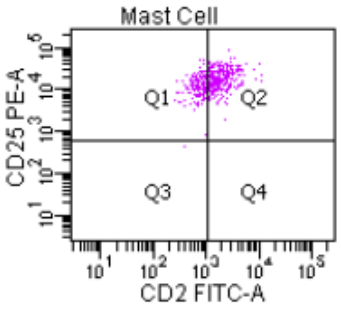

HP039

Transcriptomic analysis reveals novel PAX5 fusions and intragenic amplifications in patients with PAX5alt B-cell acute lymphoblastic leukaemia

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Aim: *PAX5*alt has recently been identified as a distinct genomic subtype of B-cell acute lymphoblastic leukaemia (B-ALL), defined by various *PAX5* alterations and a unique gene expression profile. This study explored the genomic characteristics of Australian paediatric and adolescent/young adult *PAX5*alt cases.

Method: Philadelphia chromosome-negative (Ph-neg) B-ALL samples (n=540) underwent transcriptomic sequencing to identify gene fusions and sequence variants. *PAX5*alt cases were detected through gene expression profiling using the Allspice and AllCatchR analysis packages. Multiplex ligation-dependent probe amplification (MLPA, n=370) detected gene deletions. *PAX5* intragenic amplifications (*PAX5*amp) were detected using RaScALL and confirmed by MLPA.

Results: *PAX5*alt was detected in 7.8% (n=42/540) of Ph-neg B-ALL patients, comprising 7.2% children (<15yrs, n=26/360) and 8.9% adolescent/young adults (16-39yrs, n=16/180). *PAX5* fusions were present in 45.2% of cases (n=19/42), predominantly with established 3' fusion partners (*ETV6*, *ZNF521*, *ARHGAP22, ZCCHC7*, *NOL4L, FBRSL1, DACH1, CBFA2T3, FOXP1*). Novel *PAX5* fusions with *SRCIN1*, *ATF7IP* and *ZBTB16* were also identified (n=1 each). *PAX5*amp and *PAX5* mutations were mutually exclusive, each identified in 19% of patients (n=8/42). Monoallelic deletion was the sole *PAX5* alteration in the remaining 16.7% of cases (n=7/42). *CDKN2A/B* deletions were significantly enriched in *PAX5*alt (n=30/31, 96.8%) and *PAX5* p.P80R (n=8/10, 80%) patients compared to the remaining cohort (n=92/329, 27.9%, p<0.01).

Conclusion: This study characterised a large cohort of Australian *PAX5*alt patients, identifying novel *PAX5* fusions. While monoallelic deletion of *PAX5* is not considered a disease driver, it was the sole *PAX5* alteration in a subset of cases. Additional research is required to uncover other mutations driving disease in these patients.

HP040

Myeloid Neoplasm with UBTF-TD post Cytotoxic Therapy for AITL

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Tandem duplications of the upstream binding transcription factor (UBTF-TD) have recently been identified as a recurrent mutation in *de novo* paediatric and young adult acute myeloid leukaemia (AML), characterised by poor response to conventional therapy and a similar transcriptional profile to *KMT2A*-rearranged and *NPM1*-mutated AML, and are potentially targetable by menin inhibitors.

Here, we report a case of a 78-year-old female with AML following cytotoxic therapy for angioimmunoblastic T-cell lymphoma (AITL). AITL was initially diagnosed in 2022 on a lymph node biopsy with a typical mutation profile identified by targeted NGS panel: *DNMT3A* Arg882His, *TET2* Ile1444Phefs*4, *TET2* Gln644*, *RHOA* Gly17Val, and *IDH2* Arg172Gly. Complete metabolic remission was achieved post 6 cycles of CHOP chemotherapy. Seventeen months later, the patient presented with hyperleukocytosis and 91% myeloblasts in bone marrow diagnostic of AML. Molecular testing revealed *FLT3*-ITD and a 90-bp duplication in *UBTF*, in addition to the *DNMT3A* and *TET2* mutations previously detected in the tissue sample containing AITL; *RHOA* and *IDH2* were not detected in the AML sample.

Follicular helper T-cell (TFH) lymphoma, such as AITL, commonly derives from an ancestral clone with mutations observed in age-related clonal haematopoiesis. Divergent evolution of myeloid neoplasms and TFH lymphomas have been described in the literature. In our case, both neoplasms shared the *DNMT3A* and *TET2* mutations but showed divergent clonal evolution in the development of AITL (acquisition of *RHOA* and *IDH2*) and the subsequent AML (*FLT3*-ITD and *UBTF*-TD).

This case highlights the first observation of *UBTF*-TD in a post-cytotoxic therapy setting and underscores divergent clonal evolution in a patient with prior AITL, in the oldest known individual with UBTF-TD.

HP041

The unfolded Protein response governs immune control of Acute Myeloid Leukaemia

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Introduction: Evasion from immune destruction is a well-recognized hallmark of cancer and growing evidence now supports a functional interplay between acute myeloid leukaemia (AML) and the immune system. Immunotherapy in the form of allogeneic hematopoietic stem cell transplantation remains the most effective post-remission therapy for patients with intermediate-high risk AML but long-term overall survival remains below 50% largely attributed to relapse or resistance to current therapies. Harnessing lymphocyte function is crucial for improving cancer immunotherapy, however the importance of natural immune surveillance against AML remains to be fully characterized. We hypothesise that regulation of the unfolded protein response (UPR), an evolutionarily conserved adaptation mechanism that senses perturbations in the endoplasmic reticulum, dictates immune control of AML. The PERK arm of the UPR is overrepresented in AML patient cells with diverse cytogenetics compared to normal hematopoietic stem cells and therefore presents a therapeutic opportunity.

Results: Using a genetically engineered syngeneic model of an intermediate-risk AML subset driven by the t(9;11)(p22;q23) translocation, we have identified that regulation of the UPR by GADD34 protects AML from anti-tumour immunity. Loss of GADD34 in leukemic cells inhibited expansion in immunocompetent hosts but enabled rapid growth in immunodeficient settings suggesting enhanced sensitivity to immune-mediated control. Similarly, therapeutic targeting of the UPR improved allogeneic human $CD8^+$ T cell-mediated cytotoxicity and interferon-γ production against human AML lines. Notably, immunotherapy in the form of T-cell-engaging bispecific antibody (T-BsAb) targeting CD33 was more effective in the presence of small molecules targeting UPR in co-culture assays.

Conclusion: An intact immune system is not only essential for effective immunotherapy, but outcomes of chemotherapy can also be influenced by the host immune system. Work herein proposes that UPR plays a critical role in shaping immune responses to AML and presents evidence that manipulating the regulatory activity of UPR may augment anti-leukaemia immunity.

HP042

Single-institution outcomes of standard-of-care tisagenlecleucel for relapsed/refractory B-cell acute lymphoblastic leukaemia: an Australian real-world experience

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Aim: Chimeric antigen receptor T-cells (CART) targeting CD19 (tisagenlecleucel, tisa-cel, Kymriah®) has been publicly funded for Australian patients ≤25 since February 2020 for treatment of relapsed/refractory (R/R) B-cell acute lymphoblastic leukaemia (B-ALL). We present single centre outcomes for adult patients who received tisa-cel as standard of care.

Method: Data were collected retrospectively for all patients with R/R B-ALL who underwent leukapheresis with intent to receive tisa-cel.

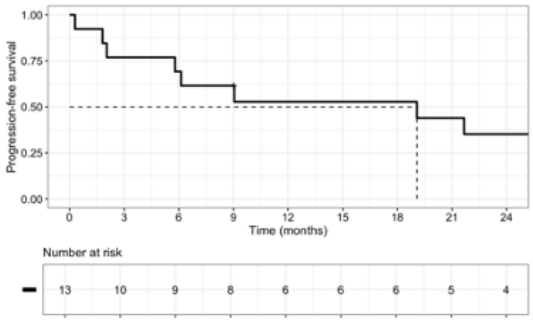
Results: Thirteen patients underwent leukapheresis and all were subsequently infused with tisa-cel (baseline characteristics, Figure A). Eight patients (62%) received bridging therapy; 4 (31%) were minimal residual disease (MRD)-negative, 1 (8%) was MRD-positive and 3 (27%) had morphologic disease on bone marrow assessment prior to lymphodepletion. Complete response (CR/CRi) was seen in 12 patients (92%), of which 12/12 (100%) were MRD-negative. Progression-free survival (PFS) at 12 months was 0.53 (95% CI: 0.31–0.89), noting that 2 patients relapsed beyond 12 months in our cohort (Figure B). Cytokine release syndrome (CRS) occurred in 9 patients (70%); 1 patient developed Grade 3 CRS, no Grade 4 or 5 CRS was observed. Immune-effector cell associated neurotoxicity syndrome (ICANS) occurred in 2 patients (16%) – 1 of each Grade 1 and 3. One patient required intensive care unit admission. Three patients received a subsequent allogeneic stem cell transplant (alloSCT) following tisa-cel; 1 for persistent MRD-positive status, 1 for subsequent relapse after achieving CR/CRi following tisa-cel, and 1 for prolonged cytopenias/aplasia. Two patients received a second tisa-cel infusion, indicated for molecular relapse of Ph+ B-ALL and morphological relapse of Ph- B-ALL post alloHSCT. Both patients remain in MRD-negative CR at >12 months since second infusion.

Conclusion: Our single-institution outcomes with tisa-cel for R/R B-ALL in the Australian real-world context are comparable with pivotal trial data. Further data is required to understand the impact of bridging therapies on outcomes and mechanism of disease relapse following tisa-cel.

A

All patients (N=13)			
Age (years)		**Systemic bridging**	
med (min-max)	20 (19-26)	None	5 (38%)
Sex		Steroid alone	0 (0%)
Male	7 (54%)	Chemotherapy	4 (31%)
Female	6 (46%)	Inotuzumab	4 (31%)
B-ALL Subtype		**Bridging response**	
B-ALL NOS	9 (69%)	MRD negative (blasts <0.01%)	4 (31%)
Ph+ B-ALL	1 (8%)	MRD positive (blasts 0.01-5%)	1 (8%)
B-ALL TCF3-PBX1	1 (8%)	Persistent/relapsed disease (>5% blasts)	3 (23%)
B-ALL Hyperdiploid	2 (15%)	No bridging	5 (38%)
Number of prior lines		**Prior AlloSCT**	
1	3 (23%)	No	7 (54%)
2	5 (38%)	Yes	6 (46%)
3	2 (15%)		
4 or more	3 (23%)		

B



HP043

Amplification of MYC and KMT2A in patients with AML and a karyotype with dmin: a 10 year retrospective analysis.

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Aim: Recurrent genetic aberrations identified by cytogenetics +/- fluorescence *in situ* hybridisation (FISH) represent the cornerstone of acute myeloid leukaemia (AML) classification and risk stratification. Double minute chromosomes (dmin) are small chromatin bodies, lacking a centromere, characterised by gene amplification. While rare, they often involve *MYC* or *KMT2A* and their prognostic significance in AML is largely unknown. Here we present results from a 10-year retrospective review of AML cases with dmin.

Method: From 01/1/2014 to 31/12/2023, we saw a total of 3448 new AML cases and identified dmin by conventional cytogenetics in 49 [1.4%; 41 *de novo* AML (incl. 1 mixed-phenotype AL, B/myeloid), 4 secondary (MDS), 4 AML with clonal evolution; median age 71 years (range: 4 – 93)]. To characterise the nature of genes amplified, we retrospectively performed FISH (47/49 with available sample) using the *MYC* (8q24) and *KMT2A* (11q23) (both MetaSystems) break-apart probes. Where neither *MYC* nor *KMT2A* were amplified, and stored DNA (3/26), a SNP-microarray was performed.

Results: Dmin were seen in association with European LeukemiaNet (ELN) intermediate (n=7; 14%; sole abnormality in 6/7) or adverse (n=42; 86%) risk karyotypes including 39 (80%) with complex karyotype. In 23/49 (47%) of cases the amplified genes were *MYC* (n=18; 37%), *KMT2A* (n=4; 8%) and 1 case of t(15;17) – *PML::RARA* with *ERG* amplification identified by microarray. Further microarray data and correlation to clinical outcomes is to follow.

Conclusion: Double minute chromosomes are rare in AML, commonly involve *MYC* and *KMT2A*, and are seen in association with complex karyotype but >50% involve genes other than *MYC* or *KMT2A*. In the era of targeted therapies, detailed dmin characterisation may guide therapy.

HP044

Prognostic impact of clonal haematopoiesis of indeterminate potential (CHIP): A systematic review and meta-analysis

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Background: With advances in sequencing, individuals with clonal haematopoiesis of indeterminate potential (CHIP) are increasingly being identified, making it essential to understand its prognostic implications.

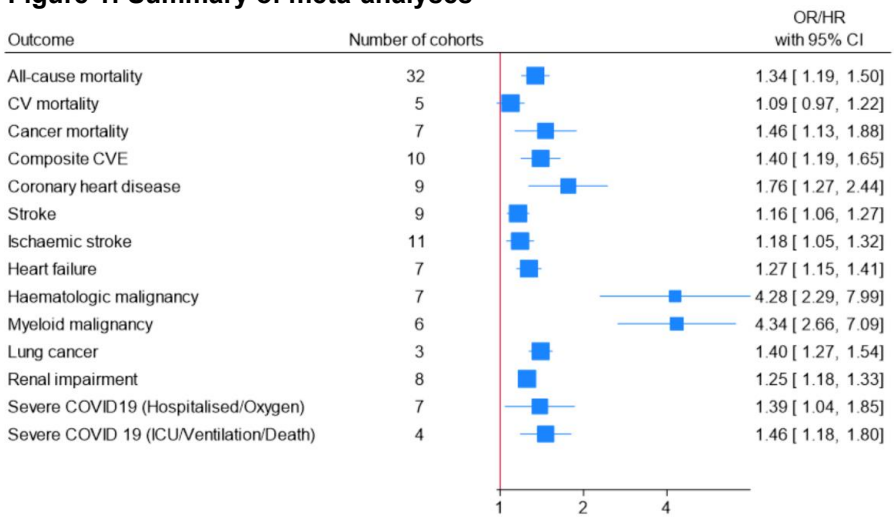
Aim: To conduct a systematic review of studies comparing the risk of clinical outcomes in individuals with and without CHIP.

Method: We searched MEDLINE and EMBASE up to Sept 30th 2023, and included original research reporting a risk measure (adjusted for the effect of age) for an outcome in individuals with CHIP. Abstract and full text screening, data extraction and quality assessments were performed by two reviewers, with conflicts resolved by a third reviewer. Bias was assessed using the QUIPS tool. Random effects meta-analyses using restricted maximum likelihood estimation were performed for outcomes reported in at least 3 studies. Subgroup analyses were performed for subgroups of VAF or gene, where sufficient information was available.

Results: 3305 studies were screened, and 88 studies included, of 45 to 470960 participants. Most studies had low to moderate risk of bias in all domains of the QUIPS tool. CHIP conferred increased risk of all-cause mortality (hazard ratio [HR] 1.34 [95% CI 1.19-1.50]), cancer-mortality (HR 1.46 [1.13-1.88]), composite cardiovascular events (HR 1.40 [1.19-1.65]), coronary heart disease (HR = 1.76 [1.27-2.44]), stroke (HR 1.16 [1.05-1.28]), heart failure (HR 1.27 [1.15-1.41]), haematologic malignancy (HR 4.28 [2.29-7.98]), lung cancer (HR 1.40 [1.27-1.54]), renal impairment (HR 1.25 [1.18-1.33]) and severe COVID19 (odds ratio [OR] 1.46 [1.18-1.80]) (Figure 1). CHIP was not associated with cardiovascular mortality (HR 1.09 [0.97-1.22]), except in subgroup analysis restricted to larger clones (HR 1.31 [1.12-1.54]). Isolated *DNMT3A* mutations did not increase risk of myeloid malignancy, all-cause mortality or renal impairment. Reasons for heterogeneity between studies included differences in definitions and measurement of CHIP and outcomes, and populations studied.

Conclusion: CHIP is associated with diverse clinical outcomes, with clone size, specific gene and inherent patient characteristics important mediators of risk.

Figure 1: Summary of meta-analyses



HP045

PARP inhibitors potentiate the cytotoxic activity of daunorubicin in ALL cells in vitro and ex vivo

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Aim: Poly (ADP-ribose) polymerase (PARP) is a critical component of DNA repair that is used by cancer cells to restore the damage caused by chemotherapeutic agents. PARP inhibitors (PARPi) are currently used for the treatment of several solid tumours, however, their therapeutic potential in paediatric ALL has not been investigated. The aim of this study was to test the efficacy of PARPi in paediatric ALL, singly and in combination with existing chemotherapeutics.

Method: Three ALL cell lines were treated with the PARPi veliparib (ABT-888), olaparib (AZD-2281), rucaparib (AG-014699) and pamiparib (BGB-290) alone, or in combination with daunorubicin, cytarabine, vincristine or etoposide. Cell viability was determined using a resazurin assay and synergistic/antagonistic effects of combination were determined using the HSA model in SynergyFinder Plus. Paediatric T- (n=3) and B- (n=37) ALL patient samples were examined for sensitivity to our panel of PARP inhibitors *ex vivo*.

Results: Jurkat, CCRF-CEM and CCRF-HSB2 cell lines *in vitro* as well as ALL *ex vivo* patient samples, were sensitive to all 4 PARPi examined, with rucaparib being the most potent *in vitro* (IC_{50} from 11.63-19.83 μM). Combining all four PARPi with chemotherapeutics (except for pamiparib in combination with cytarabine) resulted in at least additive effects *in vitro*. Combining PARPi with chemotherapeutics increased cell death *ex vivo*, except when combined with etoposide. Combining all PARPi with daunorubicin resulted in the greatest enhancement of cell death *ex vivo*.

Conclusion: PARPi demonstrate efficacy against ALL cell lines and patient samples and potentiate the cytotoxic activity of chemotherapeutics, particularly daunorubicin *in vitro* and *ex vivo*, suggesting that administration of PARPi in combination with daunorubicin may provide benefits to improving ALL patient outcomes.

HP046

An unusual case of newly acquired FLT3-ITD mutation in a patient with MDS overlap syndrome

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Acute myeloid leukaemia (AML) is a highly heterogenous malignancy characterised by genetic abnormalities causing abnormal haematopoietic cell differentiation and proliferation. We report an unusual case of newly acquired FLT3-internal tandem duplication (FLT3-ITD) mutation in a patient with myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/ MPN-RS-T) who progressed to AML.

The patient initially presented following a fall with trauma and was incidentally found to have a macrocytic anaemia and thrombocytosis with a leucoerythroblastic film. Bone marrow biopsy was consistent with MDS with ring sideroblasts. Cytogenetics were unremarkable and next generation sequencing detected DNMT3A and SF3B1 mutations. He required monthly transfusion support for 1.5 years from diagnosis after which he began developing progressive leucostasis and renal dysfunction. A repeat bone marrow biopsy showed 5% blasts and a newly acquired FLT3-ITD mutation which was not present at initial diagnosis, and treatment with hydroxyurea was initiated. A subsequent bone marrow biopsy demonstrated a hypercellular marrow with 20% blasts, marking the progression to AML.

The acquisition of FLT3-ITD mutations is typically associated with de novo AML and is considered a poor prognostic marker. However, in this case, the development of FLT3-ITD in the context of MDS/MPN-RS-T progression to AML represents an unusual clinical scenario and a phenomenon that has been scarcely reported in the literature.

HP047

Real-world treatment outcomes in non-favorable risk AML - Data linkage between the ALLG National Blood Cancer Registry (NBCR) and the Australia and New Zealand Transplant and Cellular Therapy (ANZTCT) Registry

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There is limited real-world Australia and New Zealand data on allogeneic transplant (HSCT) patterns and outcomes in AML patients with non-favourable cytogenetics in first remission (CR1). We sought to establish a data linkage between the ALLG National Blood Cancer Registry and the ANZTCT) registry.

Aim a) To describe treatment patterns and outcomes including HSCT for non-favourable risk AML in CR1 registered in the NBCR b) to corelate treatment with MRC 2010 cytogenetic risk score c) to describe time to transplant in CR1 d) To describe transplant demographics using the ANZTCT registry data.

Methods NBCR AML participants treated with intensive chemotherapy were matched to the ANZTCT registry using date of birth, sex, date of diagnosis (DOD) and diagnosis (AML). In event of mismatch in DOD (permitted up to 5 days) date of transplant was used additionally.

Results: 600 new diagnosed AML participants were identified from NBCR between 2013 - 2018. Eighty-Two were excluded due to non-intensive treatment, other diagnosis, favourable/ no cytogenetics, and incomplete data. Eleven participants were excluded from transplant analysis due to absence of patient data use consent. Of the final cohort of 507 intensively treated AML participants – 177 (36%) proceeded to HSCT and 330 were treated with intensive chemotherapy without HSCT. 34% and 42% of intermediate and adverse-risk participants proceeded to HSCT respectively.

	Transplant N= 177(%) *	No Transplant N= 330 (%)	Total N=507 (%)
Age yrs (range)	50 (17-69)	62 (18-78)	59 (17-78)
Sex female	87 (49)	157 (47)	244 (48)
Intermediate-risk	129 (72)	259 (78)	388 (76)
Adverse-risk	48 (28)	71 (22)	119 (23)

*n=188 (11 excluded from analysis)

Median time to matched sibling and unrelated donor HSCT from CR1 was 2.3 and 3.4 months respectively. Median overall survival in intermediate-risk and adverse-risk AML patients with HSCT was not reached and 12 months respectively. Outcomes based on MRC risk, receipt of HSCT, donor type and time to HSCT will be presented.

Conclusions: This data reflects the treatment and HSCT utilization practice in AML in Australia and New Zealand

HP048

Retrospective single-laboratory review of acute promyelocytic leukaemia (APL) measurable residual disease (MRD) testing in Australia

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Aim: To evaluate the real-world practice of measurable residual disease (MRD) monitoring in acute promyelocytic leukaemia (APL) to identify potential areas of practice improvement.

Method: Patients with ≥2 MRD tests between Jul-2017 to Mar-2024 were included in this retrospective review. *PML::RARA* RT-qPCR was performed using Ipsogen bcr1 and bcr3 FusionQuant® kits and expressed as % of *ABL1*. MRD relapse was as per European LeukemiaNet (ELN) 2021 recommendations.

Results: 2026 tests from 223 patients were identified. Median baseline *PML*::*RARA* was 18% (range 0.06–142%) in 120 diagnostic specimens. ELN 2021 recommends MRD testing at end-of-treatment (approximately 3 and 9 months for high and standard-risk APL, respectively). In comparison, median time to first MRD assessment was 1.6 months and 23% of samples were received < 1 month, of which the median MRD level was 0.08% (max 80%), with potential for result misinterpretation and no impact on clinical decision making. Within 12 months of diagnosis, the median number of tests per patient was 4 (19% had ≥6 tests; max = 8 tests).

During the post-treatment period, two patients had MRD relapse at 12 and 23 months post diagnosis of high and low-risk APL, respectively. With current usage patterns, the number needed to test (NNT) to detect one MRD relapse was 1013 tests/111 patients.

At data cut-off date, the median duration of disease monitoring was 30 months from diagnosis; current guidelines recommend 2 years from end of treatment but unclear if this included maintenance therapy. 100/150 (67%) and 56/94 (60%) patients had >3 and 5 years of monitoring, respectively. Notably, 15 patients were monitored for over 10 years.

Conclusion: The majority of MRD testing in APL is inappropriately requested and significant opportunities for quality improvement exist. Optimal testing frequency and duration should be re-evaluated, especially in the context of highly effective ATO/ATRA therapy.

HP049

Cytogenetic profile of acute myeloid leukaemia patients in Victoria, Australia

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Aim: The classification of acute myeloid leukaemia (AML) is continually being refined and the 2022 World Health Organisation (WHO) recognises three main categories including AML with recurrent, defining genetic abnormalities (AML-RGA), AML with other defined genetic alterations (AML-Other RGA) and AML defined by differentiation. Conventional cytogenetics and molecular studies screening for mutations which define disease and risk categories are integral to the accurate diagnosis and risk stratification, often informing treatment decisions. Our laboratory is a state-based service and here we present the first systemic data on cytogenetic aberrations of newly diagnosed Victorian AML patients.

Method: We performed a retrospective analysis of the karyotype results from January 2021 to December 2023 inclusive, in a Victorian state reference laboratory. The results were categorised according to the 2022 WHO and European LeukemiaNet (ELN) classifications. No clinical data was collected or correlation to treatments/outcomes.

Results: During the study period, we received a total of 1056 new cases of AML [733 (73%) *de novo*; 273 (27%) secondary AML including 111 (11%) with prior MDS, 52 (5%) with prior MPD, 50 (5%) with prior MDS/MPD and 65 (6%) with other predisposing conditions]. A successful karyotype was obtained in 1006 [95%; 50 (5%) no metaphases] cases [910 bone marrow (BM) aspirate, 21 BM trephine, 75 peripheral blood; 629 (63%) male, 377 (37%) female, median age 73 years, range: 3-97 years]. A normal karyotype (NK) was observed in 366 (37%) cases while clonal karyotype was seen in 640 (64%) (Table 1). According to the ELN classification of AML, 121 cases (12%) met criteria for favourable karyotypes, 585 (58%) intermediate, and 300 (30%) adverse risk karyotype. Comparison to other international registries to follow.

Conclusion: We describe the cytogenetic profile of a large cohort of Victorian AML patients. Data presented may inform local testing guidelines and guide the design of local clinical trials investigating genomic risk directed therapeutic approaches in AML.

Table 1 Clonal karyotype of AML according to WHO classification.

	Patients, no. (%)				
	Total	<45 yo	45-60 yo	61-75 yo	>75 yo
AML with defining genetic abnormalities	170 (17)	39 (4)	39 (4)	50 (5)	30 (3)
Acute promyelocytic leukaemia with *PML::RARA* fusion	65 (6)	19 (2)	21 (2)	18 (2)	7 (1)

AML with *RUNX1::RUNX1T1* fusion	20 (2)	5 (<.5)	6 (1)	7 (1)	2 (<.5)
AML with *CBFB::MYH11* fusion	36 (4)	11 (1)	12(1)	7 (1)	6 (1)
AML with *DEK::NUP214* fusion	3 (<.5)		2 (<.5)		1 (<.5)
AML with *BCR::ABL1* fusion	4 (<.5)	2 (<.5)		1 (<.5)	1 (<.5)
AML with *KMT2A* rearrangement	19 (2)	3 (<.5)	3 (<.5)	8 (1)	5 (<.5)
AML with *MECOM* rearrangement	21 (2)	3 (<.5)	3 (<.5)	7 (1)	8 (1)
AML with *NUP98* rearrangement	2 (<.5)			2 (<.5)	
AML, myelodysplasia-related	295 (30)	14 (1)	26 (3)	108 (11)	147 (15)
Complex karyotype (≥3 abnormalities)	231 (23)	10 (1)	20 (2)	86 (9)	115 (11)
5q deletion or loss of 5q due to unbalanced translocation	13 (1)	1 (<.5)		3 (1)	9 (1)
Monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation	39 (3)	1 (<.5)	5 (<.5)	15 (1)	18 (2)
11q deletion	5 (<.5)	2 (<.5)		3 (<.5)	1 (<.5)
12p deletion or loss of 12p due to unbalanced translocation	4 (<.5)			1 (<.5)	3 (<.5)
Monosomy 13 or 13q deletion	2 (<.5)				2 (<.5)
17p deletion or loss of 17p due to unbalanced translocation	6 (1)	1 (<.5)	1 (<.5)	2 (<.5)	2 (<.5)
AML, other recurrent genetic abnormalities	175 (17)	13 (1)	13 (1)	62 (6)	87 (9)

HP050

The mutation landscape of hematologic malignancies in Korea: 2010-2023

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Aim: Genetic variant is increasingly emphasized in diagnosis of hematologic malignancies. In this study, the variants spectra of many related genes in Korean leukemic patients were investigated during 2010-2023. We examined specimens from hematologic malignancies and retrospectively reviewed variants and rearrangement to estimate frequencies and analyze mutational landscape in Korea.

Method: A total of 5426 specimens which were referred from hematology department of tertiary hospitals were included. Direct sequencing or fragment analysis, multiplex nested RT-PCR and chromosomal analysis were performed on specimens. The tests covered exons and flanking intronic sequences of the CALR, c-Kit, JAK2, NPM1, MPL, TP53 genes. All variants are scored, interpretated and reported according to Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists guideline (AMP/ASCO/CAP).

Results: A total of 943 pathogenic variants or rearrangement were detected in 5426 samples (17.4%). JAK2 gene mutation tests were most frequently performed (526/2273, 23.1%), followed by NPM1(159/1103, 14.4%), and then c-Kit (186/878, 21.2%) mutation test. NPM1 mutation test. In NPM1 test, as in the previous report, type A was the most common, followed by type D. Among those genes, eight novel variants were detected in CALR, c-Kit, JAKs, MPL genes, which were suspected as tier I, variants with strong clinical significance. Those mutations were not reported before through database or literature reviews, so they were reported as novel pathogenic variants. Many different types of rearrangement were also detected.

Conclusion: Our findings provide spectrum of various pathogenic variants which are helpful for diagnosis of hematologic malignancies from the 14-years s in Korean patients. These data could be valuable to understanding each hematologic malignancies and further research is required to identify frequencies with larger population-based study.

HP051

Prognostic impact of Iron Overload on Overall Survival of Acute Myeloid Leukaemia

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Aim: This study examines the impact of iron overload on the outcome of AML overall survival (OS).

Method: This is a retrospective single centre study of 71 sequentially diagnosed AML patients between 2018 and 2020. Iron studies performed as routine at diagnosis were compared against diagnostic bone marrow iron stores and analysed against overall survival. Univariate linear regression survival analysis was used to explore the relationship between iron status, ELN2022 risk group, age at diagnosis, sex of patient, and overall survival. OS rates were estimated by Kaplan-Meier method and prognostic factors were evaluated by Cox regression on R statistical platform.

Results: Of the 71 patients, 54% (N=39) patients had died. According to ELN 2022, 22% (N=16) were favourable risk, 19% (N=14) were intermediate risk, and 51% (N=36) were adverse risk AML. 33% (N=24) had increased bone marrow iron stores (Grade 4 or above). 45% (N=32) patients had iron overload with both elevated ferritin and elevated transferrin saturation. Lower OS was associated with age >60 years of age (HR 8.17, P<0.001, CI 3.15-21.19, N=38) and increased bone marrow iron stores at time of diagnosis (HR 5.34, P = 0.017, CI 1.35-21.14, N=24). Interestingly, iron overload defined by both elevated ferritin and elevated transferrin saturation was not associated with worse OS (HR 1.09, P = 0.8, CI 0.56-2.15), although it is known AML-induced loss of erythroblasts is responsible for iron redistribution and altered iron studies results (Lopex et al Blood Advances 2021).

Conclusion: Increased bone marrow iron stores are associated with significantly worse OS in AML. More studies should be performed examining iron-related cell death pathways in AML pathogenesis and their potential as prognostic biomarkers and therapeutic targets.

HP052

Acute myeloid leukaemia, myelodysplasia-related in homozygous sickle cell disease.

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Aim: To describe the clinical course of acute myeloid leukaemia in a patient with homozygous sickle cell disease and review the literature.

Background/method: Sickle cell disease is a chronic and debilitating hemoglobinopathy characterized by the presence of abnormal haemoglobin. The risk of haematologic malignancy has been reported to be elevated compared to the general population.

Case report: A 48-year-old male with sickle cell disease presented with a pain crisis and was subsequently diagnosed with acute myeloid leukaemia, myelodysplasia-related. Laboratory findings revealed pancytopenia and circulating blasts positive for cytMPO, CD117, CD33, CD13, and partially for CD34. Further examination via bone marrow aspirate and trephine showed increased blasts accompanied by significant fibrosis and disruption of normal hematopoietic marrow spaces. Cytogenetic analysis revealed a complex monosomal karyotype with loss of both TP53 and 17 centromere signals in 54% of cells, while molecular testing detected two TP53 mutations with a variant allele frequency of 22% and 5%. Treatment involved Liposomal Daunorubicin/Cytarabine alongside weekly red cell exchanges using phenotype-matched blood. Despite these interventions, Day 28 marrow analysis indicated persistent disease, leading to the initiation of Venetoclax/Azacitadine. Regrettably, the patient experienced rapid disease progression with multi-organ dysfunction, including massive hepatomegaly and oliguric renal failure, ultimately passing away less than 2 months from diagnosis.

Conclusion: Acute myeloid leukaemia has been reported as a rare complication of sickle cell disease. Various pathophysiologic mechanisms have been described, including chronic inflammation and persistent marrow stress resulting in genomic instability. The management of acute myeloid leukaemia in the setting of sickle cell disease is challenging due to adverse risk disease and underlying organ impairment.

BMT

HP053

Blood product use in CAR T-cell recipients

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Aim: To understand the transfusion requirements for patients undergoing CAR T-cell reinfusions.

Method: All CAR T-cell recipients were identified. Review of medical records for transfusion requirements in the post reinfusion period was undertaken.

Results: 71 patients received infusions between 1/2/22 and 18/3/24, 11 died. Time from reinfusion ranged from 8 weeks to 119 weeks (median 54 weeks).

Table 1. Demographics

Characteristic	**Number (%)**
Gender: F/M	27 (38) / 44 (62)
Age: Median / range	68 / 20-82
Diagnosis:	
Myeloma	31 (44)
Diffuse large B-cell lymphoma (DLBCL)	29 (41)
Other	11 (15)

Table 2. . shows post CAR-T reinfusion transfusion requirements. Transfusion, all patient groups

Component	**No. patients (%)**	**Total units**	**Median**	**Range**	**Pre transfusion Hb /plt count median**	**Range**
Red cells (RC)	40 (56)	200	3	1-26	76	56-88
Platelets	28 (39)	186	4	1-25	15	2-75
FFP	5 (7)	17	2	1-10		
Cryoprecipitate	13 (18)	295*	20	5-50		
No transfusion	11 (15)					

*One apheresis bag recorded as 2 units

Table 3. Comparing Transfusion use in Myeloma [M] (21/31 transfused) and DLBCL [D] (18/29 transfused) patients

Component	**No. pts**		**Total units**		**Median (range)**	
Pt group	M	D	M	D	M	D
RC	21	14	105	77	4 (1-18)	2 (1-26)
Platelets	12	9	96	49	6 (2-23)	2 (1-18)
FFP	2	3	3	14	1.5 (1-2)	2 (2-10)
Cryo	6	6	120	170	15 (10-45)	25 (10-50)

Most transfusions occurred within 1-2 months of re-infusion (77%) with only 6/36 (17%) patients requiring any transfusion >6 months post re-infusion.

Conclusion: CAR-T cell reinfusion is associated with a high transfusion requirement with red cell and platelet use the most common product transfused. Further review will assess transfusion indications, any predictors of transfusion requirements and potential strategies that could optimise this aspect of patient care.

HP054

Outcomes in Acute Myeloid Leukaemia (AML) patients proceeding to Allogeneic Stem Cell Transplant (alloSCT) post Venetoclax/Azacitidine (Ven+Aza).

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Aim: Evaluate post alloSCT outcomes in patients treated with VEN+AZA for newly diagnosed (upfront) or relapsed/refractory (R/R) AML prior to transplant.

Background: VEN+AZA has emerged as standard of care for comorbid or older AML patients unable to tolerate Intensive Chemotherapy (IC). AlloSCT is a potentially curative option for eligible AML patients, with evidence suggesting that VEN+AZA treatment prior to alloSCT may be non-inferior to IC regimens.

Method: Between January 2020 and May 2024, all alloSCT patients who received VEN+AZA and proceeded to alloSCT were identified (n=14). Patient demographics, European LeukemiaNet (ELN) risk classification, conditioning intensity, donor type, and disease status pre-transplant were analysed. Overall survival (OS), relapse free survival (RFS), incidence of relapse and non-relapse mortality (NRM) post alloSCT were reported. Cumulative incidence and median duration in months was calculated.

Results: Fourteen patients were included, all classified as ELN adverse risk. 36% received VEN+AZA upfront and 64% in the R/R setting. The median age at alloSCT was 58.5 (range 49-67) with 58% having ECOG status of 0 at transplant. 71% of patients received reduced intensity conditioning and 71% had a matched unrelated donor. All patients were in morphological CR prior to alloSCT, with 50% MRD positive by flow cytometry. Median follow-up was 10.6 months, with median OS and RFS of 17.4 and 18.1 months, respectively. 1-year OS and RFS was 49% and 37% respectively with median duration to relapse of 6.8 months. NRM at 12 months post-alloSCT was 25%. Causes of death were veno-occlusive disease, sepsis and respiratory failure secondary to pulmonary GVHD (n=1 each).

Conclusion: VEN+AZA followed by alloSCT remains a viable option for curative intent treatment in AML. The high mortality within the first year post-alloSCT from relapse and NRM highlight the need for further research to optimise post-alloSCT strategies for AML patients.

HP055

Methotrexate dose modification does not impact on graft versus host disease in allograft patients given thymoglobulin prophylaxis.

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Aim: Methotrexate (MTX) and a calcineurin inhibitor form the backbone of GVHD prophylaxis, often with the addition of T-cell depletion with rabbit-ATG (thymoglobulin) in high-risk patients. However MTX doses are commonly withheld or reduced in the context of toxicity; whether this impacts on GVHD outcomes is not well documented. Hence we examined whether dose modification impacts rates of acute and chronic GVHD in thymoglobulin recipients.

Method: A retrospective study of 99 allograft recipients who received thymoglobulin 4.5mg/kg and planned to receive MTX 15mg/m2 d1 and 10mg/m2 d3,6 and 11 together with cyclosporin. Matched unrelated donors (MUD) and sibling donors were included. Outcome comparisons were between full-dose MTX and dose reduction or deletion. Primary endpoints were difference in cumulative incidence of acute GVHD (any grade and grade 3-4) and chronic GVHD requiring systemic immunosuppression. These were analysed using Gray's test to account for competing risks of death, relapse, or donor lymphocyte infusion use. Categorical variables were analysed using chi-square test and continuous variables using T-test

Results: Fifty patients had MTX dose modifications, with d11 omission the most common (63%) and most commonly due to mucositis (78%); 49 patients received full dose. The modified cohort was significantly younger (median age 53 vs 57 years, p=0.03), more frequently received myeloablative conditioning (48% vs 20%,p=0.04) and more frequently required TPN (90% vs 63%,p=0.002). There was no difference in the proportion of MUD vs sibling donors. There was no significant difference in acute GVHD of any grade (40% vs 39%,p=0.98) or grade 3-4 (10% vs 6%,p=0.47), or chronic GVHD requiring immunosuppression (24% vs 18%,p=0.43).

Conclusion: Modifying MTX dosing in thymoglobulin treated patients does not impact the rates or severity of acute or chronic GVHD. These observations suggests that lower than standard doses of MTX could be considered in this context, and may reduce mucositis and hasten engraftment.

HP056

Desensitisation Therapy for Donor specific antibodies prior to Allogeneic stem cell transplantation

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T cell replete haploidentical and mismatched unrelated donor transplants (HSCT) are increasingly being performed for patients without matched donors. A limitation is the presence of recipient antibodies directed against the mismatched donor alleles (donor specific antibodies (DSA)) which have been associated with graft failure (GF). Several strategies have been reported to reduce circulating DSA levels in the recipient's serum to mitigate antibody-mediated rejection.

Aim: We present a multi-institutional experience of DSA desensitisation prior to HSCT.

Methods: Haploidentical and unrelated donor transplant recipients with circulating DSA who underwent desensitisation therapy were identified from institutional records. DSA level was determined by using the LUMINEX technique. Single antigen testing was used to identify each HLA class antibody-specificity. DSA values were expressed in mean fluorescence intensity (MFI). Desensitisation treatments included a varying combination of immunosuppressive agents, rituximab, bortezomib, plasma exchange and intravenous immunoglobulin. Flow crossmatch assays (FXM), C1q positivity and DSA MFI levels were monitored at regular intervals.

Results -17 patients from 6 institutions were identified.

Age Median years (range)	55 (39 - 66)
Sex:	Female (15)
Diagnosis/Indication: AML/MDS ALL CML NHL/CLL SAA Graft failure	 6 3 2 4 1 1
Donor relationship: Unrelated Haploidentical - sibling Haploidentical - child	 3 9 5
Stem cell source	HPC(A) (16) HPC(M) (1)
Conditioning Intensity: Myeloablative Reduced intensity	 5 12
CD34 dose median $x10^6$/kg (range)	5 (4 – 10.63)
NCC x 10^8/kg (HPC(M)) n=1	1.95
Number of DSA/patient, mean (range)	1.94 (1-6)
DSA MFI pre-treatment, median (range)	4778 (588-26413)
DSA MFI pre-stem cell infusion, median (range)	1359 (0-20479)

Mean reduction in DSA MFI from screening to day-1 was 60.5%. All patients proceeded with HSCT with a median neutrophil and platelet engraftment of 20 (range 14-37) and 32 days (range 18-73) respectively. 2 patients did not achieve platelet engraftment. All donors achieved 100% donor chimerism by day 60.

Conclusion: Desensitisation treatment is effective in reducing DSA and allowing successful engraftment in HSCT**.**

HP057

ABO-mismatched Allogeneic Haemopoietic Transplantation – the W.A. Experience with Red Cell Aplasia

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Aim: Allogeneic haematopoietic stem cell transplantation (HSCT) frequently involves major ABO mismatch between recipient and donor, occasionally leading to pure red cell aplasia (PRCA) and transfusion dependence. Various therapeutic strategies have been reported, but there is no established standard of care.

We present the case of a 69-year-old female with AML arising from MDS, who developed PRCA following a major ABO mismatch sibling allograft, which spontaneously resolved after fourteen months. Additionally, we review the management and outcomes of similar cases in Western Australia and existing literature.

Method: Retrospective review of electronic records and laboratory data for the case report and patients who underwent allograft with major ABO incompatibility between 2020 to 2023. Data included antibody titres, development of PRCA, management strategies and time to resolution.

Results: The patient received a peripheral blood stem cell infusion (7.3x10^6 CD34+ cells per kilogram) from a sibling donor. The total infused volume was 72mL, including 2.2mL of red blood cells. The patient's blood group was O Rh positive with baseline anti-A IgG titre of 1024 and anti-B IgG titre of 512. The donor blood group was AB Rhesus positive. Post-transplant there was persistent anaemia and reticulocytopenia. Transfusion independence was eventually achieved 14 months after transplant, concurrent with resolution of anti-A/anti-B antibodies. From 2020 to 2023, 56 patients in W.A. underwent allograft with major ABO incompatibility, with 7 developing PRCA. Management strategies included supportive care, weaning immune suppression and Rituximab. PRCA resolution occurred in all patients, with median resolution time of 180 days post-transplant (range 95-427 days).

Conclusion: PRCA is a recognized complication of major ABO incompatible allogeneic HSCT, often leading to prolonged transfusion dependence. It is associated with the persistence of recipient antibodies which tend to be self-limited in duration. While various therapeutic strategies have been reported, their effectiveness remains unclear and may cause additional toxicities.

HP058

Rural / Regional place of residence impacts Post Allogeneic Bone Marrow Transplant overall survival of Australian patients with Acute Myeloid Leukaemia: an ANZTCT Registry study

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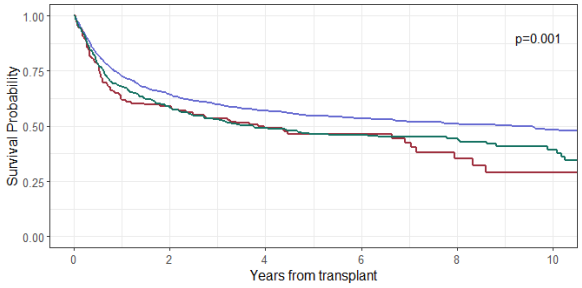
Aims: The aims of this study were to examine the relationship between-rurality-based-on a recipient's nominated residential postcode and mortality in patients with acute myeloid leukaemia who received an allogeneic bone marrow transplant (alloHCT).

Methods: Using data submitted to the Australia-and-New Zealand-Transplant-and-Cellular-Therapies-(ANZTCT)-Registry, a retrospective analysis was used to assess the outcomes of alloHCT recipients by postcode as classified in the Modified-Monash-Model-(MMM) of-remoteness1,2. Data was obtained for the 2009-2019 period, for adult patients undergoing an alloHCT at Australian transplant centres. The primary outcomes were overall-survival-(OS) defined as death from-any-cause and non-relapse mortality -(NRM) defined as death from any cause other than relapse3. Association between MMM-category, and other pre-transplant patient criteria, on the endpoints were analysed using multivariable-Cox-Regression. Patient, disease, and alloHCT related characteristics, were compared according to postcode-classification.

Results: Initial analyses of the 1729 patients included in the study (1201-metropolitan, 151-regional and 377-residing in remote areas) showed that patient age-at-alloHCT, donor-type and disease-response-status at transplant were associated with patient OS in addition to the MMM area of residence. Cumulative incidence of NRM by area-of-residence was similar between groups (p=0.2) while relapse-related-mortality showed a weak-association (p=0.04). After adjusting for age, donor type and disease response status in multivariate analyses, our study showed that there was a difference in-OS between areas-of-remoteness with HR 1.36 (CI:1.08-1.70) p=0.008 for regional-patients and HR: 1.27 (CI:1.08-1.49) p=0.003 for rural/remote.

Conclusion: Our study demonstrated a statistically significant difference in OS based on nominated residential postcode for those undergoing-alloHCT. This study represents the first registry-based study demonstrating disparity in alloHCT outcomes of Australian patients based on their primary residence. One potential explanation for this finding could be ease of access to specialist care based at metropolitan transplant centres. Differences in social determinants of health between MMM-groups could not be addressed in this retrospective-analysis.

Fig 1. Overall survival of AML patients by area of residence



At Risk						
Metro	1201	741	577	370	220	122
Regional	151	88	65	28	13	3
Rural/Remote	377	214	159	91	58	26

Events						
Metro	1	426	507	538	551	559
Regional	0	62	76	79	84	86
Rural/Remote	0	155	189	197	200	205

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HP059

Real world outcomes of ruxolitinib treatment of steroid refractory/dependent acute graft versus host disease.

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Aim: Steroid-refractory and/or dependent acute graft versus host disease (SR/SD-aGVHD) is a life-threatening complication following allogeneic haematopoietic stem cell transplantation (HSCT). The REACH-2 study established ruxolitinib as standard of care compared to historical salvage options, however patients with lower GI involvement still have poor outcomes[1]. We aimed to review local outcomes of patients treated with ruxolitinib for SR/SD-aGVHD.

Method: We performed a retrospective analysis of HSCT recipients treated between 2021 and March 2024. The primary endpoint was overall survival (OS), with secondary endpoints including non-relapse mortality (NRM) and requirement for third line therapy.

Results: We identified 37 patients with SR/SD-aGVHD, median age of 52 years at time of HSCT. All patients underwent T-replete HSCT using GCSF-stimulated PBSC. Donor source was matched sibling (27%), matched unrelated (44%), and haploidentical/mismatched (24%); with myeloablative conditioning in 35%. GVHD prophylaxis was cyclosporin/methotrexate (78%) or post-transplant cyclophosphamide/tacrolimus/mycophenolate (22%).

Acute GVHD occurred at median 41 days post-HSCT with grade III-IV disease (48%), lower gastrointestinal (GI) involvement (68%) and skin-only disease (27%). Following ruxolitinib commencement, the cumulative incidence of response was 78% at D+28 and 81% at D+56; with 73% complete and 11% partial response. Ruxolitinib failure occurred more frequently in patients with lower GI involvement compared to those without (overall response 76% vs 100%), and flares of aGVHD after initial response requiring third-line therapy occurred in 42% vs 0%.

At median follow-up of 159 days post ruxolitinib commencement, overall survival was 51% with mortality due to GVHD (56%), infection (22%) and relapse (6%). NRM occurred more frequently in patients with lower GI aGVHD (64% vs 8%).

Conclusion: Our single-centre data supports ruxolitinib as second-line therapy for SR/SD-aGVHD. However, patients with lower GI involvement remain at significant risk for non-sustained response requiring third-line therapy and non-relapse mortality.

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HP060

An Audit of measurable Residual Disease (MRD) testing in Patients Diagnosed with Acute Myeloid Leukaemia in Western Australia between 2019-2022 who underwent Allogeneic Stem Cell Transplant (SCT).

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Aim: MRD is a strong independent predictor of allograft outcomes in AML. The European LeukemiaNet published recommendations for MRD testing in patients who undergo allogeneic SCT for AML.(1,2) The 2018 ELN guideline recommends:

1. Pre-allograft MRD in PB and BM after last conventional chemotherapy, but < 4 weeks before conditioning.
2. Post-allograft MRD.

The 2021 updated did not expand on these recommendations.

We performed an audit of MRD testing over a 52-month period (January 2019-April 2023) for patients who were diagnosed with AML in WA between 2019-2022 and underwent allogeneic SCT. The aim of the audit was to identify areas of testing that were amenable to improvement and to develop clinical tools to improve patient care.

Method: Patient demographics, treatment regimens and MRD results were obtained from SCT registry data and the Pathwest laboratory information system after institutional approval was granted (GEKO #49469).

We determined the type and frequency of MRD markers in this cohort and assessed adherence to ELN allograft MRD testing recommendations. We recorded MRD testing for non-validated molecular markers and the use of MRD directed donor lymphocyte infusion (DLI).

Results: Eighty-eight patients underwent allograft. Twenty-six patients (30%) had a ELN validated molecular marker (NPM1, CBFB-MYH11, RUNX1-RUNX1T1, PML-RARA). In this group, at least one pre-transplant and at least one post-transplant MRD test was performed in 69% and 81% respectively. For the other 62 patients (70%) flow MRD was not performed. MRD testing for non-validated molecular markers was infrequent. MRD directed DLI was rare.

Conclusion: This audit demonstrated low adherence with ELN MRD recommendations. *Interventions to improve testing were identified. Clinical tools, including an electronic MRD tracking spreadsheet, local allograft testing guidelines and weekly MDT review of MRD have subsequently been implemented in WA. Universal availability of flow MRD testing in WA is an unmet need.*

HP061

Allogeneic Haematopoietic Stem Cell Transplantation is safe and effective for Myeloid Neoplasms with Germline DDX41 mutation.

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Aim: Germline DDX41 mutations define specific myeloid neoplasm subtypes including AML and MDS. Whilst DDX41-mutated patients often undergo allogeneic haematopoietic stem cell transplant (HSCT), recent retrospective analyses have reported higher severe acute and chronic graft vs host disease (GVHD)[1] and inferior survival[2] compared to non-DDX41 mutated patients. We aimed to review the outcomes of patients transplanted at our centre for myeloid neoplasms with germline DDX41 (MN-DDX41).

Method: We conducted a retrospective analysis of all patients treated at our institution for MN-DDX41 between 01/2019-01/2024. Data collected included disease characteristics, genomic data, treatment details, response outcomes and survival. The primary endpoint was overall survival (OS), with secondary endpoints including treatment-related mortality (TRM), relapse, and GVHD incidence.

Results: 22 patients with MN-DDX41 were identified (8 AML, 14 MDS). Median age at diagnosis was 64 (range 59-75 years), with 18 (87%) male. Donor source was matched sibling (1; 7%), matched unrelated (11; 79%) or mismatched unrelated (2; 14%); conditioning was reduced-intensity or non-myeloablative in 13 and 1 respectively; GVHD prophylaxis was CsA/MTX in 8 (57%) and PTCy/tacrolimus/MMF in 6 (43%). After median follow-up of 27 months (range 6-64mo), 17 (77%) are alive; 4 patients not receiving HSCT died from progressive/refractory disease, and 1 HSCT recipient died from infection soon after engraftment. For HSCT recipients, after median follow-up 18 months post-HSCT (range 1-45mo), 13 (93%) remain alive in remission. The cumulative incidences of acute (grade II-IV) and moderate-severe chronic GVHD are 35% and 50% respectively. OS following original diagnosis showed a non-significant trend for HSCT recipients vs non-recipients (2-yr OS 90% vs 65%; p=0.19).

Conclusion: Despite adverse risk factors our early single-centre experience suggests that allogeneic HSCT is acceptably safe and efficacious for patients with MN-DDX41, and supports its use compared to non-HSCT alternatives. Confirmation in larger, multicentre studies with longer follow-up is warranted.

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HP062

Relapsed AML post allo-HSCT: review of outcomes and prognostic factors impacting survival

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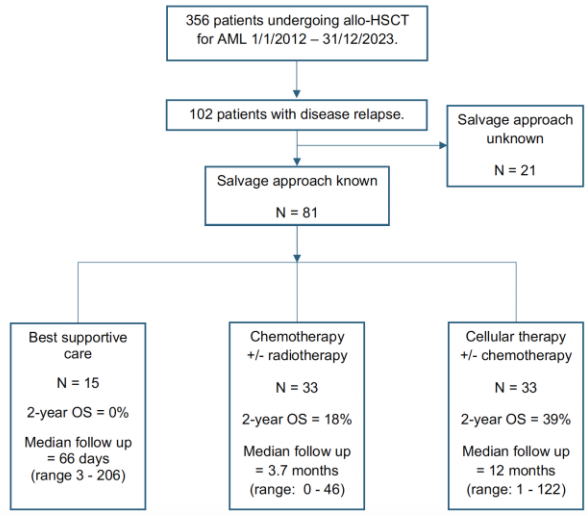
Aim: Relapsed disease is the leading cause of treatment failure for acute myeloid leukaemia (AML) post allogeneic haematopoietic stem cell transplantation (allo-HSCT). However, in the last decade, significant advances in disease monitoring, molecular prognostication and targeted treatment options may contribute to improved outcomes. We provide a single-centre review of outcomes following relapsed AML post-HSCT in this new era.

Method: Between 2012 and 2023, all patients with relapsed AML following first allo-HSCT in our institution were identified. Patients were grouped according to salvage treatment approach. Demographic information, disease characteristics and survival were analysed. Univariable and multivariable analyses will be undertaken to identify prognostic features.

Results: Among 356 patients undertaking first allo-HSCT for AML, 102 patients relapsed (29%). Median age was 52.5 years. Median time to disease relapse was 6 months (range 0.5 – 90 months). De novo AML as a transplant indication, reduced intensity conditioning and matched unrelated donors were present in 92(90%), 58(57%), and 56(50%) patients, respectively. T cell depletion was used in 50(49%) patients. 21 patients returned to referral centre and therefore salvage approach was unknown. Of the 81 remaining patients, 19% (n=15) had best supportive care, 32%(n=33) were treated with a combination approach of chemotherapy and/or targeted therapy and/or radiotherapy, and 32%(n=33) received cellular therapy such as second allograft or donor lymphocyte infusion, with chemotherapy (Figure 1). The 2-year overall survival (OS) was 23%. 2-year OS was greatest (39%) in recipients of cellular therapy. Multivariable analysis of predictors of OS will be presented.

Conclusion: Relapsed AML post allo-HSCT has high mortality regardless of salvage intervention utilised. Further sub analysis of which patients would benefit from salvage therapy in the era of targeted therapy will be described at time of abstract presentation.

Figure 1. Consort diagram



HP063

High dose valaciclovir for management of low level cytomegalovirus reactivation post allogeneic haematopoietic stem cell transplantation

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Aim: To determine the efficacy of high dose Valaciclovir (HDV) in treating low-level cytomegalovirus (CMV) reactivation (<1000 IU/ml) post allogeneic Haematopoietic Stem Cell Transplantation (allo-HSCT).

Method: A retrospective review of 140 patients who underwent allo-HSCT at Royal North Shore Hospital between June 2021 and May 2024. Patients with CMV viral load >34 and <1000 IU/mL were treated with HDV 1g QID. If CMV viral load increased (>1000 IU/mL) treatment changed to Valganciclovir until CMV undetectable on two consecutive tests, then Valaciclovir prophylaxis recommenced. Patients at high risk of CMV reactivation (donor negativity, recipient positivity) were given Letermovir and Valaciclovir. No patient on Letermovir developed CMV reactivation.

Results: 48 patients (34%) developed CMV reactivation post HSCT – 77%(n=37) <100 days post allo-HSCT and 23%(n=11) >100 days post-HSCT. All initially treated with HDV. Of those patients who reactivated CMV <100 days post- allo-HSCT 57%(n= 21) became CMV negative, 43%(n=16) within 4 weeks and 14% (n=5) within 8 weeks. 43%(n=16) failed HDV. Of those who failed HDV, 11 patients became CMV negative with Valganciclovir. One failed Valganciclovir and required alternative therapy. Remaining 4 patients received Aciclovir and/or Foscarnet after failing HDV. Of those patients who reactivated CMV >100 days post-HSCT, 5 became CMV negative with HDV; 27%(n=3) within four weeks and 18%(n=2) within three months of commencing HDV. 5 patients (45%) failed HDV and became negative with Valganciclovir: One patient failed HDV and Valganciclovir and required three alternative therapies. Of the total patients who reactivated post allo-HSCT one developed CMV retinitis. No patients died from CMV disease.

Conclusion: 54% of patients who developed CMV reactivation post HSCT were treated effectively with HDV alone. HDV is an effective therapy for low-level CMV reactivation post allo-HSCT, is well tolerated, a lower incidence of cytopenias and is relatively inexpensive compared to other CMV therapies.

HP064

Oral Herpes Simplex Virus-1 infection with DNA Polymerase R700G mutation following allogeneic haematopoietic stem cell transplantation.

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Aim: Mucositis is a common complication post allogeneic haematopoietic stem cell transplantation (HSCT) (1). Prophylactic acyclovir effectively prevents Herpes Simplex Virus-1 (HSV-1) stomatitis following HSCT, but rare cases of acyclovir resistant HSV (ACV-R HSV) occur (2,3). Primary foscarnet resistance is very uncommon. The mechanisms of resistance are through genetic mutations of thymidine kinase or DNA polymerase (4).

Method: A 68-year-old developed ACV-R HSV 7 months following reduced intensity haploidentical allogeneic HSCT for refractory myelofibrosis. He was compliant with valaciclovir prophylaxis pre- and post-transplant. Pre-transplant, donor and recipient were IgG positive for HSV-1.

Results: The patient developed steroid refractory gut graft versus host disease (GVHD) and was treated with Ruxolitinib. He developed Cytomegalovirus viraemia which was treated with 14 days of ganciclovir. However, on day 10, painful oral mucocutaneous ulcers appeared, with PCR confirming HSV-1 DNA. ACV-R HSV was suspected following no clinical improvement after 5 days each of treatment dose valaciclovir and IV acyclovir. Foscarnet was commenced but resulted in severe electrolyte disturbance. Treatment was changed to weekly IV cidofovir, which improved but did not resolve the stomatitis. Genotype testing confirmed HSV-1 DNA Polymerase R700G mutation which confers acyclovir and foscarnet resistance. Whilst it is not known whether it confers cidofovir resistance, we suspected clinical resistance given persistence of stomatitis. We obtained compassionate access Pritelivir and await to see response. Steroids were ceased. The patient had ongoing gut GVHD and remains on tacrolimus and Ruxolitinib.

Conclusion: ACV and Foscarnet resistant HSV following HSCT is rare but should be suspected if there is no clinical improvement with acyclovir. Risk factors were prolonged valaciclovir exposure and T cell suppression. Treatment and maintenance therapy is challenging, with toxic, intravenous, second-line agents. There is a need for new oral therapies like Pritelivir.

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HP065

Nonmyeloablative autologous stem cell transplantation as treatment for relapsing remitting tumefactive multiple sclerosis: A case report of excellent clinical and radiological disease response

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Tumefactive Multiple Sclerosis (TMS) is a rare variant of MS in which patients present with large, inflammatory, tumour-like central nervous system lesions. It represents between 0.2 - 8% of all MS cases and can be difficult to treat with standard therapies, which makes management quite challenging, given there are no formal treatment guidelines.(1) Here, we present a case of Nonmyeloablative autologous stem cell transplantation (NMA AutoSCT) in TMS which is rarely described in the literature.

Case presentation: A 22-year-old female presented to ED with a one-week history of right sided hemiparesis. MRI revealed peripherally enhancing lesions in the left frontal and right occipital lobes. Biopsy confirmed demyelination, and a diagnosis of TMS was made. Over the course of 15 months, she went on to relapse a total of 6 times. During this time, she was trialled on high dose intravenous steroids, TPE and disease modifying therapies (DMTs) including Natalizumab and Alemtuzumab, however she continued to progress through all treatments. Following her 6th relapse, she underwent a high dose Cyclophosphamide + Thymoglobulin AutoSCT in March 2023, which she tolerated very well. Following treatment, her expanded disability status scale (EDSS) improved from 5.5, to 2.5. Now 14 months post-transplant, she remains in remission with almost full resolution of neurological symptoms. Her imaging also shows stable disease, with no new or active lesions present.

There is evidence to suggest that NMA-AutoSCT results in lower progression and relapse rates in comparison to DMTs in MS. It is unclear whether this is the case for TMS, given the rare nature of the disease, which makes it challenging to perform robust clinical trials or retrospective research. This case report hopes to highlight NMA-AutoSCT as a potentially safe and effective option in reducing disability and disease activity in RRTMS.

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CLL

HP066

Real-world utilisation of Bruton tyrosine kinase inhibitors (BTKi's) in relapsed/refractory chronic lymphocytic leukaemia (CLL) in Australia

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Aim: This study examines usage patterns for the two most commonly prescribed BTKi's for CLL in Australia: ibrutinib (IBRU) and acalabrutinib (ACA). We report: (1) use of IBRU and ACA by line of therapy, (2) patient characteristics; and (3) therapies preceding and following BTKi use and co-medications; , and (4) treatment duration and adherence to BTKi treatment.

Method: A retrospective cohort analysis was conducted using Australian Department of Human Services Pharmaceutical Benefits Scheme (PBS) 10% data sample from December 2017 to August 2023. PBS indications identified ibrutinib and acalabrutinib scripts for R/R CLL. Utilisation was considered persistent until 6-months without a script. Duration on treatment was evaluated graphically using Kaplan-Meier curves. Unadjusted and adjusted comparisons between treatment duration curves were made using Cox Proportional Hazard models. Different adjusted and sensitivity analyses were performed for robustness.

Results: The 10% sample yielded 278 patients prescribed IBRU for R/R CLL since listed on the Australian PBS in December 2017, and 66 ACA patients since 1 September 2020. Median age of initiation on IBR was 75 years and 77 for ACA. 68% of the use of IBRU has been in 2nd line vs 77% of acalabrutinib. Median duration on treatment was 28 months for IBRU and not reached for ACA. The differences were not statistically significant in both conventional unadjusted analysis and adjusting for covariates.

Conclusion: PBS analysis shows IBRU and ACA are most frequently used in CLL 2nd line therapy. Treatment durations between IBRU and ACA are not statistically different, but ACA was only made available recently evidenced by lower patient numbers and more censoring. Age and comedication profiles are similar among both agents.

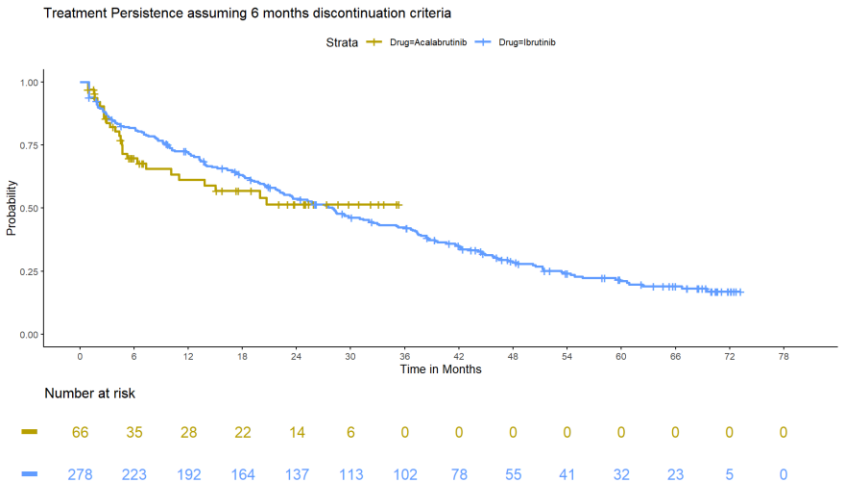

Figure 1: Treatment duration IBRU vs ACA

HP067

Acquired ATM and TP53 deletion detected by fluorescence in-situ hybridisation in patients with chronic lymphocytic leukaemia

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Aim: The *ATM* (11q22) and *TP53* (17p13) genes play a fundamental role in DNA damage response pathway and their disruption confers poor outcomes in chronic lymphocytic leukaemia (CLL). Patients with del(17p) may benefit from BTK inhibitors and detection of *TP53* deletion is funded at time of diagnosis, disease relapse and/or progression. Little is known about the rate of acquisition of *ATM* and *TP53* deletion and we aim to report on the incidence of acquiring *ATM* and *TP53* deletion.

Method: We conducted a 14-year, retrospective audit of our FISH database (01/Jan/2010-31/Jan/2024) identifying a total of 4372 newly diagnosed patients with baseline *ATM* and *TP53* status. 1009 (23%) had repeat *ATM/TP53* FISH during their clinical course. Here we report on a review of the initial 300 (30%) cases with the remainder to follow. No patient information, disease or treatment characteristics have been collected to date.

Results: Of the 300 pts (30% of the CLL cohort) reviewed to date, median number of repeat tests was 2 (Range 1-9) at a median interval of 12 months (Range 1-150m). At baseline, *ATM* deletion was identified in 55 (18.3%), *TP53* deletion in 23 (7.7%) and co-deletion in 6 (2.0%) of patients. *ATM* deletion was acquired in 15 pts (5%) only if *TP53* was not deleted at baseline. *TP53* deletion was acquired in 43 (14.3%) of cohort irrespective of baseline *ATM* status (see Table 1). Further data to follow.

Conclusion: At baseline, *ATM* deletion is more common than *TP53* deletion while *TP53* deletion is acquired in 20% of patients. From limited data available to-date it appears that patients with baseline *TP53* deletion have increased number of tests at shorter intervals. Final results of this audit may further inform and guide testing practice.

Total Patient Cohort		**Diagnostic FISH results for *ATM* (11q22) and *TP53* (17p13) deletion**			
		ATM Normal *TP53* Normal	*ATM* Deleted *TP53* Normal	*ATM* Normal *TP53* Deleted	*ATM* Deleted *TP53* Deleted
Number of patients	300	228	49	17	6
Number of repeat tests; median (range)	2 (01-09)	1 (01-07)	1 (01-09)	2(01-08)	2.5(01-03)
Interval (months) btw episodes; median (range)	12 (1-150)	14 (1-150)	10 (1-136)	7(1-93)	11(1-64)
Acquired *ATM* deletion (n; %)	15 (5%)	15 (7%)	N/A	0	N/A
Acquired *TP53* deletion (n; %)	43 (14%)	36 (16%)	7 (14%)	N/A	N/A

HP068

Combination treatment with sonrotoclax (BGB-11417) + zanubrutinib is well tolerated and achieves deep responses in patients with treatment-naive (TN) CLL/SLL: data from an ongoing phase 1/2 study

Tam C[1], Anderson M[2,3], Lasica M[4], Verner E[5,6], Opat S[7], Ma S[8], Weinkove R[9,10], Cordoba R[11], Soumerai J[12], Ghia P[13,14], Leitch S[15], Hilger J[16], Fang Y[17], Simpson D[16], Guo H[18], Cheah C[19,20,21]

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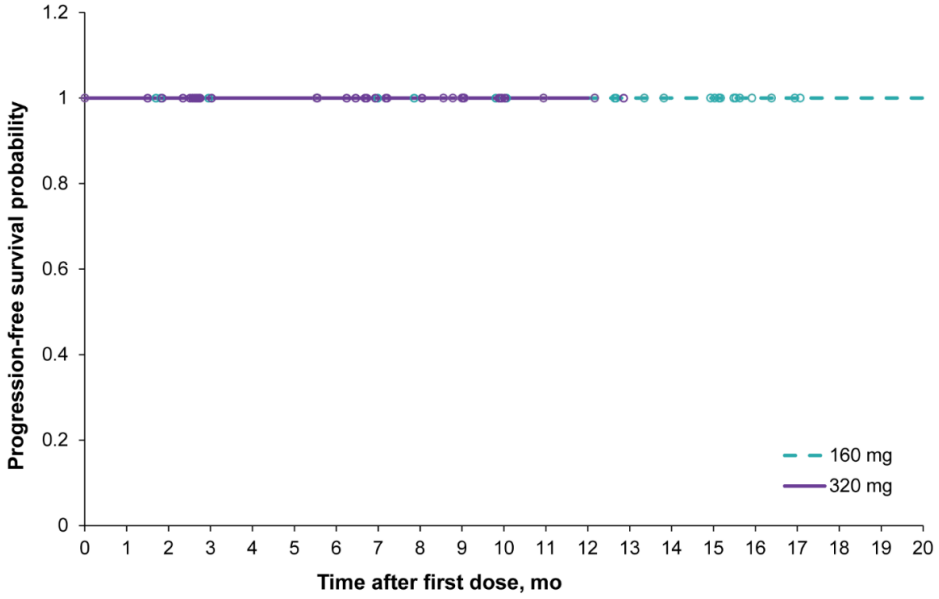
Aim: Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is more selective and potent than venetoclax in biochemical assays. Zanubrutinib, a next-generation BTK inhibitor, improved PFS with fewer cardiac AEs than ibrutinib in patients with CLL/SLL. BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, dose-escalation/expansion study of sonrotoclax + zanubrutinib for B-cell malignancies. Data from patients with TN CLL/SLL are presented.

Method: Patients received zanubrutinib (320mg QD/160mg BID) 8-12 weeks before sonrotoclax target dose (160mg/320mg QD) ramp-up. TLS was assessed per Howard 2011 criteria. Endpoints included safety (CTCAEv5.0), ORR (iwCLL 2008 criteria), and minimal residual disease (uMRD4) in blood.

Results: As of 21May2023, 94 patients were enrolled; 15 were still in zanubrutinib lead-in and 79 started sonrotoclax (160mg, n=32; 320mg, n=47). Overall, median follow-up was 8.5 months. No deaths occurred; all patients remain on study. TEAEs in ≥20% of patients who received sonrotoclax + zanubrutinib were contusion (35%), neutropenia (35%), COVID-19 (23%), and diarrhea (23%; grade ≥3, n=1). Neutropenia was the most common grade ≥3 TEAE (17%). No TLS or atrial fibrillation occurred. One TEAE (cryptococcal meningitis) led to treatment discontinuation. Sonrotoclax dose holds occurred in 17 patients; 3 patients had dose reduction. In 56 response-evaluable patients, ORR was 100% (CR: 160mg, 36%; 320mg, 19%). CR rate increased with time; median time to CR was 10.1 months. No progression events were reported (Figure). Week 24 blood uMRD4 rates were 50% (160mg) and 65% (320mg). Week 48 blood uMRD4 rates were 73% (160mg) and 100% (320mg).

Conclusion: Sonrotoclax (160mg/320mg) + zanubrutinib was well tolerated in patients with TN CLL/SLL. Only 1 treatment discontinuation and 3 dose reductions occurred. No TLS was seen. Efficacy is encouraging, with 100% ORR in assessed patients, no PFS events, and high blood uMRD4 rates occurring early. A phase 3 study assessing this combination is planned.

Figure: Progression-Free Survival With BGB-11417 + Zanubrutinib in Patients With TN-CLL by Dose



No. of patients at risk:

160 mg	41	29	27	26	25	25	25	24	22	22	19	18	18	15	13	12	3	1	0	0	0
320 mg	53	42	39	31	30	30	28	22	19	15	4	2	2	0	0	0	0	0	0	0	0

HP069

Pirtobrutinib in Post-cBTKi CLL/SLL: ~30 Months Follow-Up and Subgroup Analysis With/Without Prior BCL2i from the Phase 1/2 BRUIN Study

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Aim: We report the efficacy of pirtobrutinib treatment in CLL/SLL in the post-cBTKi setting, including subgroups with/without prior BCL2i, from the BRUIN study (NCT03740529) with more than 2 years FU.

Method: Pts with pretreated CLL/SLL were eligible for treatment with pirtobrutinib in the multicenter Phase 1/2 BRUIN study. Key endpoints included ORR (including PR-L) as assessed by an IRC per 2018 iwCLL response criteria, DoR, PFS, OS, and safety. A data cut of 05MAY2023 was utilized.

Results: In total, 282 pts with CLL/SLL received prior cBTKi. Median age was 69 years (range, 36-88), median number of prior therapies was 4 (1-11), 154 (55%) were BCL2i-N and 128 (45%) were BCL2i-E. BCL2i-N pts received fewer prior therapies than BCL2i-E pts (median prior therapies 3 and 5, respectively). ORR for all post-cBTKi pts was 72% (95% CI, 66.4-77.1). Post-cBTKi pts included 19 pts with one prior line of cBTKi-based therapy and 2L pirtobrutinib, who had ORR including PR-L of 89.5% (CI 95%, 66.9-98.7). Median OS was NE for all , BCL2i-N, and BCL2i-E pts (median FU 29.3 mos).The most frequent TEAEs, regardless of attribution, were fatigue (36.9%), diarrhea (28.4%) and cough (27.3%). The most frequent Grade ≥3 TEAE was neutropenia* (28.4%). Grade ≥3 TEAEs of hypertension (4.3%) and atrial fibrillation/flutter (1.8%) were infrequent. The AE profile of BCL2i-N and BCL2i-E pts was overall similar. In total, 7 (2.5%; 4 BCL2i-N, 3 BCL2i-E) pts had TRAE leading to pirtobrutinib discontinuation.

Conclusion: Pirtobrutinib continues to demonstrate promising and durable efficacy in pts with post-cBTKi heavily pretreated CLL/SLL. ORR was high regardless of prior BCL2i status. Longer PFS was observed in BCL2i-N than BCL2i-E pts, likely due to the more heavily pretreated status of the BCL2i-E population. Pirtobrutinib was well-tolerated with low-rates of discontinuation due to drug-related toxicity among both BTKi-N and BTKi-E pts.

Table. Clinical outcomes

	All post-cBTKi pts	BCL2i-N pts	BCL2i-E pts
ORR including PR-L, % (95% CI)	82 (76.5-85.9)	83.1 (76.2-88.7)	79.7 (71.7-86.3)
Median DoR, mos (95% CI)	18.4 (15.3-20.4)	24.9 (18.4-32.0)	14.8 (12.0-17.4)
Median PFS, mos (95% CI) [median FU – 27.5 mos]	19.4 (16.6-22.1)	23.0 (19.6-28.4)	15.9 (13.6-17.5)
24-month OS rates, % (95% CI)	73.2 (67.4-78.2)	83.1 (75.9-88.2)	60.6 (50.9-68.9)

Abbreviations: BCL2i = B-cell lymphoma 2 protein inhibitor; BCL2i-N = BCL2i-Naïve (had not received prior BCL2i); BCL2i-E = BCL2i-Exposed (had received prior BCL2i); cBTKi = covalent Bruton tyrosine kinase inhibitors; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; DoR = duration of response; FU = follow up; IRC = independent review committee; mos = months; NE = not estimable; neutropenia = neutropenia and neutrophil count decreased; ORR = overall response rate; PFS = progression-free survival; pts = patients; PR-L = partial response with lymphocytosis; TEAE = treatment-emergent adverse events; TRAE = treatment-related AE; 2L = second line.

HP070

Outcomes in high-risk subgroups after fixed-duration ibrutinib plus venetoclax for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): up to 5.5 years of follow-up in the phase 2 CAPTIVATE study

Tam C[1], Jacobs R[2], Barr P[3], Allan J[4], Siddiqi T[5], Tedeschi A[6], Kipps T[7], O'Brien S[8], Badoux X[9], Visentin A[10], Lasica M[11], Carney D[12], Elinder-Camburn A[13], De la Serna J[14], Szafer-Glusman E[15], Zhou C[15], Szoke A[15], Dean J[15], Ghia P[16,17], Wierda W[18]

[1]Alfred Health And Monash University, [2]Levine Cancer Institute, [3]Wilmot Cancer Institute, University of Rochester Medical Center, [4]Weill Cornell Medicine, [5]City of Hope National Medical Center, [6]ASST Grande Ospedale Metropolitano Niguarda, [7]University of California San Diego Moores Cancer Center, [8]UC Irvine, Chao Comprehensive Cancer Center, [9]Ministry of Health, [10]University of Padova, [11]St Vincent's Hospital Melbourne, [12]Peter MacCallum Cancer Centre, [13]North Shore Hospital, [14]Hospital Universitario 12 de Octubre, [15]AbbVie, [16]Università Vita-Salute San Raffaele, [17]IRCCS Ospedale San Raffaele, [18]The University of Texas MD Anderson Cancer Center

Aim: The phase 2 CAPTIVATE study evaluated first-line ibrutinib (Ibr) + venetoclax (Ven) for CLL/SLL in 2 cohorts: minimal residual disease (MRD)-guided randomized discontinuation (MRD cohort) and Fixed Duration (FD cohort). Ibr±Ven retreatment was allowed after progressive disease (PD). We report outcomes for patients with high-risk genomic features (FD cohort) and retreatment outcomes (FD cohort and MRD cohort placebo arm).

Method: Patients aged ≤70 years with previously untreated CLL/SLL received 3 cycles of Ibr, then 12 cycles of Ibr+Ven (Ibr, 420 mg/day orally; Ven, 5-week ramp-up to 400 mg/day orally). On-study retreatment included single-agent Ibr (FD cohort or MRD cohort placebo arm); patients with PD >2 years after end of treatment (EOT) could reinitiate FD Ibr+Ven (FD cohort).

Results: In the FD cohort (n=159; median follow-up 61.2 months [range, 0.8-66.3]), 5-year PFS and OS rates (95% CI) were 67% (59-74) and 96% (91-98), respectively. Five-year PFS rates were higher in patients with undetectable MRD at 3 months after EOT in peripheral blood (83%) or bone marrow (84%) versus those without (48% and 50%, respectively). The Table shows 5-year PFS rates in high-risk subgroups.

Of 202 patients who completed Ibr+Ven (FD cohort, n=159; MRD cohort placebo arm, n=43), 63 had PD to date; 32/63 (51%) initiated retreatment with Ibr (n=25) or Ibr+Ven (n=7). With median time on Ibr retreatment of 21.9 months, ORR was 86% in 22 evaluable patients (best response: 1 CR; 1 nodular PR; 17 PR; 2 SD; 1 PD [Richter transformation]). With median time on Ibr+Ven retreatment of 13.8 months, ORR was 71% in 7 evaluable patients (best response: 1 CR; 4 PR; 1 PR with lymphocytosis; 1 SD).

Conclusion: With up to 5.5 years of follow-up, FD Ibr+Ven continues to provide clinically meaningful PFS overall and in patients with high-risk genomic features. Ibr-based retreatment provides promising responses.

Table.

FD cohort	With high-risk genomic feature[a]		Without high-risk genomic feature[a]	
	n	5-year PFS rate, % (95% CI)	n	5-year PFS rate, % (95% CI)
del(17p)/mutated *TP53*	27	41 (21-59)	129	73 (64-80)
Complex karyotype[b]	31	57 (37-72)	102	72 (61-80)
Unmutated IGHV[c]	40	68 (50-80)	44	85 (69-93)
del(11q)[c]	11	64 (30-85)	74	79 (67-87)

[a]Among patients with known baseline status. [b]Defined as ≥3 chromosomal abnormalities. [c]Excluding patients with del(17p)/mutated *TP53* or complex karyotype.

HP071

Results from the phase 1 study of the novel BCL2 inhibitor sonrotoclax (BGB-11417) in combination with zanubrutinib for relapsed/refractory (R/R) CLL/SLL show deep and durable responses

Tam C[1], Anderson M[2,3], Tedeschi A[4], Verner E[5,6], Lasica M[7], Arbelaez A[8], Stilgenbauer S[9], Browett P[10], Leitch S[11], Gonzalez-Barca E[12], Shadman M[13,14], Hou J[15], Eradat H[16], Ma S[17], Westerman D[18,19], Fang Y[20], Hilger J[21], Patel S[21], Ding W[21], Guo H[22], Opat S[23]

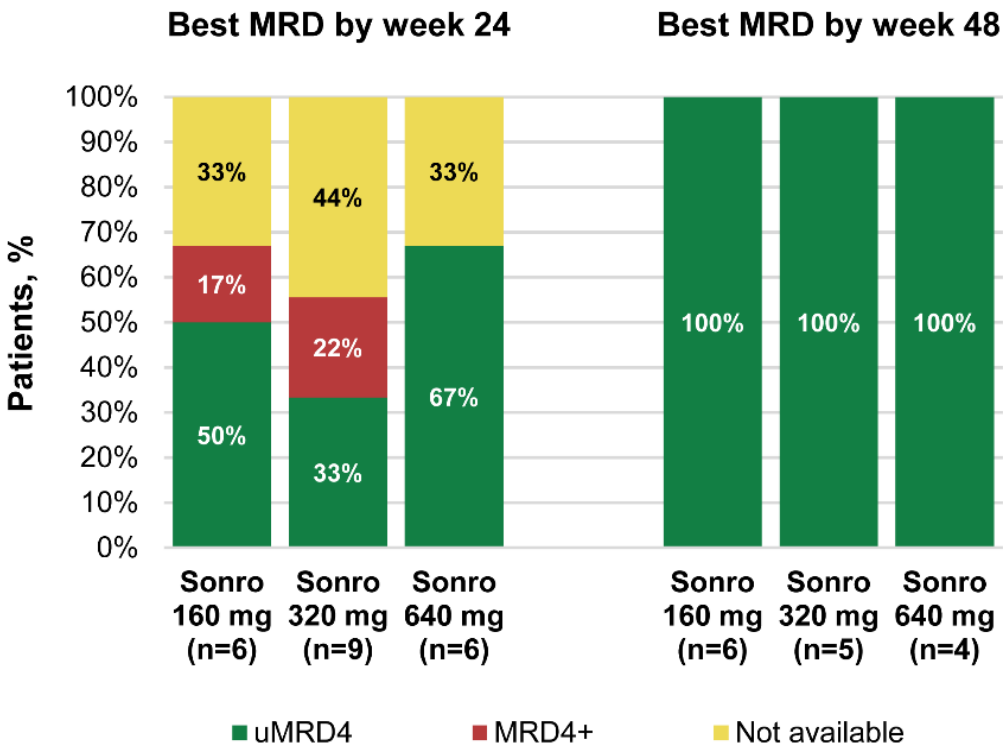
[1]Alfred Hospital and Monash University, [2]Royal Melbourne Hospital and Peter MacCallum Cancer Centre, [3]The Walter and Eliza Hall Institute, [4]ASST Grande Ospedale Metropolitano Niguarda, [5]Concord Repatriation General Hospital, [6]University of Sydney, [7]St Vincent's Hospital Melbourne, [8]Pindara Private Hospital, [9]Ulm University, [10]Auckland City Hospital, [11]Te Whatu Ora Health New Zealand - Waitemata, [12]Institut Català d'Oncologia Hospitalet, Universitat de Barcelona, IDIBELL, [13]Fred Hutchinson Cancer Research Center, [14]University of Washington, [15]University of Pittsburgh Medical Center, [16]David Geffen School of Medicine at UCLA, [17]Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, [18]Peter MacCallum Cancer Centre, [19]University of Melbourne, [20]BeiGene (Beijing) Co, Ltd, [21]BeiGene USA, Inc, [22]BeiGene (Shanghai) Co, Ltd, [23]Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University

Aim: Sonrotoclax is a more selective and potent BCL2 inhibitor than venetoclax in biochemical assays. Zanubrutinib, a next-generation BTK inhibitor (BTKi), has improved PFS and tolerability vs ibrutinib in R/R CLL/SLL. Updated data for sonrotoclax + zanubrutinib in patients with R/R CLL/SLL in the ongoing BGB-11417-101 (NCT04277637) study are presented.

Method: Patients received zanubrutinib (320mg QD/160mg BID) 8-12 weeks before starting sonrotoclax with target dose (40/80/160/320/640mg QD) ramp-up. Endpoints included safety (CTCAE v5.0), ORR (iwCLL 2008 criteria), and minimal residual disease in blood (uMRD4).

Results: As of 31Oct2023, 45 patients were enrolled (40mg, n=4; 80mg, n=9; 160mg, n=6; 320mg, n=20; 640mg, n=6); four were in zanubrutinib lead-in, 41 started sonrotoclax. Of tested patients, 28% (11/40) had del(17p) and 72% (13/18) had unmutated IGHV. The median number of prior treatments was 1; seven patients had a BTK inhibitor (BTKi) as their last therapy. The median follow-up was 17 months (range, 0.5-32.6). No DLTs occurred; MTD was not reached up to 640mg. Dose expansion was completed with a recommended phase 2 dose of 320mg. Treatment-emergent AEs (TEAEs) in ≥20% were COVID-19 (27%), contusion (27%), neutropenia (27%), diarrhea (24%), nausea (24%), and fatigue (24%). Neutropenia was the most common grade ≥3 TEAE (20%). No tumor lysis syndrome or atrial fibrillation occurred. No TEAEs led to death, discontinuation, or dose reduction. Fourteen patients had sonrotoclax dose holds. For 32 response-evaluable patients, ORR was 97%. CR rate was 50%; median time to CR was 9.8 months. Of 4 patients with prior BTKi, 3 had PR or CR. All patients reaching week 48 achieved uMRD4 (Figure). Treatment is ongoing for all but 1 patient.

Conclusion: Efficacy of sonrotoclax + zanubrutinib is encouraging, with a 97% ORR and deep responses, including uMRD, in patients with R/R CLL/SLL. This combination has demonstrated tolerability across all dose levels tested.


Best MRD by week 24
Best MRD by week 48
Patients, %
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
33%
17%
50%
44%
22%
33%
33%
67%
100%
100%
100%
Sonro 160 mg (n=6)
Sonro 320 mg (n=9)
Sonro 640 mg (n=6)
Sonro 160 mg (n=6)
Sonro 320 mg (n=5)
Sonro 640 mg (n=4)
uMRD4
MRD4+
Not available

HP072

Pirtobrutinib in Relapsed/Refractory CLL/SLL: Results from BTKi Naïve Cohort in the Phase 1/2 BRUIN Study

Eyre T[1], Maranda E[2], Roeker L[3], Patel M[4], Fukuhara N[5], Woyach J[6], Wierda W[7], Brown J[8], Patel K[9], Tam C[10], Fakhri B[11], Abada P[12], Tsai D[12], Sizelove R[13], Jurczak W[14]

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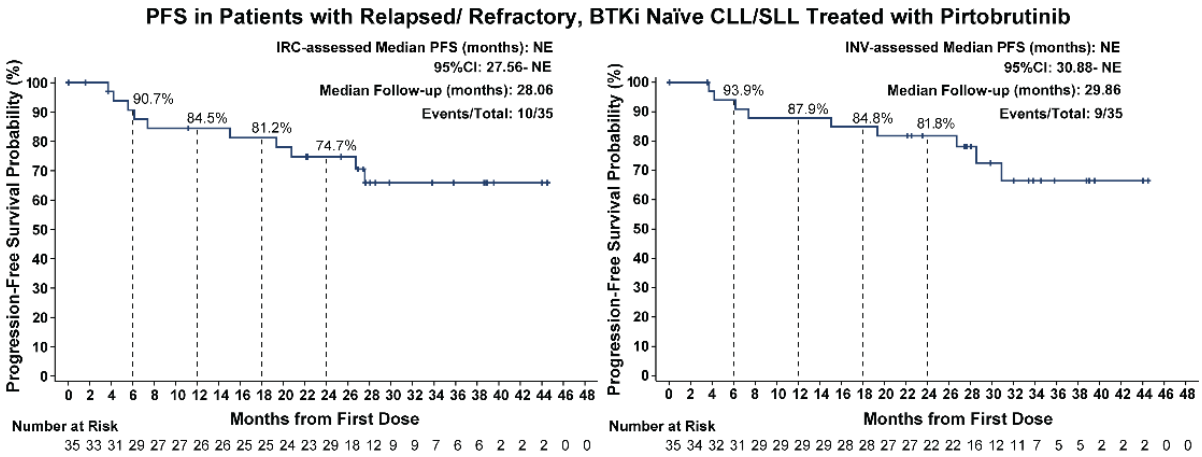
Aim: We report safety and efficacy of pirtobrutinib in BTKi naïve pts with R/R CLL/SLL from the phase 1/2 BRUIN study (NCT03740529).

Method: Pts with R/R BTKi naïve CLL/SLL received pirtobrutinib. Key endpoints included ORR; including PR-L as assessed by an IRC and INV per 2018 iwCLL response criteria, PFS, and safety. Data cutoff was 05May2023.

Results: This analysis included 35 pts with R/R BTKi naïve CLL/SLL treated with pirtobrutinib: 51.4% were male, and 94.3% had ECOG PS 0-1. Median number of prior therapies was 2 (range, 1-8). Of pts with available data, 20/25 pts (80.0%) had unmutated IGHV, and 10/27 (37.0%) had *TP53* mutation and/or del(17p). Median ToT was 28.8 mo, and median ToS was 31.5 mo. IRC-assessed ORR was 88.6% (95%CI, 73.3-96.8), with 1 (2.9%) CR and 30 (85.7%) PRs. ORR including PR-L was 91.4% (95%CI, 76.9-98.2) with 1 pt (2.9%) achieving PR-L. INV-assessed ORR was 85.7% (95%CI, 69.7-95.2), and including PR-L (n=3, 8.6%), was 94.3% (95%CI, 80.8-99.3). IRC-assessed mPFS was NE (95%CI, 27.6-NE), and 24-mo PFS rate was 74.7% (95%CI, 55.7-86.5) (median fu 28.1 mo). INV-assessed mPFS was also NE (95%CI, 30.9-NE), and 24-mo PFS rate was 81.8% (95%CI, 63.9-91.4). The most frequent TEAE, regardless of attribution, were COVID-19 (n=16, 45.7%), neutropenia* (n=15, 42.9%) and diarrhea (n=11, 31.4%). The most frequent grade ≥3 TEAE were infection (n=16, 45.7%; n=9, 25.7% excluding COVID-19) and neutropenia* (n=12, 34.3%). Grade ≥3 TEAE of hypertension (8.6%, n=3), hemorrhage/hematoma (n=1, 2.9%) and atrial fibrillation/flutter (2.9%, n=1) were observed. TEAE led to pirtobrutinib dose reduction in 5 pts (14.3%) and discontinuation in 2 (5.7%). Two pts (5.7%) experienced fatal TEAE, both due to COVID-19 infection considered by INV unrelated to pirtobrutinib.

Conclusion: Pirtobrutinib demonstrated promising efficacy in pts with R/R BTKi naïve CLL/SLL and was well tolerated with a low rate of discontinuation.



Abbreviations/notes: BTKi = Bruton tyrosine kinase inhibitors; cBTKi = covalent BTKi; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; CR = complete response; fu = follow-up; INV = investigator; IRC = independent review committee; mo = months; mPFS = median progression-free survival; NE = non-estimable; neutropenia = neutropenia and neutrophil count decreased; ORR = overall response rate; PR = partial response; PR-L = partial response with lymphocytosis; PFS = progression-free survival; pts = patients; R/R = relapsed or refractory; TEAE = treatment-emergent adverse events; ToS = time on study; ToT = time on treatment.

HP073

Severe hypoglycaemia due to venetoclax-augmented inhibition of gliclazide metabolism by high dose trimethoprim/sulfamethoxazole: a case report

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Aim/Methods: We report a case of co-administration of gliclazide with high dose trimethoprim/sulfamethoxazole (HDTS) in a patient treated with chronic lymphocytic leukaemia-directed venetoclax therapy resulting in severe refractory hypoglycaemia. Given the severity of the side effects noted in our patient, we hypothesize that venetoclax potentiated the adverse effect profile of the HDTS and sulfonylureas in combination.

Results: Trimethoprim inhibits cytochrome P450 (CYP450) isoform 2C8 and sulfamethoxazole inhibits CYP450 isoform 2C9. Sulphonylureas, such as gliclazide, are metabolised to their inactive metabolite by these CYP450 isoforms. Therefore, the active drug can accumulate when used concurrently with HDTS, causing exaggerated adverse effects. Whilst venetoclax is primarily metabolised by CYP3A4, it acts as a weak inhibitor of CYP2C8 and 2C9. As such, we postulate that venetoclax may have further inhibited the metabolism of gliclazide.

Conclusion: In an immunosuppressed haematology patient population, trimethoprim/sulfamethoxazole is frequently co-administered with chemo-immunotherapy agents . An awareness of the inhibition of gliclazide metabolism by HDTS, and potentiation of this effect by venetoclax, is vital to prevent patient harm from hypoglycaemia.

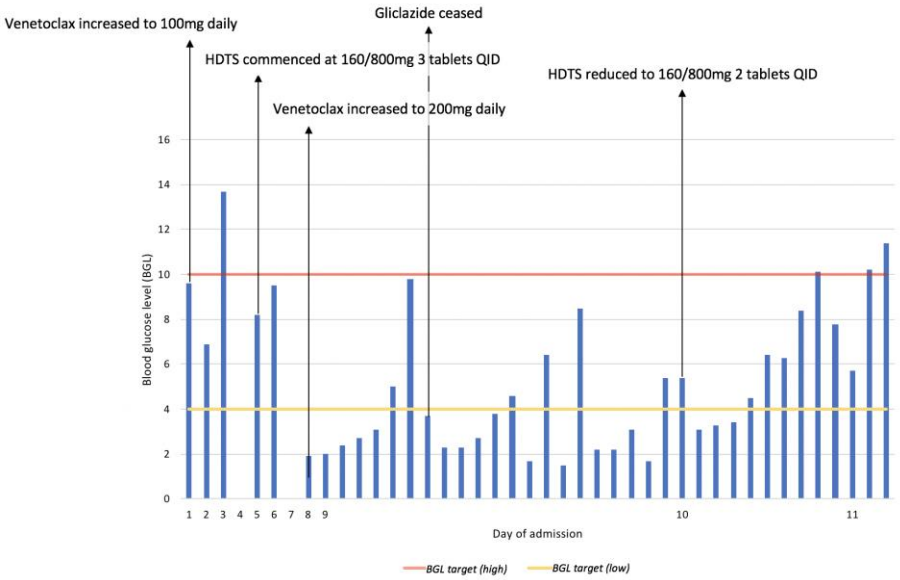

Figure 1: Relationship of medication changes and blood glucose levels (BGL)

CML

HP074

Treatment-free-remission for Chronic Myeloid Leukaemia: A single centre retrospective cross-sectional study in Johor, Malaysia.

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Aim: To study the safety and clinical outcomes of patients with Chronic Myeloid Leukaemia (CML) undergoing treatment-free remission (TFR) exercises in a regional haematology referral centre in Malaysia

Method: The clinical records of 14 patients with CML in chronic phase who had been on first line tyrosine kinase inhibitor (TKI) treatment for at least 3 years with at least 24 months of consecutive deep molecular response (DMR) and attempted TFR from January 2015 to December 2021 were scrutinized. Data consisted of patients' demographics, disease-related characteristics, therapeutic dose and duration of TKI used and clinical outcomes were extracted and analysed using Statistical Package for Social Science (SPSS) version 26.0 (IBM Inc.).

Results:

Table 1: Characteristics of Patients

Characteristics	Total Subjects (n=14)
Age at Diagnosis of CML, years	41.5 (17 - 63)
Age at enrolment of TFR trial, years	51.5 (22 - 70)
Gender, n (%)	
Male	5 (35.7)
Female	9 (64.3)
Types of TKI used, n (%)	
Imatinib	14 (100%)
Sokal Score*	0.8 (0.5 - 2.2)
Duration on TKI, months	91 (57 - 141)
Duration of consecutive DMR, months	60.5 (32 - 133)

* *Data is incomplete for 7 of the subjects and hence not included here*
^ *Figures of age and duration are expressed in median with their range in parentheses*

Table 2: Outcomes of Patients

Outcome	Total Subjects (n=14)
Time of Follow Up, months	48.5 (18 - 63)
Successful Treatment Free Remission (TFR), n (%)	7 (50%)
Molecular Relapse, n (%)	7 (50%)
0-6 months	3 (21.4%)
7-12 months	0 (0%)
12-24 months	2 (14.2%)
> 24 months	2 (14.2%)
Outcome After Molecular Relapse (MR), n (%)	
Disease progression	0 (0%)
Returned to at least MMR	7 (100%)
Returned to DMR	7 (100%)
Time to MMR after reintroduction of TKI in MR, months	2 (1-6)
Time to DMR after reintroduction of TKI in MR, months	5 (1-13)

^ *Figures of duration of time are expressed in median with their range in parentheses*

All patients were on first line Imatinib at a dose of 400mg OD and had a median time of treatment of 91 months and a median time of consecutive DMR of 60.5 months. With a median time of follow up of 48.5 months, 50% TFR success rate was achieved. Of the 7 who developed molecular relapse, all of whom achieved DMR after reintroduction of the same TKI used in the first line therapy. The median time to achieve MMR and DMR was 2 and 5 months respectively after reintroduction of TKI.

Conclusion:
While the sample size was small, the outcomes were in line with findings of TFR practices worldwide and were safe to undertake.

HP075

Frequent Pleural Effusions in CML- Dasatinib & Other Causes

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Background: Patients with chronic myeloid leukaemia (CML) commonly develop pleural effusion, which is frequently attributed as being a side effect of treatment with the tyrosine kinase inhibitor (TKI), dasatinib. However, causes of pleural effusion are numerous, including cardiac, infective, inflammatory, and malignant causes, in addition to an adverse effect of TKI treatment. Careful consideration the aetiology of pleural effusions is crucial in order to minimise interruptions to antileukaemic TKI treatment.

Aim: To review the prevalence and clinical information regarding CML patients at a major teaching hospital developing pleural effusions, including aetiology and drug causes, clinical management and outcomes, and review published literature on the subject.

Method: We investigated the cause, management, and outcomes of CML patients with pleural effusions in Fiona Stanley Hospital, Western Australia, from January 2015 until December 2022. Medical records, including the digital medical record (BossNet, DMR), laboratory results, and imaging reports were analysed.

Results: We identified 55 patients diagnosed with CML in the time period. Of these, 10 (18%) developed pleural effusions; six of these (60%) were caused by dasatinib, and the remaining four (40%) were attributed to other causes (cardiac failure, infective exacerbation of chronic obstructive pulmonary disease, sepsis, and transformation to acute myeloid leukaemia, respectively). Four patients with pleural effusions died, all from infection or infectious complications, three of whom did not experience resolution of pleural effusion. Of note, the management of patients with dasatinib-related pleural effusion was extremely heterogenous.

Conclusion: This case series is an important contribution to the scarce literature in all-cause pleural effusion in CML. Whilst in a small sample size, it demonstrates that pleural effusion in CML patients are not always attributed to dasatinib, and that other causes must be considered. Furthermore, identification of the heterogeneity of treatment of dasatinib-related effusion may encourage centres to promote a more standardised management approach.

HP076

Tale of Imatinib-induced Fulminant Liver failure

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Introduction: Treatment of chronic myeloid leukaemia (CML) with BCR-ABL tyrosine kinase inhibitor (TKI) imatinib is known to cause acute hepatotoxicity in rare cases. The optimal approach to treatment of imatinib-induced hepatotoxicity and subsequent management of CML remains unclear.[1]

Case report: We report a unique case of a 52-year-old woman who was referred for inpatient assessment of acute liver failure. She had received seven months of front-line imatinib therapy for CML in chronic phase (CML-CP) with good response to therapy, shown by a reduction in her BCR-ABL transcript level from 45.52% down to 0.52%. On admission, her aspartate aminotransferase and alanine aminotransferase levels were 2,081 IU/L and 3290 IU/L respectively. Bilirubin was raised at 139 micromol/L. Coagulation profile was mildly deranged with an INR of 1.6. Investigations were undertaken to exclude other potential causes of acute liver failure including autoimmune and infective aetiologies. Imatinib was withheld with no immediate improvement in her liver enzyme levels. Liver biopsy was performed, demonstrating severe acute hepatitis with multifocal perivenular and bridging necrosis. She was diagnosed with imatinib-induced hepatotoxicity.

Prednisolone (60 mg daily) was commenced which resulted in dramatic improvement of liver enzyme abnormalities. She was weaned off corticosteroids over three months, with liver enzymes returning to baseline. Following two months off TKI, there was a significant increase in her BCR-ABL transcript level to 15.81%. She was commenced on the second-generation TKI dasatinib, achieving a major molecular response (MMR) within three months. Her liver enzymes remained normal throughout this period.

Discussion: Management of imatinib-induced liver failure can be challenging as there is paucity of evidence-based management of this specific TKI side effect. It would appear that drug-induced liver injury due to imatinib is not a class effect of tyrosine kinase inhibitors. Dasatinib is an option for CML therapy following discontinuation of imatinib secondary to hepatotoxicity.

References:

1. Nacif LS, Waisberg DR, Pinheiro RS, et al. Imatinib-induced fulminant liver failure in chronic myeloid leukemia: role of liver transplant and second-generation tyrosine kinase inhibitors: a case report. J Med Case Reports. . 2018;12(1):63. doi:10.1186/s13256-018-1588-0

HP077

Switching of Tyrosine Kinase inhibitors for intolerance does not impact survival and achievement of Treatment-free remission in Chronic phase (CP) - Chronic Myeloid Leukaemia (CML)

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Aim: First-line treatment of CML consists of a tyrosine kinase inhibitor (TKI), such as imatinib, dasatinib or nilotinib. This study assessed the response of different TKIs, reasons for a switch in therapy and the success rates of treatment-free remission (TFR).

Method: 71 patients who initiated TKI therapy for CP-CML at the Royal Melbourne Hospital and Peter MacCallum Cancer Centre from 2010 to 2019 were identified. A switch in TKI therapy was defined as a change to therapy. An independent t-test compared the associations between a switch in TKIs and clinical outcomes. Overall survival was assessed using Kaplan-Meier curves.

Results: Over 10 years of prescribing for CML in chronic phase, 61% (n=53) of patients were started on Imatinib, 24.4% (n=11) on Dasatinib and 12.2% (n=5) on Nilotinib. 70.7% of patients switched from first-line TKI therapy, of which 48.8% were due to intolerance (Table 1). There was no difference in overall survival (93% vs 83%, p-value 0.371) or the rate of TFR attempts (50% vs 33%, p-value 0.31) in patients who switched therapy due to intolerance, compared with those who continued first-line treatment. There was a trend to improved overall survival with patients who were intolerant to first-line therapy than patients with suboptimal response/resistance (Figure 1), however this was not statistically significant (p-value 0.11). 31.7% of patients on first-line therapy or switched due to intolerance attempted TFR, of which 65% failed to maintain TFR with a median duration of 121 days.

Conclusion: Our study has demonstrated that many patients require a switch from first-line TKI therapy due to intolerance. However, this has no impact on overall survival or the rate of TFR attempts/ success, compared to patients who remain on first-line therapy. Consequently, intolerance to TKI therapy should not serve as a barrier to switching TKI therapy.

1st-line therapy (n)	Continued 1st-line	Switched therapy	Switch due to intolerance
Imatinib (53)	21 (39.6%)	32 (60.4%)	13 of 32 (40.6%)
Dasatinib (11)	6 (54.5%)	5 (45.5%)	3 out of 5 (60%)
Nilotinib (5)	3 (50%)	3 (50%)	3 out of 3 (100%)
Ponatinib (1)	0 (0%)	1 (100%)	1 out of 1 (100%)

Table 1: Outline of first-line therapies and proportion of patients who switched to a different therapy due to intolerance

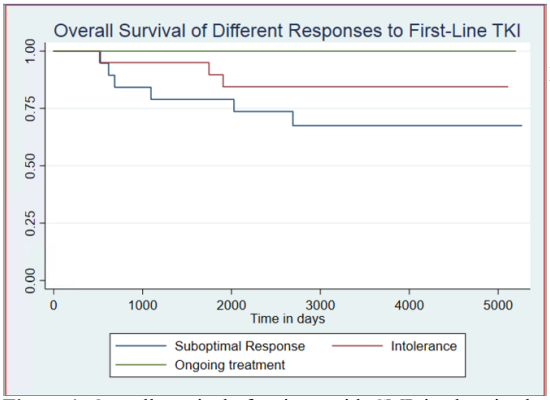

Figure 1: Overall survival of patients with CML in chronic phase, separating groups into response to first-line therapy: Ongoing first-line TKI due to adequate molecular response, switch in TKI due to suboptimal response, switch in TKI due to intolerance and death.

HP078

Pirtobrutinib in relapsed/refractory (R/R) mantle cell lymphoma (MCL) patients with prior cBTKi: Updated safety and efficacy including high-risk subgroup analyses from the phase 1/2 BRUIN study

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Aim: We report updated results of pirtobrutinib therapy in all pts, including those with biologically high-risk R/R MCL with a median survival follow-up of 24.2 mos (range, 18.2-29.8).

Method: Pts with R/R MCL received pirtobrutinib in the multicenter Phase 1/2 BRUIN trial (NCT03740529). Efficacy was assessed in all cBTKi pretreated pts. Key endpoints included ORR as assessed by IRC per Lugano 2014 criteria, DOR, PFS, OS, and safety. Pts were included across the dose escalation range and expansion (25-300 mg/day) with 93% (n=141) receiving at least one dose of 200 mg/day, the FDA-approved dose. A data cut of 05May2023 was utilized.

Results: Among all 152 cBTKi pretreated pts with R/R MCL, median age was 70 years (range, 46-88) and median prior lines of therapy were 3 (1-9). ORR for cBTKi pretreated pts was 49.3% (95% CI, 41.1-57.6), including 15.8% CRs (n=24) and 33.6% PRs (n=51). Among 75 responding cBTKi pretreated pts, median DOR was 21.6 mos (95% CI, 9.2-27.2). The 18- and 24-mo DOR rates were 51.9% (95% CI, 37-64.8) and 38.9% (95% CI, 22.7-54.8), respectively. In the total MCL cohort (n=166), the most frequent TEAEs were fatigue (31.9%), diarrhea (22.3%), and dyspnea (17.5%). The most common Grade ≥3 TEAE was neutropenia/neutrophil count decreased (13.3%) and the rate of Grade ≥3 infections was (19.9%). Grade ≥3 hemorrhage/hematoma (2.4%) and all-grade atrial fibrillation/flutter (3.6%) were infrequent. Overall, 8 pts (5%) had TRAEs leading to dose reductions and 5 (3%) had TRAEs leading to pirtobrutinib d/c.

Conclusion: Pirtobrutinib continues to demonstrate durable efficacy and a favorable safety profile in heavily pre-treated R/R MCL cBTKi pretreated pts. High ORRs were observed in pts who had PD on a prior cBTKi, and in pts with high-risk disease features including blastoid/pleomorphic variants, elevated Ki-67 index, and *TP53* mutations.

Table. ORR and DOR in cBTKi pre-treated pts and high-risk subgroups

		cBTKi pre-treated MCL (n [%])	Number with Response (n)	ORR, % (95% CI)	DOR, median (95% CI)
Overall		152 (100)	75	49.3 (41.1-57.6)	21.6 (9.2-27.2)
MCL histology	Classic/Leukemic	120 (78.9)	61	50.8 (41.5-60.1)	17.7 (7.7-NE)
	Blastoid	15 (9.9)	6	40.0 (16.3-67.7)	NE (1.4-NE)
	Pleomorphic	17 (11.2)	8	47.1 (23.0-72.2)	21.6 (3.7-NE)
***TP53* mutation**[a]	Yes	30 (50)	13	43.3 (25.5-62.6)	17.6 (1.7-NE)
	No	30 (50)	15	50.0 (31.3-68.7)	14.8 (1.9-NE)
Ki-67 Index[a]	<30%	18 (28.6)	12	66.7 (41.0-86.7)	17.7 (1.9-NE)
	≥30%	45 (71.4)	20	44.4 (29.6-60.0)	21.6 (5.6-27.2)
D/c from any prior BTKi[a, b]	Disease Progression	128 (85.9)	55	43.0 (34.3-52.0)	14.8 (7.3-27.2)
	Toxicity/Other	21 (14.1)	19	90.5 (69.6-98.8)	25.3 (9.2-NE)

[a]Patients with missing data were not included in the analysis.

[b]Disease Progression" is selected if "PD" for any prior BTK; otherwise "Toxicity" is selected if toxicity from any prior BTK; otherwise "Other".

Abbreviations: cBTKi = covalent BTK inhibitor; CR = complete response; d/c = discontinuation; DoR = duration of response; IRC = independent review committee; mo = month; NE = not estimable; ORR = overall response rate; PFS = progression-free survival; PR = partial response; pts = patients; TEAE = treatment-emergent adverse event; TRAE = treatment-related AE

Lymphoma

HP079

The use of Cobimetinib in histiocytic neoplasms: A Western Australia case report series and literature review.

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Background: Histiocytic neoplasms (HNs) are rare neoplasms originating from cells of the myeloid lineage and include Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD) and Rosai-Dorfman disease (RCD). These disorders commonly show mutations in genes of the MAPK pathway, albeit with highly variable frequencies. Traditional therapies for these neoplasms often yield limited success, necessitating novel treatments. Cobimetinib, a MEK inhibitor, has shown promise in various malignancies, including HNs.

Aim: We report three patients with NHs to outline the efficacy potential and relative safety of the use of Cobimetinib in a Western Australian cohort with HNs.

Case report: Case 1: A 48 year old female with RDD who started Cobimetinib in August 2021 and continues on a reduced dose from cycle 2 due to skin rash. Case 2: A 34 year old man with ECD who commenced Cobimetinib in July 2021 however developed a severe acneiform drug rash which necessitated dose reduction. While initially responding, he developed disease progression due to non-compliance. Case 3: A 52 year old male with ophthalmic involvement of RDD commenced Cobimetinib in May of 2023 and continues on drug with significant improvement in unilateral visual acuity. He also developed an acneiform rash which resolved spontaneously. Case 1 and 2 had no mutations identified and case 3 had a KRAS variant identified.

Conclusion: Cobimetinib demonstrates substantial efficacy and a manageable safety profile in treating HNs. Further, in our small case series, our patients had a good response to Cobimetinib single therapy regardless of KRAS mutation status, similar to previous larger studies. These results support broader utilization and access to Cobimetinib for HNs in Australia, potentially influencing future patient management strategies for these rare disorders.

HP080

Sub-optimal radiotherapy utilisation for cutaneous T-cell lymphomas (CTCL)

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Aim: CTCL are rare, typically incurable, highly morbid malignancies. Patients frequently require multi-lined therapies, over decades. Radiotherapy is associated with high rates of response and infield local control, and constitutes the historical cornerstone of treatment for CTCL. Total skin electron therapy (TSE) is a highly technical form of radiotherapy, with quality-of-life benefits for CTCL patients. However, with the advent of newer skin-directed and systemic therapies, no consensus currently exists on the optimal treatment sequencing.[1] In 2013, the estimated optimal radiotherapy-utilisation rate was reported at 83%.[2] We hypothesised that radiotherapy and TSE are now under-utilised in Australia.

Method: A retrospective study of New South Wales (NSW) Cancer Registry dataset for all patients newly diagnosed with CTCL from 2009-2018, with data linkage to the NSW Outpatients Radiotherapy database. Patients with dual malignancies and/or whose closest radiotherapy centre (calculated by ArcGIS) was across NSW borders, were excluded from radiotherapy analyses.

Results: 553 patients were newly diagnosed with CTCL in NSW, with incidence of 7.1/million/year (<1 in 140,000 people). Median age at diagnosis was 64 years (range, 11-98 years); 61% were men; 1.6% identified as Aboriginal. 33% of all CTCL patients lived in the 2 most disadvantaged IRSD quintiles. 13% resided in remote or moderately accessible locations; 16% resided >50km from the nearest radiotherapy centre.

Over 10 years, the radiotherapy-utilisation rate was 29%, with patients residing in highly accessible areas having the lowest radiotherapy-utilisation (24%). No pattern was observed between distance to the nearest radiotherapy centre and radiotherapy-utilisation. TSE-utilisation was only 1.8%, over 10-years.

Conclusion: For patients with CTCL in NSW, the radiotherapy-utilisation rate was only 29%, far lower than the reported optimal radiotherapy-utilisation rate. TSE-utilisation was extremely low. Curiously, radiotherapy-utilisation was lowest in patients living in highly accessible areas, possibly suggesting that referral bias may be a contributing factor.

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HP081

International study of Sezary Syndrome reveals improved disease-specific survival from modern systemic therapies

Campbell B[1,2], Dobos G[3,4], Haider Z[5], Bagot M[4], Evison F[6], van der Weyden C[1,2], McCormack C[1,2], Ram-Wolff C[4], Miladi M[4], *Prince M[1,2], *Scarisbrick J[7]

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Aim: Traditionally, Sezary syndrome (SS) has been associated with few therapeutic options and poor prognosis, with 5-year disease-specific survival (DSS) less than one-third in historical cohorts. Newer therapies and combinations are associated with impressive time-to-next-treatment (TTNT), particularly allogeneic stem-cell transplantation (AlloSCT) and combination therapies including extracorporeal photopheresis.(1) In this multicentre, international study, we explored the prognostic outcomes of patients managed for SS in the modern therapeutic era.

Methods: Three international quaternary centers participated in this retrospective study: University Hospitals Birmingham, United Kingdom, Peter MacCallum Cancer Centre, Australia, and Hôpital Saint-Louis, France. Eligibility required clinicopathological diagnoses of mycosis fungoides (MF)/SS with B2 blood involvement(2, 3), diagnosed between 1/1/2012-31/12/2020.(1)

Results: 178 patients were eligible. 58 different therapies were delivered, 13.5% of patients received AlloSCT. Long-term survival exceeded historical reports with 5-year DSS and overall survival (OS) of 56.4% and 53.4%, respectively. In patients receiving AlloSCT, prognosis was excellent: 5-year DSS and OS were 90.5% and 78.0%, respectively. For patients ineligible for AlloSCT, prognosis remained poor. Confirming the results from the Cutaneous Lymphoma International Consortium (CLIC)(4), LDH and large cell transformation had significant prognostic impact. Unlike earlier studies, stage did not have prognostic impact.

Conclusion: Outcomes for patients with SS have improved. Patients with nodal effacement (N3, stage IVA2) may be deriving greatest relative benefit from modern therapeutic strategies. AlloSCT provides the only potentially curative therapy with impressive survival gains for eligible patients. For patients ineligible for AlloSCT, the overall poor prognosis demonstrates an ongoing unmet need for improved therapeutics and combinations for patients with SS.

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HP082

Geospatial analyses demonstrate disparity in cutaneous T-cell lymphoma (CTCL) diagnoses across Australia

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Aim: CTCL are typically incurable, associated with high symptom burden and long natural history. Further contributing to the unique unmet needs of these patients are disease rarity, diagnostic challenges and limited availability of specialist expertise. Equitable access to care is a national priority.(1) We investigate the incidence and geospatial distribution of CTCL, and compare to that of all rare cancers(2). We consider possible geographical-based influences on causality (including ultraviolet (UV) exposure) and diagnosis rates.

Method: All CTCL diagnoses from 1/1/2000-31/12/2019 and in persons >15 years, were obtained from the nation-wide dataset of mandatorily reported cancer diagnoses. Areas of residence were defined using federally-standard approved boundaries. Bayesian spatial incidence models were applied.

Results: The overall age-standardised incidence of CTCL was 7.7 [95%CI 7.4-7.9] per million people, equating to 285 new diagnoses per year in Australia.

Diagnostic disparity was seen between states/territories, with lower diagnosis rates in rural/remote and socio-economically disadvantaged areas. Standardised incidence ratios (SIR) exceeded the national average within the more densely populated capital cities of Sydney, Melbourne, Perth, Brisbane and particularly Adelaide.

Compared to spatial patterns for all rare cancers combined(2,3), marked geospatial differences were observed, particularly across northern and central Australia and Tasmania where diagnoses of CTCL are most rare.

Conclusion: CTCL is rare, with incidence in Australia towards the upper end of international reports. Geographical heterogeneity exists in the distribution of diagnoses across Australia, with SIR tending to reflect population density. The geospatial pattern of CTCL substantially differs from that of all rare cancers in Australia, with implications for the unique diagnostic challenges and unmet needs of this patient population. Although these data do not support a causative link with UV exposure, the parallels between the geographical distributions of CTCL and dermatologist-density may suggest diagnostic scrutiny as a confounding association at this national level.

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HP083

Follow-up beyond 2.5 years shows long-term efficacy in complete responders following epcoritamab monotherapy in relapsed or refractory large B-cell lymphoma (R/R LBCL)

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Aim: Epcoritamab, a CD3xCD20 bispecific antibody, demonstrated high rates of complete response (CR) and minimal residual disease (MRD) negativity, durable responses, and manageable safety in patients with challenging-to-treat R/R LBCL in EPCORE® NHL-1 (pivotal phase 2; NCT03625037). We show long-term follow-up and cycle 1 optimization (C1 OPT) data.

Method: Patients with R/R CD20$^+$ LBCL and ≥2 prior treatment lines received subcutaneous epcoritamab in 28-d cycles (per label) in an expansion cohort. The primary endpoint of the expansion was overall response rate (ORR) by Lugano criteria per independent review committee (IRC). C1 OPT (with hydration and dexamethasone highly recommended) assessed CRS in a separate diffuse LBCL (DLBCL) cohort; hospitalization was not mandated.

Results: The LBCL expansion cohort enrolled 157 patients (DLBCL, n=139). As of Apr 21, 2023 (median follow-up, 25.1 mo), ORR/CR rates by IRC were 63%/40% (LBCL) and 62%/40% (DLBCL). CRS was the most common AE (51% any grade [G]; 32% G1, 16% G2, 3% G3). As of Oct 16, 2023, 24-/30-mo estimates in 65 patients with CR (median follow-up, 31.3 mo; investigator) were 62%/54% remaining in CR, 65%/55% progression free, and 76%/71% alive. Of 49 MRD-evaluable patients with CR, 92% were MRD negative. Patients with low (≤80 cm^3; n=67) and high (>80 cm^3; n=81) baseline tumor volume had CR rates of 52% and 32%, respectively, per investigator, and an estimated 68% and 66% of these patients with CR remained in response at 24 mo, respectively. C1 OPT enrolled 60 patients (median follow-up, 1.7 mo), and 22% of 36 CRS-evaluable patients had CRS; events were low grade (14% G1, 8% G2), mostly followed the first full dose, resolved, and did not lead to discontinuation. One patient had G1 ICANS.

Conclusion: Epcoritamab drives deep responses beyond 2.5 y, underscoring long-term benefits in R/R LBCL. Simple measures in C1 decreased CRS rates/severity.
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HP084

Platinum substitution in salvage chemotherapy for relapsed/refractory non-Hodgkin lymphoma: a LaRDR study

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Aim: Salvage chemotherapy and autologous transplantation is recommended for fit patients (pts) with relapsed/refractory high-grade B and T cell non-Hodgkin lymphoma (RR NHL). Extensive evidence supports use of DHAP (cisplatin [P]) but other platinum agents (carboplatin [C], Oxaliplatin [Ox]) simplify chemotherapy administration, reduce toxicity and may have differential efficacy. In this study, we aimed to assess the impact of platinum substitution in a real-world setting using the Australasian Lymphoma Registry (LaRDR).

Method: Multi-centre retrospective study of pts >18y, diagnosed 2010-23, commencing first salvage with DHAP/C/Ox for RR NHL. Primary endpoint was objective response rate (ORR); key secondary endpoints were progression free survival (PFS), overall survival (OS), transplant realization rate, blood product use, and safety. Descriptive statistics were used, survival analysis by Kaplan-Meier method, impact of baseline variables assessed, and toxicity graded by CTCAE v5.

Results: 104 pts identified, 66 males, median (IQR) age 64y (56-71) received DHAC (80), DHAP (22) or DHAOx (2). 72 pts were age <70. Most frequent diagnosis was DLBCL (66), follicular 3b (15) and T cell NHL (10). 66 pts received first line (R)CHOP; ORR 53% (40% CR, 14% PR); 63% refractory or relapsing <12 mo. Pts received median 2 cycles of DHAP/C/Ox at a median (IQR) 9.1 (5.5-22.3) mo from initial diagnosis; ORR 32%, no difference between regimens (DHAP 15%, DHAC 36%) [table 1]. After median follow-up of 28 mo, mPFS (DHAC 4 vs DHAP 2 mo, p=0.27) and mOS (DHAC 12.5 vs DHAP 10.3 mo, p=0.69) were similar. 47/55 pts receiving DHAC required platelet transfusion. Autograft occurred in 20 pts; CR in 11/16 (69%) with mOS, not reached.

Conclusion: Comparable outcomes support platinum substitution in pts with RR NHL. Survival remains poor with few pts undergoing potentially curative autograft. Novel therapies are required to improve outcomes further.

Table 1. Response to Salvage Chemotherapy

	DHAC N=80	DHAP N=22	DHAOx N=2	
ORR, n (%)	25/69 (36.2)	3/20 (15.0)	1/1 (100)	p=0.07
CR, n (%)	20/69 (29.0)	3/20 (15.0)	0/1 (0)	
PR, n (%)	5/69 (7.2)	0/20 (0)	1/1 (100)	
SD, n (%)	6/69 (8.7)	2/20 (10.0)	0/1 (0)	
PD, n (%)	38/69 (55.1)	15/20 (75.0)	0/1 (0)	
Received autograft, n (%)	17 (21.2)	3 (13.6)	0/2 (0)	
mPFS (mo), 95% CI	4.0 (2.3-7.3)	2.8 (1.3-3.6)	NA	p=0.27
mOS (mo), 95% CI	12.5 (8.3-15.6)	10.3 (4.6-34.1)	NA	p=0.69

ORR, objective response rate, CR, complete response, PR, partial response, SD, stable disease, PD, progressive disease, PFS, progression free survival, OS, overall survival, CI, confidence interval, DHAC, dexamethasone-cytarabine-carboplatin, DHAP, dexamethasone-cytarabine-cisplatin, DHAOx, dexamethasone-cytarabine-oxaliplatin, ND, not done

HP085

Distribution and use of bulky disease in lymphoma care: A study from the Australasian Lymphoma and Related Diseases Registry (LaRDR)

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Aim: To describe baseline characteristics, treatment and outcomes of newly diagnosed lymphoma patients according to the presence of disease bulk, defined as a single large tumour site >5cm in LaRDR.

Method: Diffuse large B-cell, follicular, marginal zone, T-cell, Hodgkin and Burkitt lymphomas (DLBCL, FL, MZL, TCL, HL, BL) were included. Data on patient demographics, presence of bulk, laboratory results, staging, nodal and extranodal involvement, treatment intensity (low, standard, high) were collected on patients ≥18 years in LaRDR and presented in descriptive analyses. Progression-free survival (PFS) and overall survival (OS) were analysed using Kaplan-Meier and Cox proportional hazard methods. LaRDR affiliated clinicians were surveyed to provide their commonly used bulk definitions for sensitivity analyses.

Results: Characteristics and survival outcomes of the 4271 patients were described in Table 1. Patients with bulk in the study cohort more frequently received systemic chemotherapy alone and less frequently received localised treatment, compared to those without bulk (p<0.001). Similar findings were observed in FL patients (p<0.001). No significant variations in treatment intensity were observed in any subtypes. Presence of bulk using registry definition of >5cm conferred inferior PFS and OS for DLBCL (p=0.04, p=0.04) and inferior OS for MZL (0=0.04), but superior OS for HL (p=0.03) when using the registry definition. Inferior OS was found in BL when using clinician definition >10cm (p = 0.03).

Conclusion: This is the first Australian registry study describing the presence of tumour bulk and its impact on treatment selection and prognostic value across lymphoma subtypes. We observed survival differences between patients with and without bulky disease in DLBCL, MZL and all-stage HL using bulk definition >5cm, also in BL using >10cm. International prospective studies are required to standardise the definition of bulk for ongoing utility in prognostications inform treatment decisions.

Table 1. Patient characteristics and survival outcomes according to presence of bulk in each disease subtype.

	All patients		**DLBCL**		**FL**		**MZL**		**TCL**		**HL**		**BL**	
N evaluable (%)		4271	1823/4271 (43)		1000/4271 (23)		406/4271 (10)		300/4271 (7)		666/4271 (15)		76/4271 (2)	
Bulk yes/no	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y
	2551	1141	990	574	641	248	283	52	217	40	371	204	49	23
Median age (range)	**65 (18-103)**	**63 (18-99)**	69 (20-103)	69 (24-99)	65 (25-91)	65 (34-98)	67 (32-96)	69 (39-90)	63 (19-93)	58 (24-87)	**41 (18-93)**	**31 (18-88)**	50 (19-82)	56 (18-88)
Male sex (%)	**1406 (55)**	**685 (60)**	553 (56)	343 (60)	**333 (52)**	**152 (61)**	129 (46)	30 (58)	136 (63)	29 (73)	215 (58)	113 (55)	40 (82)	18 (78)
Stage III-IV (%)	**1410 (60)**	**744 (69)**	**582 (63)**	**388 (71)**	**383 (63)**	**189 (79)**	**105 (46)**	**32 (71)**	**129 (71)**	**31 (91)**	186 (51)	90 (45)	25 (61)	14 (70)
Elevated LDH (%)	**846 (40)**	**596 (58)**	**441 (53)**	**382 (72)**	**107 (20)**	**66 (30)**	63 (29)	11 (28)	111 (61)	27 (75)	-	-	29 (63)	17 (81)
B symptoms (%)	**582 (24)**	**386 (35)**	**239 (26)**	**189 (34)**	**84 (14)**	**64 (26)**	**37 (14)**	**13 (27)**	**81 (40)**	**21 (60)**	129 (36)	90 (45)	12 (26)	9 (43)
Extranodal involvement (%)	1485 (58)	705 (62)	774 (68)	410 (71)	268 (42)	133 (54)	212 (75)	37 (71)	153 (71)	28 (70)	142 (38)	82 (39)	36 (74)	17 (74)
Bulk (5 cm)														
PFS (95% CI)		1.04 (0.90 – 1.20)		**1.22 (1.00 – 1.48)**		0.90 (0.63 – 1.31)		1.26 (0.60 – 2.65)		1.17 (0.76 – 1.82)		0.80 (0.49 – 1.33)		1.87 (0.61 – 5.75)
OS (95% CI)		1.12 (0.96 – 1.30)		**1.22 (1.01 – 1.49)**		0.94 (0.6 – 1.46)		**2.12 (1.02 – 4.41)**		1.0 (0.63 – 1.59)		**0.35 (0.13 – 0.93)**		1.70 (0.54 –5.35)
Bulk (clinicians)^														
PFS (95% CI)		-		1.17 (0.93 – 1.48)		0.96 (0.63 – 1.46)		0.87 (0.31 – 2.51)		0.93 (0.53 – 1.63)		0.48 (0.18 – 1.33)		3.19 (0.98 – 10.36)
OS (95% CI)		-		1.13 (0.89 – 1.43)		0.9 (0.53 – 1.56)		1.74 (0.61 – 4.94)		0.78 (0.43 – 1.41)		Not evaluable		**3.73 (1.11 – 12.46)**

Bold font denotes statistically significant difference (p ≤ 0.05). ^Clinician cut-off used in the sensitivity analysis: DLBCL, 7.5 cm; FL, 7 cm; MZL, 7.5 cm; TCL, 7.5 cm; HL, 10 cm; BL, 7.5 cm.

HP086

Epcoritamab induces deep responses in relapsed or refractory (R/R) follicular lymphoma (FL): Safety and pooled efficacy from the pivotal and cycle (C) 1 optimization (OPT) EPCORE NHL-1 FL cohorts

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Aim: In the pivotal cohort of EPCORE® NHL-1 (phase 1/2; NCT03625037), treatment with epcoritamab, a CD3xCD20 bispecific antibody, led to deep, durable responses with manageable safety in patients with multiply R/R FL. Additional CRS mitigation strategies without mandatory hospitalization and their effects on safety and efficacy are being evaluated in a C1 OPT cohort of EPCORE NHL-1

Method: Patients with CD20^{+} R/R FL grade (G) 1–3A and ≥2 prior lines of systemic treatment received subcutaneous epcoritamab in 28-d Cs: step-up doses (0.16/0.8/3 mg, D1/D8/D15) followed by 48-mg full doses (QW, C1–3; Q2W, C4–9; Q4W, C≥10) until disease progression. Adequate hydration and dexamethasone (preferred steroid for mandatory CRS prophylaxis) were recommended in C1. Primary endpoints were any-grade and G≥2 CRS event rates. Secondary endpoints included response per Lugano criteria, minimal residual disease (MRD) negativity, and safety/tolerability.

Results: As of Jan 8, 2024, 86 patients (median prior treatment lines, 2; 92% stage III–IV; 63% double refractory; 44% primary refractory; 42% POD24) were treated in C1 OPT. Median follow-up was 5.7 mo. CRS occurred in 49% of patients (Table), mostly in C1; all events were low grade (40% G1, 9% G2) and did not lead to discontinuation. No patients had ICANS. Of 82 patients who received the first full dose, 54% had outpatient CRS monitoring. Pooled pivotal and C1 OPT cohorts (214 patients) had overall response/complete response (CR) rates of 84%/65% per investigator (median time to response/CR, 1.4/1.5 mo). Of 135 MRD-evaluable patients, 66% had MRD negativity (clonoSEQ®; 10^{-6} cutoff). CR and MRD negativity were associated with improved progression-free survival.

Conclusion: In the largest R/R FL population receiving a T-cell–engaging treatment to date, epcoritamab showed early, deep responses with manageable safety, including reduced CRS with C1 OPT. Results support continued evaluation of outpatient epcoritamab treatment.

Table. CRS events in the pivotal and C1 OPT cohorts

n (%)	**Pivotal cohort[a] N=128**	**C1 OPT cohort N=86**
Any-grade CRS	85 (66)	42 (49)
G1	51 (40)	34 (40)
G2	32 (25)	8 (9)
G3	2 (2)	0
G≥4	0	0

[a]Data cutoff: April 21, 2023.

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HP087

Hairy Cell Leukaemia in Pregnancy: A Review of Cases in the Literature

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Background: Hairy cell leukemia (HCL) is an uncommon, indolent, mature B cell lymphoproliferative disorder representing less than 1% of all lymphoid neoplasms. Cases are rarely reported in pregnancy.

Aim: To review all cases of HCL in pregnancy in the literature to determine maternal and foetal management recommendations.

Methods: A systematic search of Ovid MEDLINE and EMBASE for the terms 'Hairy Cell Leukemia' and 'Pregnancy' was undertaken. Studies with full text available in English were included. Cases were excluded if they lacked sufficient data. We collected information on patient demographics, pregnancy and fetal outcomes as well as HCL characteristics and treatment received.

Results: We found 10 patients across 9 case reports of HCL in pregnancy and 3 within our own institutions. Two patients were diagnosed prior to pregnancy and the remaining patients were diagnosed during the first (n = 3) and second (n = 8) trimesters only. Moderate to severe pancytopenia was reported in all cases at diagnosis (Mean Haemoglobin – 88g/L; White blood cells - 3.4 $x10^9$/L; Platelets – 57 $x10^9$/L). Splenomegaly was described in 70% of patients. Diagnoses were confirmed with bone marrow and flow cytometry with Immunophenotyping was described in all cases but one from 1988. Two pregnancies were terminated. Observation only was the management in n=1 cases. Documentation of transfusions of packed red blood cells was noted in n=6 cases. Gestation at birth ranged between 34 weeks and full term and natural vaginal birth was the main mode of birth (54%). Neonatal birth weight was recorded in only n = 6 cases and ranging between 1587 – and 3200 grams. Post-partum haemorrhage and neuraxial anaesthesia was/not documented.

Conclusion: A paucity of data makes recommendations for optimal management of HCL in pregnancy difficult. A malignancy in pregnancy registry may help gain more reliable data outcomes.

HP088

Successful bridging with R-CHOP in a case of relapsed refractory mantle cell lymphoma: A bridge to CAR-T cell therapy.

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Aim: To describe a case of relapsed refractory mantle cell lymphoma (RR MCL) with rapidly proliferating lymphocytosis successfully bridged to brexucabtagene autoleucel chimeric antigen T-cell CAR-T therapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R- CHOP).

Clinical case: A 61-year-old man was electively admitted to hospital requiring bridging therapy to CAR-T cell therapy for management of tumour protein 53 mutated RR MCL. Other medical history included asthma, hepatosteatosis, ischaemic heart disease and excessive alcohol intake.

MCL was diagnosed in 2022 and was refractory to the first line therapy of rituximab, dexamethasone, cytarabine and cisplatin (R- DHAP). Subsequently, the patient had a partial response to zanubrutinib, which was maintained for 16 months. However, he then developed overt disease progression with rapidly increasing lymphocytosis, splenomegaly (measuring 18cm) and progressive thrombocytopaenia. Allogenic stem cell transplant was considered however the patient was deemed ineligible due to comorbidities, social factors and personal preferences. The hospital's Therapeutics Committee approved an Individual Patient Use (IPU) request for venetoclax as bridging therapy, since venetoclax is not reimbursed by the Pharmaceutical Benefits Scheme for this indication. Prior to commencing venetoclax, results showed a white cell count (WCC) of 253.7 x10^9/L and a lymphocyte count of 4.22x10^9/L. Venetoclax was dosed with weekly ramp-ups from 20mg to 50mg to 100mg to 200mg to 400mg dosing. Pre-existing therapy with zanubrutinib 160mg twice daily was continued.

After four days of venetoclax 400mg daily, the venetoclax and zanubrutinib were ceased due to lack of response. R-CHOP chemo-immunotherapy was commenced with rapid resolution of lymphocytosis with WCC down trending to 3.1 x10^9/L and lymphocytes 0.8x10^9/L. Notability, there was also a reduction in spleen size to 10cm.

Outcome: Although there were complications with marked cytopenias, the patient completed 2 cycles of R- CHOP chemotherapy and went on to successful T-cell apheresis and brexucabtagene autoleucel CAR-T infusion.

HP089

Assessment of Cognitive Changes Following CAR-T Therapy – a Western Australian Experience

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Aim: To assess cognitive performance in patients undergoing CAR-T therapy for haematological malignancies and to investigate if immune effector cell-associated neurotoxicity syndrome (ICANS) is correlated with cognitive decline.

Method: A total of 52 adult patients underwent CAR-T infusion between May 2020 and January 2024. Cognition was assessed by the Montreal Cognitive Assessment (MoCA) tool at baseline and 12 weeks post infusion. Patient demographics, treatment details and toxicity were identified from medical records. At 12 weeks, patients who had died, had disease relapse or had not completed both MOCA assessments were excluded. Independent and paired t tests were utilised for statistical analysis.

Results: 30 patients had sufficient data for analysis. The median age was 67 years (range, 49 – 81) and 67% were male. 25 patients (pts) had relapsed/refractory DLBCL with 14 receiving Axicabtagene Ciloleucel and 11 Tisagenlecleucel; 5 had Multiple Myeloma and received Ciltacabtagene. At baseline, the median MoCA score was 26 (range, 15-30). 15 pts scored 25 or less, consistent with cognitive impairment. For the overall cohort, there was no significant change in MoCA from baseline to 12 weeks (p=0.57). ICANS was diagnosed in 10 patients. There was no significant difference in the change of MoCA score between patients who experienced ICANS and those who did not (p=0.40).

Conclusion: In our CAR-T treated cohort, baseline cognition was impaired in 50%, treatment did not significantly alter cognitive function at 12 weeks and the presence of ICANS was not associated with a decline in cognitive function.

HP090

A diagnostic dilemma – mature phenotype B-Lymphoblastic Leukaemia/Lymphoma versus High-Grade B-Cell Lymphoma: A case report

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Background: B-lymphoblastic leukaemia/lymphoma (B-ALL/LBL) and High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements (HGBCL-*MYC*/*BCL2*) are aggressive B-cell malignancies which can present with overlapping diagnostic features, however are important to differentiate given they have distinct treatment pathways.

Case discussion: A 37 year old female presented with dyspnoea and was found to have a leukoerythroblastic film with 22% circulating abnormal immature lymphoid cells. CT demonstrated splenomegaly and abdominal lymphadenopathy. A bone marrow biopsy showed a diffuse infiltration (>90%) of cells resembling lymphoblasts, with flow cytometry identifying them in the blast region with low expression of CD45 and co-expression of CD10(66%), CD19, CD20, icCD79a and kappa light chains. B-ALL can lack CD34 expression[1] and whilst rare, light chain restriction can also be seen[2] and does not necessarily indicate maturity. Rapid FISH testing identified a *MYC* rearrangement and *TP53* deletion, which can occur in many aggressive B-cell malignancies. Histopathology of a soft tissue mass favoured the diagnosis of B-LBL with some TdT expression and flow cytometry showing indeterminate light chain expression. The patient was diagnosed with B-ALL and was commenced on B-ALL induction therapy. A post induction PET scan and bone marrow biopsy demonstrated refractory disease, with flow cytometry demonstrating brighter CD20 expression. Comprehensive genomics including karyotype, FISH, SNP array and DNA/RNA sequencing revealed an extremely complex karyotype with multiple abnormal clones, a three-way translocation involving *IGH*, *BCL2* and *MYC* [t(14;18;8)(q32;q21;q24)] and the known *TP53* deletion. The diagnosis was revised to HGBCL-*MYC*/*BCL2* and a change in treatment resulted in complete remission after one cycle. Interestingly, somatic NGS testing showed a *TP53*c.159G>A(Trp53*) variant at 91% VAF, which was not detected on germline testing. *TP53* mutations are associated with an unfavourable prognosis and chemotherapy resistance[3].

Conclusion: This case illustrates the diagnostic challenges in differentiating between aggressive B-cell malignancies, describing a leukaemic presentation of HGBCL-*MYC*/*BCL*.

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HP091

Clinicopathological features of tumour flare with Epcoritamab post CAR-T cell relapse

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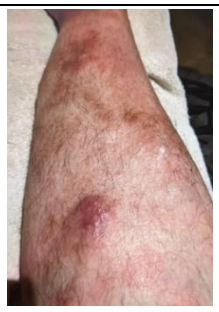
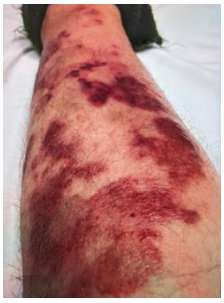
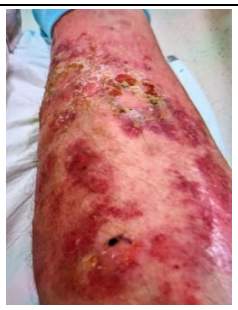
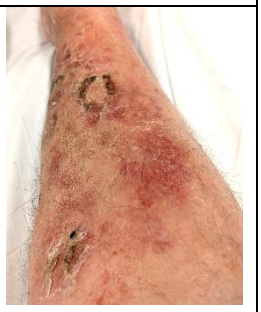
Aim: Bispecific antibodies represent a new treatment era for B cell lymphomas and can induce tumour flare before responding to treatment. The clinicopathologic features of tumour flare are not well described. We present the clinicopathological course of tumour flare in a patient with cutaneous DLBCL treated with Epcoritamab post CAR-T cell relapse.

Method: Sequential clinical and pathological data were collected for a patient with DLBCL receiving Epcoritamab three months post tisagenlecleucel failure. Skin biopsies were obtained pre- and during Epcoritamab dosing. CD19 and CD20 expression were maintained post CAR-T failure. Epcoritamab was administered subcutaneously weekly (0.16mg, 0.8mg, 48mg thereafter).

Results:

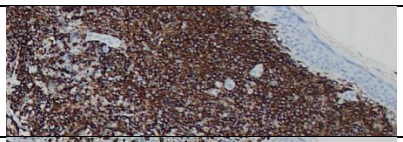
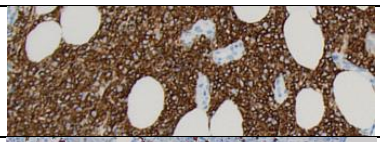
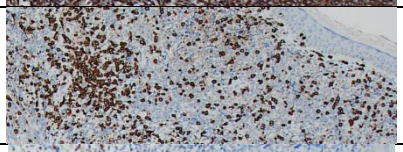
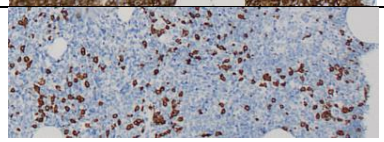
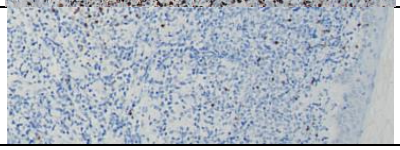
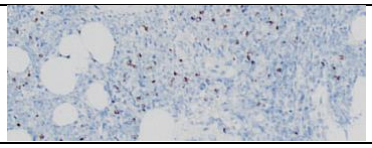
Timeline	**Day 1**	**Day 5**	**Day 15**	**Day 22**
Clinical progression of tumour flare				

The baseline appearance of cutaneous DLBCL (right leg) is pictured on **Day 1**.
Patient first noticed emergence of serpiginous port wine, non-blanching rash from **Day 5**. He presented to hospital on **Day 8** for his second dose of Epcoritamab. A **skin biopsy** was taken.

Patient then represented with worsening fever and confusion and was subsequently admitted to ICU with Grade 3 ICANS and Grade 2 CRS on **Day 10.** He improved rapidly with high dose Dexamethasone and Tocilizumab, with improvement of ICE score from 2 to 10 within 4 hours.

On **Day 15,** there was noticeable improvement of his skin lesions.
On **Day 22,** there was regression of cutaneous lymphoma.

Skin biopsy	**Pre- Epcoritamab therapy**	**Day 8 of Epcoritamab therapy**

CD20 IHC		
CD3 IHC		
Granzyme B IHC		

Conclusion: The cutaneous distribution of lymphoma has allowed us to demonstrate the clinicopathologic course of tumour flare with Epcoritamab**.** In this case, Epcoritamab resulted in increased expression of cytotoxic markers without a significant increase in tumour-infiltrating T-lymphocytes. We hypothesize a similar course occurs at other nodal and extra-nodal sites.

HP092

Combined intrathecal and systemic Alemtuzumab for T-cell Prolymphocytic Leukaemia with central nervous system involvement

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Background: T-cell prolymphocytic leukaemia (T-PLL) accounts for 2% of chronic leukaemias in adults. CNS involvement occurs in <10% of patients and evidence guiding the treatment of CNS disease is limited. Intravenous Alemtuzumab is recommended as first-line therapy for T-PLL and is associated with an overall response rate of >90%. Despite high response rates, relapse is inevitable and allogeneic-SCT is recommended in CR1. The use of intrathecal Alemtuzumab in T-PLL has only been reported twice in the published literature.

Case report: A 64-year-old male was referred to haematology after a lymphocytosis was detected on routine FBC. Flow cytometry demonstrated a CD4+ T-cell population co-expressing CD3br/4br/5br/2/7/26/28/cyTCL1 and uniformly positive for TRBC1, consistent with T-PLL. Cytogenetics demonstrated a complex clone including deletion of 11q, 22q and loss of TP53. NGS demonstrated a STAT5B mutation. Whilst undergoing diagnostic work-up he presented with dysarthria and evidence of cranial nerve IX and XII palsies. MRI brain did not demonstrate evidence of CNS disease. CNS involvement was demonstrated by flow cytometry on CSF. The patient was commenced on intravenous Alemtuzumab 30mg thrice weekly and twice weekly intrathecal chemotherapy (cytarabine/methotrexate/dexamethasone). The CSF remained positive by flow cytometry after 9 intrathecal chemotherapy administrations and intrathecal therapy was changed to twice weekly 3mg Alemtuzumab/50mg hydrocortisone. The CSF was clear of T-PLL after a single intrathecal dose of Alemtuzumab. FDG-PET after 12 weeks of intravenous Alemtuzumab demonstrated new area of nodal uptake and a cycle of intravenous high-dose methotrexate was administered. Following high-dose methotrexate CSF, bone marrow and FDG-PET scans were negative for residual disease. The patient is currently undergoing allogeneic-SCT with Fludarabine/8Gy TBI conditioning and a 24Gy CNS radiation boost.

Conclusion: CNS involvement in T-PLL is a rare manifestation of a rare disease. This case describes the successful use of intrathecal Alemtuzumab to treat CNS disease refractory to intrathecal chemotherapy.

HP093

Limited toxicity and durable early response in patients with early-stage unfavourable Hodgkin lymphoma treated with 2+2

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Aim: To assess the efficacy and toxicity the 2+2 regimen, as described in HD17(1) for patients with early-stage unfavourable Hodgkin lymphoma. There are no real-world data published to date.

Method: All consecutively diagnosed patients with early-stage unfavourable HL treated at Peter MacCallum Cancer Centre with 2+2 from June 2021 to February 2024 were included. Early-stage unfavourable comprised stage I or II disease with ≥1 of: B symptoms; >2 involved nodal regions; ESR >50; bulky mediastinal mass. Diagnostic data, short-term toxicity rates, response rates and survival data were extracted from electronic medical records. This study was approved by the institutional ethics board. Descriptive statistics were used for analyses.

Results: 16 patients met study inclusion criteria. Baseline demographic and clinical variables from our cohort approximated those patients treated in HD17 (Table 1). 15/16 patients (94%) had >2 involved nodal regions. 15/16 patients had PET2. 14/15 (93%) patients with available interim imaging attained a complete metabolic remission at PET2 which was sustained at a median follow up of 15 months (range 4-28), suggesting the prognostic potential of PET2. The remaining patient had progressive disease on PET2 and proceeded to salvage. Only 2/16 (13%) patients who had progressive disease/relapse required unscheduled radiation. 9/16 (56%) patients had dose reduction secondary to toxicity, in most cases (5/9) secondary to asymptomatic bleomycin-induced pulmonary toxicity. 11/20 (55%) unplanned admissions were due to febrile neutropenia and occurred more frequently during escBEACOPP compared to ABVD. Likewise, grade 3/4 cytopenias and blood product requirements were predominantly during escBEACOPP.

Conclusion: Real-world use of 2+2 results in very favourable outcomes with limited short-term toxicity, consistent with HD17. A multicentre analysis is underway to confirm our preliminary results.

Table 1. Clinical variables, toxicity and outcomes of patients treated with 2+2.

	Variable:	HD17* (n=550)	PMCC (n=16)
Clinical	Age (median)	31	30
	Stage (%) I II III	 5% 94% 1%	 0% 100% 0%
	ECOG (%) 0 1 2 3	 0% 81% 19% 1%	 13% 87% 0% 0%
	Bulky mediastinal disease[1] (%)	18%	25%
	>2 involved regions (%)	73%	94%
	Elevated ESR[2] (%)	46%	31%

Toxicity	**Anaemia (Grade 3/4) (%)**	**13%**	**56%**
	Thrombocytopenia (Grade 3/4) (%)	**33%**	**31%**
	Leucopenia (Grade 3/4) (%)	**84%**	**100%**
	Dose reduction (%)	**19%**	**56%**
	Blood products transfused (n)	**NR[3]**	**13 (77% during escBEACOPP)**
	Febrile neutropenia (n)	**NR**	**11 (82% during escBEACOPP)**
	Unplanned admissions (n)	**NR**	**20**
Outcome	**PET2 remission (%)**	**NR**	**88%**
	PET4 remission[3] (%)	**~91%**	**88%**
	Primary progression or relapse (%)	**3%**	**12%**
	Death (%)	**<1%**	**0%**

*** HD17 arm treated with PET4-guided treatment group**

[1]Bulky mediastinal disease was defined as: >1/3 diameter of the maximum transverse diameter of the thorax in HD17 and; defined as >7.5cm diameter in our cohort.

[2]Elevated ESR was defined as: >50mm/h or >30mm/h with symptoms in HD17 and; defined as >50mm/h in our cohort

[3]NR = Not reported

[4]PET4 remission defined as Deauville score <4 in HD17

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HP094

Mantle Cell Lymphoma with Extreme Plasmacytic differentiation and Ig class switch: A case report

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Mantle cell lymphoma (MCL) rarely presents with plasmacytic features.[1] We describe a rare case of a 67-year-old male presenting with progressive MCL showing extreme plasmacytic differentiation and class-switch (IgM to IgG).

The patient initially presented to hospital in December 2018 with encephalopathy and reduced mobility. Full blood count demonstrated moderate normocytic anaemia (Hb 91 g/L) and lymphocytosis (6.0 x 10^9/L). An IgM kappa paraprotein was identified (45 g/L, total IgM 61 g/L) with peripheral flow cytometry demonstrating a small monoclonal B cell population. PET scan revealed splenomegaly without lymphadenopathy. MRI head was normal however atypical lymphocytes were identified on lumbar puncture. The patient's bone marrow biopsy showed features suggestive of lymphoplasmacytic lymphoma (LPL) although the *MYD88* L265P analysis was negative, hence the diagnosis of LPL was not confirmed. Due to clinical concerns of CNS involvement on the background of significant frailty and comorbidities, the patient commenced fludarabine monotherapy followed by ibrutinib monotherapy. Serum IgM and IgM paraprotein levels improved to 30 and 15 g/L respectively and his encephalopathy resolved. After four years of ibrutinib monotherapy, the patient re-presented with right axillary lymphadenopathy and non-neutropenic fevers. Repeat PET scan demonstrated minimal uptake in the right axillary subcutaneous tissue, splenomegaly and diffuse bone marrow activity.

Excisional biopsy of the right axillary lesion demonstrated findings suggestive of MCL showing extreme plasmacytic differentiation and class-switch (IgM to IgG) with an unusual, clonally related large B-cell component, including CD30+ Hodgkin-like cells. FISH studies confirmed the presence of an *IGH::CCND1* dual fusion. Re-evaluation of the patient's original bone marrow biopsy revealed nodular and interstitial involvement by MCL with plasmacytic differentiation and IgM-kappa expression, noting Cyclin D1 positivity and SOX11 negativity in both small lymphocytes and monotypic plasma cells. This case highlights a rare presentation of MCL with extreme plasmacytic differentiation and the importance of *MYD88* testing.

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HP095

POLAR BEAR- R-mini-CHOP versus polatuzumab-R-mini-CHP for patients ≥80 years, or frail ≥75 years with DLBCL–Trial In Progress

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Aim: Overall survival for diffuse large B-cell lymphoma (DLBCL) has substantially improved, except for patients above 80 years old, a group that constitutes an increasing proportion of DLBCL patients. Safe and efficacious treatment for this population is an unmet medical need. We aim to evaluate polatuzumab-R-mini-CHP as frontline treatment for elderly/frail patients with DLBCL, compared to the treatment standard, R-mini-CHOP (NCT04332822).

Method: Patients from both European and ANZ sites with newly diagnosed DLBCL that are >80 years, or 75-80 years and frail, according to Comprehensive Geriatric Assessment, will be randomised to either R-mini-CHOP, or polatuzumab-R-mini-CHP, for 6 cycles, every 21 days. 300 patients are planned for enrolment internationally. Adverse events will be reported according to CTCAE v5, and statistical analysis will be performed by Kaplan-Meier method, and compared by log rank test.

Results: 184 patients (92 in each arm) have been enrolled from 41 sites in Sweden, Norway, Denmark, Finland, Italy and Australia. Median time of follow-up is 0.99 years (0.02-3.46). 80.7% were 80-90 years. 11.4% had ECOG 3. Similar grade 3-4 haematological toxicities were observed. Infection rates were similar as there were 13 grade 3-5 infection-related events in R-mini-CHOP arm, and 15 in polatuzumab-R-mini-CHP arm. Gastrointestinal toxicity >grade 1, particularly diarrhoea, was more common with polatuzumab-R-mini-CHP (27 patients, 29%, including one fatal event not related to treatment), vs 14 patients (15%) with R-mini-CHOP. More grade 1-3 peripheral neuropathy was seen with polatuzumab-R-mini-CHP (28 patients vs 14 patients). Patient recruitment has commenced in Australia, with 4 patients currently undergoing treatment.

Conclusion: Both treatment regimens are tolerable in this elderly and frail population. There were similar grade 3-4 haematological toxicities and infections, but with higher frequencies of lower grade gastrointestinal adverse events and peripheral neuropathy in the polatuzumab-R-MINI-CHP arm.

HP096

An atypical case of methotrexate-induced stage IVE diffuse large B cell lymphoma (DLBCL) resolving upon cessation with temporal development of malignancy-associated granuloma annulare

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We present an interesting case of a 76-year-old woman with cutaneous nodules and mucocutaneous ulcers in the context of long-term methotrexate treatment for rheumatoid arthritis. Punch biopsies demonstrated features in keeping with DLBCL. Initial staging PET demonstrated FDG avidity in multiple extra-nodal sites including cutaneous, muscle, breast, lung, peritoneal and nodal involvement in keeping with stage IVE disease. After six weeks cessation of methotrexate, re-staging PET showed complete resolution of the initial sites of disease, however new and more intense FDG uptake were seen in other nodal sites in the mediastinum and supraclavicular regions suspicious for alternate pathology. Multiple core biopsies of the nodal areas of involvement demonstrated histology consistent with non-necrotising granulomatous inflammation with elevated ACE levels and progressive renal decline. Trial of corticosteroid therapy had minimal effect for presumed sarcoidosis at the time and further investigations led to a diagnosis of breast cancer driving the granulomatous inflammation, in keeping with malignancy-associated granuloma annulare. At 12 months, she remains in remission from methotrexate-induced DLBCL and receiving active treatment for breast cancer.

Conclusion: This case highlights the importance of awareness around the entity of methotrexate-induced lymphoproliferative disorders of which DLBCL is the most common subtype[1-3]. Spontaneous regression can frequently occur with cessation of therapy, persistent disease requires management with systemic therapies[3]. This case also reminds us of the importance of PET surveillance and directed biopsies, and serves as a learning point that malignancies including lymphomas and solid organ tumours can be associated with granulomatous inflammation, an entity known as malignancy-associated granuloma annulare[4].

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HP097

Manufacturing commercial axicabtagene ciloleucel for Australian patients: a retrospective analysis

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Aim: Axicabtagene ciloleucel (YESCARTA®, axi-cel) is a CD19-directed genetically modified autologous T cell immunotherapy, approved in Australia for patients with R/R LBCL and R/R FL after ≥ 2 lines of systemic therapy. Commercial axi-cel manufacturing occurs at three sites (Santa Monica and Frederick, USA; Amsterdam, Netherlands) and supplies >400 qualified healthcare facilities worldwide. Australia represents the longest supply route for axi-cel globally. Rapid, reliable manufacturing can reduce time between leukapheresis and infusion, leading to favourable outcomes[1,2]. Median turnaround time (mTAT) for Europe and the USA are 19 (16-38)[3] and 16 days (15-49)[4], respectively. Here we discuss the Australian experience.

Method: 307 patients with R/R LBCL after two or more lines of prior therapy were registered for axi-cel in KiteKonnect™ and leukapheresed from 01 March 2021, to 29 February 2024 (Table-1). Manufacturing success rate is defined as the percentage of patient lots (lots) dispositioned as quality released or physician's release out of the total number of lots dispositioned. First-pass manufacturing success rate is defined as the percentage of first-attempt lots dispositioned as manufactured within specification, out of the total number of first-attempt lots dispositioned plus lots terminated (excluding lots terminated for withdrawal). Delivery success rate is defined as the percentage of lots shipped (dispositioned as quality released) out of the total number of patients leukapheresed (excluding those lots in process and withdrawn). TAT is defined as time from date of leukapheresis to date of quality release of final product.

Results: The mTAT was 18 days (17-39). 285 patient lots were delivered, with a manufacturing and delivery success rate of 98.0% and 98.3%, respectively. First-pass manufacturing success rate was 95.6%.

Conclusion: In Australia, the first three years of axi-cel availability demonstrate robust and reliable manufacturing capability, high delivery and manufacturing success rates and mTAT of 18 days for R/R LBCL patients.

Table 1:

Variables	**Outputs**
Date range (with final lot disposition available)	Mar 01, 2021 - Feb, 29 2024
Patients registered in Kite Konnect™ & leukapheresed	N=307
Median turnaround time (range)	18 (17 – 39) days*
Manufacturing success rate	98%
First-pass manufacturing success rate	95.6%
Delivery success rate	98.3%

Data extraction 25 Mar 2024. *based on n=285 patient lots manufactured and released.

HP098

A case of Superficial Panniculitis like T-Cell Lymphoma complicated by Haemophagocytic syndrome in a 16-year-old female.

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A previously well, 16-year-old female presented with a two-week history of swelling to the face and bilateral upper limbs with associated fever and lethargy on the background of a recent history of coryzal symptoms and cough,

A peripheral full blood count demonstrated anaemia (93g/L), neutropenia (nadir 0.97 x10^9/L) and mild thrombocytopenia (149 x10^9/L). Elevation of both LDH (964 U/L) and ferritin (1,370 ug/L) were noted on presentation. Soluble CD25 was elevated at 5367 (pg/ml).

Initial imaging demonstrated hepatosplenomegaly and extensive ill-defined subcutaneous oedema and stranding involving the face, chest, abdomen and back. PET imaging further defined extensive and intensely avid focal and linear subcutaneous activity across majority of the body with no evidence of lymphadenopathy. Hepatosplenomegaly was confirmed without evidence of abnormally increased avidity.

Bone marrow demonstrated haemophagocytosis but no morphological or flow cytometry evidence of a Lymphoproliferative disorder.

Excisional biopsy of abdominal wall lesion demonstrated marked panniculitis with riming by CD8 Positive T-Cells of individual adipocytes. Phagocytosis was also noted within this biopsy. Flow cytometry confirmed the majority of lymphocytes to be CD8+ alpha-beta T-Cells with otherwise normal expression of Pan T-cell antigens.

The above investigations supported a diagnosis of Superficial Panniculitis like T-Cell Lymphoma with associated Haemophagocytic syndrome [1-2]. Germline testing for HAVCR2 is currently pending[2]. The patient was initiated on high dose oral steroids and cyclosporin with subsequent rapid improvement in LDH, fevers and cutaneous oedema..

This case represents an opportunity to present and review a rare subtype of non-Hodgkin's lymphoma presenting as a diagnostic dilemma with evidence of haemophagocytic lymphohistiocytosis [1].

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HP099

Variable reporting of toxicity in lymphoma phase I trials

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Aim: Presentation of phase 1 (Ph1) trial toxicity is highly variable, with no criteria for what should be reported or what defines 'tolerable' toxicity.

Method: Toxicity from published Ph1 lymphoma trial abstracts from 4 international conferences in 1 year (ASH, EHA, ASCO, ICML) was analysed including reporting methods, grades, rates and language used for assessment.

Results: 174 Ph1 trials were identified; 73 ASH 2022; 36 EHA; 43 ICML; 22 ASCO all 2023. 75% included B-NHL; 30% DLBCL; 9% HL and 10% T-cell lymphoma. 90% enrolled relapsed/refractory disease.

64% reported "all grade" adverse events (AEs), 61% grade 3 AEs, 36% AEs of special interest (AESI) and 39% deaths. Only 20% reported Serious AEs.
71% of industry trials vs 39% investigator-initiated trials reported all grade AEs ($p<0.001$). AESI & deaths were reported in more final & long-term analyses compared to preliminary analyses (49% v 30% $p=0.02$; 49% v 31% $p=0.03$ respectively). AESI were reported in 66% of cellular therapy and bispecific antibody trials vs 23% 'other'; ($p<0.001$).
Dose-limiting toxicities (DLTs) were described in 69% of dose-escalation trials, and 67% of first-in-human studies; with separation by dose level in 4%. Cause for death was specified in 54%; and dose reduction or discontinuation in 23%.

90% of trials used minimising terms to describe safety. Of these; 78% reported >50% incidence of all-grade AE; 48% had >50% incidence of G3 AEs; and 31% had >50% incidence of SAEs. 49% had AEs leading to dose discontinuation; and 6% had deaths due to AEs.

Conclusion: Toxicity reporting in Ph1 lymphoma trial abstracts is highly variable. Minimising terms are used almost universally, despite often high rates and grades of toxicity. Clearer standardised reporting is required for improved transparency.

Studies using minimising terms (154/174 = 90%)				
	Reported	Rates reported	Rates >50%	Rates >90%
All grade	102 (66%)	63 (41%)	49 (78%)	34 (54%)
Grade 3	93 (60%)	93 (60%)	18 (19%)	7 (8%)
SAEs	42 (27%)	42 (27%)	13 (31%)	0 (0%)
Deaths due to AEs	9 (6%)			

HP100

A global phase 2 trial of Nanatinostat in combination with Valganciclovir in patients with EBV positive (EBV+) relapsed/refractory peripheral T-cell lymphomas (PTCL) - NAVAL-1.

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Aim: A Phase 2 study to evaluate the efficacy of nanatinostat in combination with valganciclovir in patients with relapsed/refractory (R/R) EBV-positive lymphomas.

Method: NAVAL-1 is an international, open-label, multicenter, single-arm, basket design trial (Simon, 1989). The following cohorts of R/R EBV+ lymphomas will be included in this trial: EBV+ DLBCL, NOS, PTCL (including PTCL-NOS and AITL), PTLD and EBV+ lymphoproliferative disorders other than the subtypes mentioned previously, including Extranodal NK/T-cell lymphoma (ENKTL). Eligible patients have R/R EBV+ lymphoma after ≥1 prior systemic therapies (≥1 prior systemic therapy for PTCL arm), with no curative therapy available, measurable disease according to Lugano 2007, and adequate hematopoietic, hepatic and renal function. Patients will receive nanatinostat 20 mg orally once daily, 4 days weekly with valganciclovir 900 mg orally once daily, 7 days weekly to evaluate: overall response rate, overall and progression-free survival, time to progression, safety, and pharmacokinetic parameters.

Results: As of 07FEB2024, the ORR in the 10-patient nanatinostat + valganciclovir arm was 50% (with a DOR that is maturing) with a CRR of 20% in the intent-to-treat (ITT) population (ORR 71% and CRR 29% in the efficacy-evaluable population), whereas in the 10-patient nanatinostat monotherapy arm, the ORR and CRR were 10% and 0%, respectively, in the ITT population. The most common treatment-related adverse events were hematological and gastrointestinal in nature, primarily mild to moderate severity, and manageable or reversible.

Conclusion: The combination nanatinostat and valganciclovir is emerging as a promising, generally well-tolerated treatment for patients with R/R EBV+ PTCL. Based on the objective responses achieved with nanatinostat and valganciclovir, the R/R EBV+ PTCL cohort met the efficacy threshold for expansion into Stage 2 of the study.

HP101

Trial in Progress: A Phase 2 study of Genetically Risk-stratified combination of Venetoclax, Ibrutinib, Rituximab and Navitoclax for relapsed and refractory Mantle Cell lymphoma – AIM2 study

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Aim: Ibrutinib and venetoclax is a highly effective treatment for relapsed and refractory (RR) mantle cell lymphoma (MCL)[1]. Patients with specific genomic alterations demonstrate resistance to this combination via upregulation of BCL-XL[2]. For example, only 1/5 patients with 9p24.1-24.3 deletion responded to ibrutinib and venetoclax in AIM1.[1]We aim to assess the safety and efficacy of combining the BCL-XL inhibitor navitoclax with rituximab, ibrutinib and venetoclax in genetically high-risk patients.

Method: AIM2 is an ongoing phase 2, muti-centre, investigator-initiated study evaluating genetically risk-stratified treatment of RR MCL. High-risk patients are identified via 9p24.1-24.3 copy number loss (CNL) on microarray and/or *SMARCA2/SMARCA4* mutations on next generation sequencing (NGS). Standard-risk patients are treated with ibrutinib 560mg daily (commencing week 1), venetoclax 400mg daily (commencing 20mg week 5 with weekly dose ramp-up), and 11 doses of rituximab (375mg/m2, D1/8/15/22 of C1 & D1 of C2-8). High-risk patients also receive navitoclax 200mg (commencing 50mg week 4 with weekly dose ramp-up). The primary endpoint is rate of bone marrow minimal residual disease (BM MRD) negativity at week 16 in the standard-risk cohort.

Results: Between November 2023 and April 2024, three patients have been treated in the high-risk cohort. All had additional high-risk features such as primary refractoriness (2/3), complex karyotype (3/3) and 17p*/TP53* deletion (3/3) (Table 1). All patients achieved complete metabolic response (CMR) and BM MRD negativity at week 16. There was no clinical or laboratory tumour lysis syndrome (TLS). The most common adverse events were diarrhoea (3/3) and neutropenia (3/3, Grade 4 in 2/3, all G-CSF responsive). Thrombocytopenia occurred in two patients, with a maximal severity of grade 2 at week 9-10 and no resultant delays in dose escalation.

Conclusion: The identification of genetically high-risk RR MCL is feasible and the combination of venetoclax, ibrutinib, rituximab and navitoclax appears deliverable in this context.

	Patient 1	Patient 2	Patient 3
	Demographics		
Age	66	62	62
Sex	M	M	F
First line treatment and response	R-MaxiCHOP/Ara-C x3 → refractory	HyperCVAD x4 + BuMel ASCT → CR1 (9 years)	BR x2 → Refractory R-CHP x1 → Refractory
	Disease characteristics at relapse		
Blastoid/Pleomorphic morphology	Yes	No	No
Ki67	80-90%	20%	50%
BM involvement	No	50-60%	>90%
Largest Node (mm)	18	111	64

High molecular risk features	9p24.1-24.3 del	9p24.1-24.3 del	SMARCA2 mutation
Microarray and FISH	Complex karyotype 11q deletion 17p deletion	Complex karyotype 17p deletion	Complex Karyotype 17p deletion
Other NGS	NA	BRAF mutation	TP53 & NOTCH2 mutations
TLS risk	Low	High	High
	Week 16 Response		
BM	CR, MRD neg	CR, MRD neg	CR, MRD neg
CT	CR – 14mm max LN	PR – 62mm max LN	PR – 20mm max LN
PET	CMR, DS2	CMR, DS3	CMR, DS1
Week 16 Overall response	MRD neg CMR	MRD neg CMR	MRD neg CMR

Table 1:

References:

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HP102

A Diagnostic challenge: Primary Intramedullary Spinal Cord Lymphoma mimicking CIDP

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Introduction: Primary intramedullary spinal cord lymphoma (PISCL) is a rare tumour, accounting for less than 1% of malignant lymphomas involving the central nervous system. Its progressive spinal cord symptoms often mimic various inflammatory conditions like chronic inflammatory demyelinating polyneuropathy (CIDP). Imaging findings, such as those from MRI, and clinical presentations can both be non-specific, making diagnosis challenging and often delayed. Furthermore, biopsy diagnostic yield is not high, adding to the difficulty in timely and accurate diagnosis.

Case Presentation: An 83-year-old female presented with progressive weakness and involuntary movements in her lower limbs, prompting neurological evaluation. MRI revealed a spinal cord lesion at the level of L1 vertebra with ill-defined high signal intensity on T2W1. Biopsy from the lesion showed no tumour but evidence of inflammation and oedema, leading to a clinical diagnosis of CIDP. Despite temporary improvement with steroid pulses and IVIg, recurrence of symptoms occurred shortly. As her neurological deficits worsened, a repeat contrast MRI showed abnormal high signal intensity from Th12 to L1 levels. Subsequent biopsy confirmed PISCL. She underwent a combination regimen including high-dose methotrexate and rituximab followed by radiotherapy. After 1 year of treatment, her mobility improved, and she remains alive.

Conclusion: Clinical and radiological features of PISCL are nonspecific, posing diagnostic challenges. In cases of discordance between biopsy results and clinical course or treatment resistance, considering PISCL in the differential diagnosis, serial MRI scans, and repeat biopsies if necessary are crucial for timely and accurate management.

HP103

Phenotypic, functional and pharmacokinetic evaluation of WZTL-002 third-generation CD19-directed CAR T-cells manufactured using the automated closed-system Lonza Cocoon platform.

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Aim: To evaluate the quality, function and pharmacokinetic properties of third-generation CD19-directed chimeric antigen receptor (CAR) T-cells generated using an automated closed-system manufacturing platform in comparison to manually manufactured products.

Method: The ENABLE phase 1 dose escalation and expansion trial (ClinicalTrials.gov NCT04049513) assessed a CD19-directed CAR T-cell product (WZTL-002) combining CD28 and Toll-like receptor 2 costimulatory domains. To allow scale-up, WZTL-002 manufacture was redeveloped using the automated closed-system Lonza Cocoon Cell Therapy Manufacturing Platform. The manual manufacturing process, including T cell isolation and activation, lentiviral transduction and cell expansion was adapted to the automated system by the Malaghan Institute and BioOra Ltd. Following Good Manufacturing Practice validation, clinical WZTL-002 CAR T-cell products were manufactured in the Cocoon and administered to seven patients within a dose expansion cohort of the ENABLE trial. Immunophenotypic and functional characteristics of the automated-manufacture GMP products were compared with those of 23 manually manufactured products, and cellular kinetics determined by digital PCR.

Results: Automated-manufacture WZTL-002 CAR T-cell products passed quality control criteria for identity, purity, sterility; transduction efficiency was improved compared to manual manufacture. Vector copy number was similar and CD19-specific effector function was maintained. Both automated and manually-produced CAR T-cells exhibited a balance of $CD4^+$ and $CD8^+$ subsets and differentiation stage (including central and stem cell memory-like populations). WZTL-002 cellular kinetic measurements including peak CAR T-cell level (C_{max}), time to peak CAR T-cell level (T_{max}) and area under the curve from days 0 to 28 ($AUC_{0\text{-}28}$) were similar pre- and post-implementation of the manufacturing automation.

Conclusion: Third-generation CD19-directed CAR T-cells manufactured using a closed, automated, GMP process displayed higher transduction efficiency and otherwise similar quality characteristics, phenotype, function and pharmacokinetics to manually produced CAR T-cells. The Cocoon automated manufacturing process has been adopted for WZTL-002 CAR T-cell production for a currently enrolling phase 2 clinical trial ('ENABLE-2').

HP104

Re-emergent Lymphoma with extreme Plasmacytic differentiation and new marked free light chain production treated to complete remission with Myeloma-styled therapy: a case report.

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A 75-year-old male with a history of low-grade B-cell lymphoma in 2013 treated to remission with R-CHOP and Rituximab maintenance therapy presented to hospital with epistaxis and was found to have a severe isolated thrombocytopenia (platelet count $15x10^9$/L). His medical history included anthracycline-related cardiomyopathy, type 2 diabetes mellitus, hypertension, atrial fibrillation, chronic kidney disease and mulitple non-melanomatous skin cancers. He was presumptively treated for ITP and had an improvement in his platelet count upon commencing prednisone 1mg/kg and IVIG.

Further investigations were performed including serum protein electrophoresis which demonstrated a new IgG kappa monoclonal protein peaking at 23g/L and kappa free light chains of 3200mg/L, with a Kappa/Lambda ratio of 50:1. Bone marrow aspirate and trephine (repeated in a fortnight given prednisone exposure) demonstrated only 4% kappa-restricted plasma cells with no morphologic evidence of lymphoma or myeloma. Surprisingly, the marrow was diagnostic for CMML-1 with fibrosis, and molecular studies subsequently returned ZRSR and TET2 mutations. FDG-PET demonstrated small volume avid cervical lymphadenopathy but no bone lesions. A core biopsy of a cervical lymph node revealed low-grade B-LPD with extreme plasmacytic differentiation, morphologically resembling his prior lymphoma diagnosis in 2013.

Minimal biochemical response was achieved with dose-reduced Bendamustine-Rituximab and subsequent Zanubrutinib. A decision was made to switch to myeloma-styled therapy given the lack of response and worsening renal function. He was treated with Bortezomib, Lenalidomide and Prednisolone, of which six cycles were completed and the patient achieved a complete metabolic and biochemical remission. The patient is currently on no active treatment and remains in clinical remission with stable renal function.

This case highlights an unusual and complex one and furthermore demonstrates the effectiveness of a myeloma-style therapy in lymphoma with a remarkably high light chain production.

HP106

Diagnosis of chronic active Epstein-Barr virus infection (CAEBV): establishing capacity to detect aberrant EBV infection in T/NK-cells in an Australian laboratory setting

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Aim: Chronic active Epstein-Barr virus infection (CAEBV) is a rare and progressive lymphoproliferative disease characterised by persistent infectious mononucleosis-like symptoms and EBV viraemia. A hallmark of CAEBV is the detection of aberrant EBV infection in T/NK-cells. The state-of-the-art method for identifying this aberrant infection is RNA FISH (PrimeFlow) flow cytometry, however Australian accessibility to this assay is limited by cost and technical expertise, and currently no diagnostic laboratory offers this assay. Here, we conduct a pilot of an alternative PCR-based method for comparison with PrimeFlow, for detecting T/NK-cell infection in CAEBV patient samples.

Method: To establish a PCR-based method, we developed an *ex-vivo* CAEBV model using peripheral blood mononuclear cells (PBMCs) isolated from an EBV seronegative donor. The PBMCs were FACS-sorted into $CD3^+CD56^-$ T-cell, $CD56^+CD3^-$ NK-cell, $CD19^+$ B-cell and $CD14^+$ monocyte subsets. These subsets were spiked with varying percentages (10%, 1%, 0.1%, 0.05%) of Namalwa cells (known 2 EBV copies/cell) prior to column-based gDNA extraction. EBV copies were detected by quantitative PCR targeting the *BALF5* gene, performed in triplicate (50 ng gDNA/reaction).

Results: The standard curve for *BALF5* showed efficient amplification at starting concentrations greater than 800 EBV copies/µg gDNA (C_t < 33). Reliable amplification prior to this C_t threshold (positive result) was demonstrated for each PBMC subset when spiked with ≥1% EBV-infected Namalwa cells. No amplification up to 45 cycles (negative result) was observed for negative controls. This was comparable to the sensitivity of the PrimeFlow assay, which in our hands was able to detect 0.5-1% of EBV-positive B/T/NK-cell populations.

Conclusion: The PCR-based method demonstrated reliable, cost-effective and highly sensitive detection of EBV copies in sorted cell populations using methods applicable in the Australian diagnostic laboratory setting. We will shortly commence recruitment of patient samples for validation of both PCR and PrimeFlow assays for use in the diagnostic setting.

HP107

High-risk diffuse large B-cell lymphoma in young patients: A retrospective registry study of management practices and outcomes in Australia

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Aim: To describe treatment patterns and clinical outcomes in patients aged 18-60 with high-risk diffuse large B-cell lymphoma (DLBCL), defined as an age-adjusted international prognostic index (aaIPI) of 2-3.

Method: Data on demographics, disease characteristics, treatment and outcomes of patients aged 18-60 with a histological diagnosis of DLBCL NOS between January 2016 and April 2024 were extracted from the Lymphoma and Related Disease Registry. aaIPI was calculated from available data to include patients with an aaIPI of 2-3, treated with curative intent.

Results: 2187 patients with DLBCL were identified, 166 (7.6%) fulfilled criteria for inclusion. Median follow-up was 24 months, time from diagnosis to treatment 11 days (range 7-18). Patient characteristics and survival outcomes by standard R-CHOP-21 or intensive regimens are described in Table 1. 31% were treated with intensive regimens including DA-R EPOCH (n=24), R-CHOEP-14/21 (n=7) and R-CHOP-14 (n=20). Median number of cycles completed was 6. Response was recorded in 105/115 who received R-CHOP-21: ORR 79%, CR 69.5%. Response for patients treated with intensive regimens was recorded in 46/51: ORR 78% and CR 72%. OS at 2 years was 77% and 78% for patients treated with R-CHOP 21 and more intensive regimens respectively, PFS; 65% and 66%.

Conclusion: Between 2016 and 2023, younger patients with high-risk DLBCL were predominantly prescribed the R-CHOP-21 regimen and commenced treatment rapidly. A smaller proportion of patients received a more intensive regimen, highlighting the lack of enthusiasm for intensified approaches amongst Australian clinicians. No significant difference was observed between groups in response rates or OS/PFS rates at two years. Novel combinations such as polatuzumab plus R-CHP may change treatment patterns and outcomes for these patients in the near future.

Table 1: Patient characteristics and survival outcomes by standard and intensive therapies.

Factor	All	Standard therapy	Intensive therapy	p-value
N	166	115	51	
Age at diagnosis (years), median (IQR)	53.0 (45.4, 56.9)	53.0 (43.3, 56.7)	52.7 (45.8, 57.2)	0.59
Sex				0.65
Male	90/166 (54.2%)	61/115 (53.0%)	29/51 (56.9%)	
Female	76/166 (45.8%)	54/115 (47.0%)	22/51 (43.1%)	
Elevated LDH	159/164 (97.0%)	109/114 (95.6%)	50/50 (100.0%)	0.13
Stage ≥ 3	164/165 (99.4%)	113/114 (99.1%)	51/51 (100.0%)	0.50
ECOG ≥ 2	26/158 (16.5%)	21/107 (19.6%)	5/51 (9.8%)	0.12
Double expressor (BCL-2 + MYC)	42/164 (34.8%)	24/113 (21.2%)	18/51 (47.1%)	
Age-adjusted IPI score				0.41
2	138/155 (89.0%)	92/105 (87.6%)	46/50 (92.0%)	
3	17/155 (11.0%)	13/105 (12.4%)	4/50 (8.0%)	
Bulk (>5cm)	70/153 (45.8%)	48/104 (46.2%)	22/49 (44.9%)	0.88
Survival outcomes (24 months)				
PFS	-	65%	66%	0.746
OS	-	77%	78%	0.829

IQR: interquartile range; LDH: lactate dehydrogenase; ECOG: Eastern Cooperative Oncology Group score; IPI: International Prognostic Score

HP108

Monotherapy with second-generation BCL2 inhibitor sonrotoclax (BGB-11417) is well tolerated with high response rates in relapsed/refractory (R/R) marginal zone lymphoma (MZL): data from an ongoing phase 1 study

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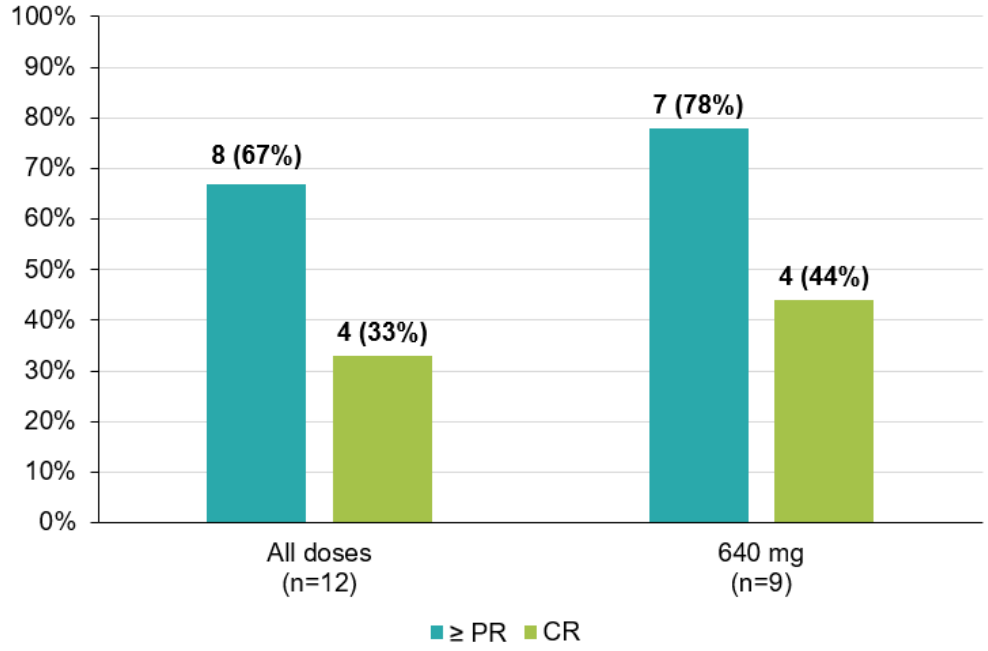
Aim: Sonrotoclax is a more selective and potent BCL2 inhibitor than venetoclax in biochemical assays. BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, dose-escalation/expansion study in patients with B-cell malignancies. Presented here are data for R/R MZL.

Method: Patients received sonrotoclax with a 3-day dose ramp-up during dose-escalation (40mg/80mg/160mg/320mg/640mg QD) and expansion (640mg/320mg). DLTs were evaluated from ramp-up through day 21 at the intended dose. The primary endpoint was safety (CTCAE v5.0); objective response rate (ORR; Lugano 2014 criteria) was a secondary endpoint. Tumor lysis syndrome (TLS) was assessed per Howard 2011 criteria.

Results: As of 24April2023, 13 patients received sonrotoclax (40mg, n=1; 160mg, n=2; 640mg, n=10). Four patients progressed on BTK inhibitors (BTKi); three had BTKi as their last therapy. Dose escalation occurred per protocol at all defined doses. MTD was not reached up to 640mg. One DLT occurred (160mg; febrile neutropenia). Median follow-up was 7.8 months (range, 2.6-36.6). TEAEs in ≥20% of patients were nausea (39%) and pyrexia, diarrhea, and constipation (31% each). The most common grade ≥3 TEAEs were neutropenia, febrile neutropenia/neutropenic sepsis, and TLS (15% each). Five patients discontinued treatment (disease progression, n=3; AE [infection], n=1; withdrawal, n=1). No TEAEs led to death. Two patients (640mg) had laboratory TLS after initial ramp-up doses. TLS resolved within 24 hrs without sequela or dose change. Of 12 response-evaluable patients across dose levels, ORR was 67% (CR 33%). Of 9 response-evaluable patients at 640mg, ORR was 78% (CR 44%; Figure). All 4 patients with prior progression on BTKi responded to treatment.

Conclusion: Sonrotoclax was tolerable and had antitumor activity across tested doses in MZL. Two patients had laboratory TLS following initial doses that resolved. No clinical TLS was observed. An exploratory 320mg cohort is enrolling.



CR, complete response; MZL, marginal zone lymphoma; PR, partial response; R/R, relapsed/refractory.

HP109

Flow cytometric detection of TRBC-1 expression in the assessment of T-cell clonality

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Aim: T-cell neoplasms are heterogeneous, making it difficult to differentiate them from reactive T-cell lymphoproliferation. Demonstrating that T-cell infiltrates are a monotypic neoplastic population often requires using a multiplicity of techniques, including molecular techniques. Recently, it has been demonstrated that T-cell receptor constant region 1 (TRBC-1) detection by flow cytometry is a rapid and reliable method for assessing T-cell clonality. The rearrangement of the TCRB gene involves the mutually exclusive expression of one of two constant β chain genes (TRBC-1 and TRBC-2), analogous to the kappa and lambda gene in B cells. Normal T-lymphocytes therefore should have be polytypic, with some expressing TRBC-1 and some not (presumptively TRBC-2 positive). In this study, we aim to validate the reference ranges of TRBC-1 expression in normal T-lymphocyte populations and confirm its clinical utility.

Method: We used a single TRBC-1 antibody clone JOVI-1, in conjunction with T-cell associated markers, to detect T-cell clonality in tissue biopsies, bone marrow, peripheral blood (PB), and body fluids. A total of 50 clinical samples, 20 normal healthy controls and 30 clinical samples. Samples were analyzed with a panel of monoclonal antibodies comprising of the markers - CD5/Tαβ/CD3/Tgd/TRBC-1/CD8/CD7/CD4/CD45/CD2. Flow cytometry results for clinical samples were correlated with the histological diagnosis.

Results: Normal Tαβ-positive populations were identified based on immunophenotypically distinct main subpopulations including CD4-positive, CD8-positive, CD4/CD8-double positive, CD4/CD8-double negative Tαβ subsets. The major Tαβ-cell populations revealed a reproducible bimodal mixture of TRBC1+ and TRBC1− cells, indicative of polytypic T-cell maturation. Using a similar gating strategy, we examined TRBC-1 expression in neoplastic T-cell populations based on their immunophenotypic aberrancies and identified monotypic TRBC-1 expression. Among total clinical samples cohort, 10 cases had concurrent clinical findings for comparison, encompassing T cell receptor gene rearrangement assays and histopathology analysis.

Conclusion: The incorporation of TRBC-1 antibody is a rapid and robust method for detection of T-cell clonality based on altered percentages of TRBC1+ Tαβ cells that could be routinely utilized in flow cytometry panels to aid diagnosis of T-cell lymphoproliferative diseases.

HP110

Evaluation of the incidence of bleeding events in real-world patients receiving Bruton tyrosine kinase inhibitors

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Aim: Bruton tyrosine kinase inhibitors (BTKi) demonstrate significant benefit for the treatment of B-cell malignancies. The first-generation BTKi ibrutinib associates with increased bleeding risk due to off-target kinase activity. Zanubrutinib and acalabrutinib possess increased kinase specificity however trial bleeding rates are comparable. The real-world bleeding risk remains to be characterised, we sought to define this.

Method: A dispensing report identified adults from 1/1/15 to 31/11/23 who received 28 days or more ibrutinib, zanubrutinib or acalabrutinib in a tertiary hospital. The medical record was reviewed for the primary outcome of all-grade bleeding, up to 30 days from BTKi cessation.

Results: Ninety-six patients were identified (ibrutinib n=52, zanubrutinib n=24, acalabrutinib n=20). Median age (IQR) was 73 years (66-80) and 66 patients (69%) were male. Most had chronic lymphocytic leukaemia/small lymphocytic lymphoma (n=37, 39%), lymphoplasmacytic lymphoma (27, 28%) or mantle cell lymphoma (17, 18%). Median (IQR) duration of treatment was: ibrutinib 30.5 months (6.6-54.6), zanubrutinib 11.2 months (8.3-18.2), acalabrutinib 20.5 months (11-28.1). Median HAS-BLED score was 2 (range 0-5) and 32 (33%) patients received concurrent anti-platelet/anticoagulant therapy.

All-grade bleeding occurred in 43 (45%; 95% CI=31-58%) patients (ibrutinib=25 (48%; 95% CI=31-71%), zanubrutinib=8 (33%; 95% CI=14-66%), acalabrutinib=10 (50%; 95% CI=24-92%)). Median time to first bleed (IQR) was 6.9 months (2.1-20.8). Recurrent bleeding occurred in 9 (9%) patients and 5 (5%) ceased BTKi due to bleeding. Grade 3 or higher bleeding occurred in 5 (5%) patients, all of whom received ibrutinib. Bruising was most common (n=28, 29%), followed by Grade 1 and 2 trauma/procedure related bleeding (n=12, 13%). Exposure-adjusted event rate for all-grade bleeding was 2.5 per 100-person-months (95% CI=1.9-3.2; ibrutinib=2.32 (1.65-3.17), zanubrutinib=2.95 (1.41-5.43), acalabrutinib=2.56 (1.28-4.58)).

Conclusion: Bleeding rate in this cohort was comparable to trials and limited real-world studies. Cohort size may have limited the detection of severe bleeding with acalabrutinib and zanubrutinib thus further study is warranted.

HP111

Outcomes for high-risk defining events in follicular lymphoma following frontline immunochemotherapy

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Background: Early progression of follicular lymphoma (FL) or transformation (tFL) within 24 months of immunochemotherapy (ICT) represent high-risk defining events (HRDE) with poor overall survival (OS). It remains to be established if the OS of patients is influenced by the nature of the HRDE.

Methods: We examined clinical characteristics, imaging metrics and outcomes for patients experiencing HRDE with an international retrospective cohort of newly diagnosed FL patients requiring ICT. We defined HRDE groups as: relapse or progression of FL within 24 months (FL24); Early tFL (≤24 months of ICT); Late tFL (>24 months of ICT).

Results: 433 patients were categorised as reference FL n=352 (no HRDE), FL24 n=43, Early tFL n=29, Late tFL n=9. ICT regimens included bendamustine (63%), CHOP (27%) or CVP (10%), 85% received rituximab and 48% received maintenance therapy. Compared to the reference group, OS from HRDE was inferior for FL24 (HR 3.93, 95% CI 2.14-7.23), Early tFL (HR 8.16, 95% CI 4.38-15.2) and Late tFL patients (HR 8.23, 95% CI 3.18-21.25). OS from HRDE for FL24 group was longer than Early tFL (HR 2.08, 95% CI 1.02-4.21). Baseline performance status raised lactate dehydrogenase and beta-2-microglobulin predicted for Early tFL. Baseline clinical biomarkers were not able to differentiate Early tFL from FL24. Baseline standardised uptake value max was higher in Early tFL but not FL24 compared to reference FL

Conclusion: Early tFL and FL24 represent different HRDEs in FL after ICT and are associated with poor outcomes. Distinguishing between early tFL and FL24 is a priority for biomarker development, to guide management and to develop and interpret clinical trials in this area of unmet need. Considering Early FL and FL24 as distinct entities will be critical to design and interpret strategies to improve the survival of patients with HRDE.

HP112

The definition and use of bulk disease in phase 3 lymphoma trials: a comprehensive literature review

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Aim: To describe the definitions of tumour bulk, how it is used and prognostic implications reported in phase 3 randomised controlled trials (RCTs) of four common lymphoma subtypes.

Method: A literature search was conducted in MEDLINE, Cochrane, and Embase between 2000-23 for phase 3 RCTs in adults with follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL), peripheral T cell lymphoma (PTCL) or Hodgkin lymphoma (HL) where bulk was used in the study design. We collected data on definitions (cm), use of bulk (eligibility, stratification, guiding additional radiotherapy/chemotherapy or in prognostic analyses) and significance on prognosis. We also reviewed the consideration of bulk in commonly used prognostic indices.

Results: Of 87 studies, FL, DLBCL, PTCL and HL comprised of 33, 19, three and 32 respectively. Definitions included 5cm, 6cm, 7cm, 7.5cm, 10cm and >1/3 mediastinal mass ratio (MMR) (Table 1). >1/3 MMR was the most common in HL (29/32), 7cm in FL (19/33), 7.5cm and 10cm in DLBCL (8/19 each) and 7.5cm in PTCL (2/3). Bulk determined eligibility in 58/87 (46 inclusion, 12 exclusion), stratification in 21/87 and guided additional therapy in 25/87 (23 radiotherapy, 2 chemotherapy). Of 32/87 studies using bulk in prognostic multivariate analyses, only five showed statistical significance on outcomes (two FL, one each in DLBCL, PTCL and HL). Bulk was considered in 9/10 prognostic indices, analysed in eight but only included in two published models.

Conclusion: Our review suggests a large variation in definitions and use of bulk in phase 3 RCTs with only a few demonstrating a significant prognostic impact in analyses, questioning its ongoing use in modern clinical practice.

Table 1. Bulk in phase 3 lymphoma RCTs.

	All studies	FL	DLBCL	PTCL	HL
N	**87**	**33**	**19***	**3**	**32**
Bulk definitions (%)					
5cm	18 (21)	7 (21)	2 (11)	1 (33)	8 (25)
6cm	2 (2)	-	-	-	2 (6)
7cm	21 (24)	19 (58)	2 (11)	-	-
7.5cm	13 (15)	3 (9)	8 (44)	2 (67)	-
10cm	24 (28)	7 (21)	8 (44)	-	9 (28)
1/3 MMR	31 (36)	2 (6)	-	-	29 (91)
Use of bulk (%)					
Eligibility	58 (67)	18 (55)	10 (53)	2 (67)	28 (88)
Stratification	21 (24)	6 (18)	6 (32)	1 (33)	8 (25)
Treatment decisions	25 (29)	5 (15)	9 (47)	1 (33)	10 (31)
Analysis of bulk	32 (37)	13 (39)	12 (63)	1 (33)	6 (19)
Prognostic	5	2	1	1	1
Type of analysis – n					
Multivariate analysis	22/32	10/13	7/12	1/1	4/6
Subgroup analysis	16/32	5/13	7/12	-	4/6

RCT; randomised controlled trial; FL, follicular lymphoma; DLBCL, diffuse large B cell lymphoma; PTCL, peripheral T cell lymphoma; HL, Hodgkin lymphoma; MMR, mediastinal mass ratio
**Xu et al 2019 did not provide discrete thresholds (therefore n=18 used for definitions)*

HP113

Indolent T cell lymphoproliferation of the gastrointestinal tract: an evolving disease entity

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Background: Indolent T cell lymphoproliferation of the gastrointestinal tract (ITLPGI) is a rare entity, newly added to the 2016 WHO classification of lymphoid neoplasms.

Optimal management remains unclear with data derived from case studies. Current consensus suggests avoiding chemotherapy given lack of demonstrated efficacy and indolent nature of disease. Management options include radiotherapy, corticosteroids with a theorised role for cyclosporine in the literature.

Here, we describe one rare case of such with excellent response to corticosteroids and cyclosporine.

Case Report: A 37-year Afghani female presented to our hospital with a 3-week history of post-prandial abdominal pain associated with nausea, vomiting, diarrhoea and 10kg weight loss. Her full blood count, liver function tests and lactate dehydrogenase level were all within normal limits. A CT abdomen/pelvis showed diffuse mild thickening of the small bowel, numerous mildly enlarged mesenteric lymph nodes (largest up to 1.4cm) and splenomegaly (16.1cm craniocaudal height). Her faecal testing was unremarkable with no ovas, cysts or parasites. Her coeliac, Strongyloidiasis and viral serology were negative with normal autoimmune screen. Endoscopy revealed macroscopically patchy, friable mucosa in the duodenum with subsequent biopsy revealing a dense lymphoid proliferation, comprising mildly atypical lymphoid cells staining strongly for CD3, CD4 and CD5 but loss of CD7, CD10. CD8, CD25 and EBV-ISH were negative. Ki67 index was low (5-10%).

A PET demonstrated mildly avid mesenteric lymphadenopathy with subsequent bone marrow and lymph node biopsy both representing a similar abnormal lymphoid proliferation seen in the duodenum based on immunohistochemistry and flow cytometry.
Given persisting symptoms, she was started on oral corticosteroids with excellent response and transitioned to cyclosporine 50mg twice daily for past 2 years with no further symptoms and stable disease on annual CT scans.

Conclusion: This case report demonstrates the successful use of cyclosporine and corticosteroids in ITLPGI with sustained clinical remission.

HP114

A rare case of synchronous cardiac and central nervous system lymphoma in a Jehovah's Witness

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Background: Primary cardiac lymphoma (PCL) is exceedingly rare, with DLBCL being the most common histological subtype. Case reports of PCL suggest an increased risk of CNS relapse; however, cardiac DLBCL with synchronous CNS involvement has not been reported in the literature.[1] We present a unique case of synchronous cardiac and CNS lymphoma, highlighting the complexity in navigating the management in a Jehovah's Witness (JW).

Case report: A 60-year-old female presented with altered consciousness, confusion, dyspnoea, and weight loss. On transthoracic echocardiogram, a large infiltrative right atrial mass extending to nearly the entire right ventricle free wall was identified; this mass was biopsy-proven as DLBCL (non-germinal centre type, non-double-expressor, and non-double-hit). PET staging showed disease isolated to the right heart. MRI brain showed multifocal CNS involvement, associated with vasogenic oedema and mass effect, although not biopsy proven due to rapid clinical deterioration.

Rituximab-hyper-CVAD was planned, with dose attenuated to mitigate treatment-related myelosuppression in a JW unable to accept blood product transfusions. Given the presence of CNS disease, she was commenced on Rituximab-hyper-CVAD part B with methotrexate 1g/m2 and cytarabine 1g/m2. The nadir platelet count was $8x10^9$/L lasting one day, and nadir haemoglobin of 80g/L, managed with tranexamic acid, eltrombopag, iron infusion, folate, and erythropoietin. She proceeded with part A Rituximab-hyper-CVAD on schedule, with dose modified to equivalently R-CHOP. The subsequent part B cycle was given with cytarabine dose reduced to 500mg/m2. Despite this, she had thrombocytopenia $<10x10^9$/L lasting 3 days without bleeding complications. Further part B cycles was abandoned. She went on to complete 6 cycles total of R-CHOP, achieving complete metabolic response.

Conclusion: This is the first reported case of synchronous cardiac and CNS DLBCL, achieving remission on 6 cycles R-CHOP and 2 cycles of attenuated methotrexate/cytarabine.

References:

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HP115

Treating CD30-positive ALK-negative anaplastic large cell lymphoma arising post-transplant with BV-CHP: A Case Report

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T-cell post-transplant lymphoproliferative disorders (PTLD) are rare lymphoid proliferations that develop post solid organ transplantation or allogeneic stem-cell transplantation and often carry a poor prognosis. In contrast to B-cell PTLD, T-cell PTLD are rare which makes treatment a challenge due to the lack of prospective data to guide management.

We describe here, to our knowledge, the first reported case of CD30-positive EBV-negative T-cell PTLD post cardiac transplantation managed with Brentuximab Vedotin plus cyclophosphamide, doxorubicin, and prednisone (BV-CHP).

A 65-year-old woman with a background of cardiac transplant 30 years prior presented with a month's history of constitutional symptoms. Full blood count demonstrated: white cells 90 x 10^9/L, haemoglobin 111g/L, platelets 181 x10^9/L, abnormal lymphoma cells 79 x10^9/L. The blood film was leucoerythroblastic with a marked infiltrate of large immature cells that were frequently disrupted. An aberrant T cell population with high forward scatter was detected on flow cytometry representing 74% of total cells co-expressing CD2(str), CD3, cyCD3, CD4, CD7(subset), CD30(var), HLA-DR, alpha-beta and TRBC1(JOV1) restricted.

The morphology and immunohistochemical findings on the bone marrow aspirate and trephine were most consistent with a diagnosis of ALK-negative anaplastic large cell lymphoma (ALCL), EBV-, post-transplant (cardiac) by the WHO 2022 diagnostic classification criteria. In addition, cytogenetic studies revealed a complex karyotype with multiple chromosomal gains and losses and gene fusion panel detected a TBL1XR::TP63 fusion consistent with TP63 rearranged ALK negative ALCL. She was commenced on BV-CHP.

Her admission was complicated by tumour lysis syndrome and septic shock from neutropenic sepsis. A bone marrow biopsy on day 17 revealed a hypocellular marrow with a significant reduction in CD30 expression consistent with treatment response. The patient passed away on day 23 from sepsis. Here we discuss challenges in the diagnosis of CD30-positive ALK-negative ALCL PTLD and the first use of BV-CHP in in this setting.

MDS

HP116

An atypical case of Bicytopenia, Myeloid Dysplasia and Complex Monosomal Daryotype including the Philadelphia chromosome

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Introduction: Myelodysplastic neoplasms (MDS) are a group of clonal myeloid disorders defined by cytopenias, dysplasia and characteristic cytogenetic and molecular aberrations. Philadelphia chromosome, arising from translocation of chromosomes 9 and 22 is essential for a diagnosis of chronic myeloid leukaemia (CML) but rarely reported in MDS. Here we describe an atypical case of bicytopenia, myeloid dysplasia and complex monosomal karyotype including t(9;22).

Case presentation: An 83yo female presented with subacute thrombocytopenia, basophilia and t(9;22) by peripheral blood Fluorescent in situ Hybridization (FISH). There were no significant B symptoms or splenomegaly. Full blood count revealed thrombocytopenia $52x10^9$/L (normal 140-$400x10^9$/L), mild anaemia 105g/L (normal 110-165g/L), basophilia $1.24x10^9$/L (normal <$0.20x10^9$L) and 2% blasts with notable absence of leucocytosis or myelocyte hump. The blood film was leucoerythroblastic with occasional tear drop cells, granulocyte cytoplasmic hypogranularity and platelet dysplasia including bare megakaryocyte nuclei and cytoplasmic fragments. Lactate dehydrogenase was mildly raised at 263U/L (normal <250U/L). Bone marrow examination revealed hypercellularity with trilineage dysplasia, marked basophil degranulation and 3% blasts. Conventional karyotype showed complex cytogenetics suspicious for clonal evolution with three abnormal clones demonstrating progressive acquisition of monosomies 2, 5 and 10, t(9;22)(q34;p11.2) and monosomy 7, respectively. FISH was positive for Philadelphia chromosome in 41% of cells. An atypical e1a2 p190 BCR-ABL fusion transcript was detected by polymerise chain reaction. Secondary causes for cytopenia and dysplasia were excluded. After 3 months of Imatinib 300mg daily, the basophilia and left shift resolved but she remained bicytopenic.

Conclusion: The cytopenias, myeloid dysplasia and karyotype suggestive of progressive clonal acquisition favours a diagnosis of MDS with t(9;22), a rare entity reported in literature. Differentials include myelodysplastic progression of CML or concurrent MDS/CML. Single cell sequencing to detail the clonal phylogeny would be informative to confirming diagnosis which would guide the optimal management approach.

HP117

Risk Factors for Clonal Haematopoiesis of Indeterminate Potential (CHIP): A Systematic Review and Meta-Analysis

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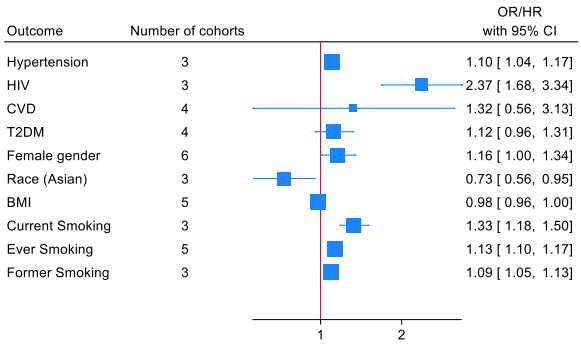
Aim: CHIP results from somatic mutations in haematopoietic stem cells that confer a fitness advantage[1]. Age is an important risk factor for CHIP[2]. Understanding other risk factors can provide important insights into the biology of how CHIP clones develop. Our study aimed to identify other risk factors associated with increased risk of CHIP through a systematic review and meta-analysis of the literature.

Method: The terms “Clonal h*ematopoiesis.mp.” OR “clonal hematopoiesis” as a subject heading were used to search OVID Medline and EMBASE for articles published up until 30th September 2023. Two reviewers screened abstracts and full texts, extracted data, and assessed risk of bias with the Quality in Prognostic Studies tool. Random effects meta-analysis was then performed for risk factors reported in a minimum of three studies. The study excluded genome wide association studies, and there was insufficient data to examine risk factors for specific CHIP mutations.

Results: 3305 abstracts and 252 full text articles were screened. 24 studies examined risk factors associated with prevalence of CHIP, after adjusting for age. 12 studies were included in the meta-analyses. Risk factors associated with an increased risk of CHIP included female gender (OR 1.16, 95% CI 1.01-1.35), HIV positive status (OR 2.37, 95% CI 1.68-3.34), current smoking (OR 1.33, 95% CI 1.18-1.50), and hypertension (OR 1.1, 95% CI 1.03-1.16). Asian ethnicity was associated with a lower risk of CHIP (OR 0.73, 95% CI 0.56-0.94). Risk factors that were not associated with a statistically significant risk of CHIP included elevated BMI, type 2 diabetes, and cardiovascular disease.

Conclusion: After adjusting for age, CHIP prevalence was increased in females, smokers and those with HIV or hypertension, and lower in people of Asian ethnicity. Identifying populations at high risk of CHIP will have important clinical implications as the impact of CHIP on disease outcomes becomes better elucidated.

Figure 1: Summary of meta-analyses



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HP118

Large clonal haematopoiesis of indeterminate potential (CHIP) is associated with increased risk of sepsis

Singh J[1,2,3], Eisen D[4], Wong N[2], Byars S[2], Leichter A[2], Lacaze P[1], McNeil J[1], Orchard S[1], Phung J[1], Ramshaw H[5], Thao L[1], Wolfe R[1], Wood E[1,6], Woods R[1], Curtis D[2,7], McQuilten Z[1,6,7]
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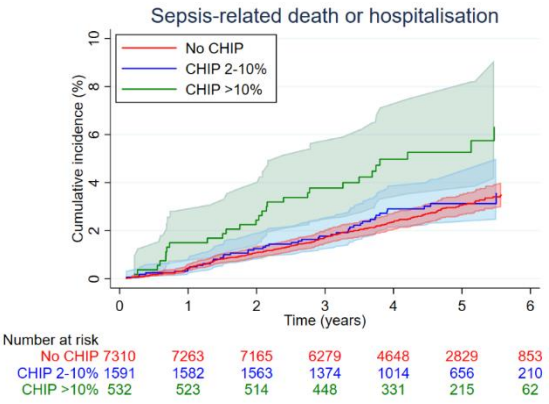
Background: CHIP has been proposed to have multi-system effects, but few studies have assessed the association between CHIP and infection risk.

Aim: To investigate the association between CHIP and sepsis risk in healthy older adults.

Method: The ASPREE trial enrolled healthy individuals ≥70 years without cardiovascular disease, dementia, disability, 5-year life-limiting illness or contraindication to aspirin. Embedded within the trial were two sub-studies: ASPREE-CHIP and ANTISEPSIS (Aspirin To Inhibit Sepsis). CHIP status was determined from peripheral blood at baseline using a targeted sequencing assay. Participants were followed for a median of 4.7 years and endpoints adjudicated by an independent, blinded committee were sepsis-related death and hospitalisation for non-fatal sepsis. The association between CHIP and time to 1) sepsis-related death or 2) first sepsis event (defined as a composite of sepsis-related death or hospitalisation for non-fatal sepsis) was assessed by multivariable-adjusted Cox proportional hazards, with death from other causes treated as a competing risk. Adjustment variables were baseline age, smoking, alcohol, diabetes, history of cancer and randomisation to aspirin. Cumulative incidence estimates were obtained using the Aalen-Johansen estimator.

Results: CHIP status was determined in 9434 people, of whom 1,592 (17%) had CHIP with variant allele fraction (VAF) = 2-10% and 532 (5.6%) had CHIP with VAF >10%. People with CHIP were older and more likely to have a history of cancer at baseline. Sepsis death (endpoint 1) occurred in 108 individuals overall. Any sepsis event (endpoint 2) occurred in 285 individuals, with the first event being hospitalisation for non-fatal sepsis in 188, and sepsis-related death in 97. In multivariable analyses, CHIP >10% increased the risk of sepsis events (cause-specific hazard ratio (HR) 1.58 [95% CI 1.06-2.35]) (Figure 1) and a similar association was found with sepsis death (HR 1.61 [95% CI 0.87-2.97]). CHIP 2-10% was not significantly associated with increased risk of sepsis.

Conclusion: Large CHIP (VAF >10%) is associated with increased risk of sepsis, independent of age. CHIP may exacerbate age-associated immunosenescence leading to increased susceptibility to infection.



MPD

HP119

Systemic mastocytosis at Gold Coast –A single regional centre experience.

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Systemic mastocytosis at Gold Coast –A single regional centre experience.

Aim: The incidence of systemic mastocytosis and mast cell leukaemia is rare. We present a case series of seven patients managed at our centre and share our experiences in challenging disease, including pitfalls in diagnosis and management, and the use of old school cytotoxics and novel targeted kinase inhibitors.

Method: A retrospective review of electronic medical records of seven patients diagnosed with systemic mastocytosis at Gold Coast University Hospital.

Result: Seven patients were identified, 5 female and 2 male. Age at diagnosis ranged from 43 to 73 years. Clinical presentations were varied and included splenomegaly, gastrointestinal or cutaneous symptoms, cytopenias, and aggressive bone and soft tissues lesions in the case of mast cell leukaemia. Treatments ranged from supportive treatment with prednisolone, antihistimines, and loperamide, to targeted therapies. Two patients were treated with avapritinib, two with pegylated interferon, and one with a novel KIT inhibitor on clinical trial. The two patients on avapritinib had a good disease response, and their symptoms remain well controlled with normalised tryptase levels after two years on therapy. There were varied response to interferon, and mastocytosis symptoms persisted in those two patients. The one mast cell leukaemia had an aggressive clinical course with poor response to the new potent KIT inhibitor requiring salvage therapy with radiation therapy and cladribine.

Conclusion: Systemic mastocytosis and mast cell leukaemia is rare. Due to the rarity of diagnosis and heterogeneity of the disease, treatment options and outcomes are varied. Challenges in treatment of systemic mastocytosis include toxicities of treatment, complications from underlying haematological malignancies if present, and the limited access to potentially beneficial treatments and clinical trials. More advocacy for better access for effective cytoreductive therapy for aggressive forms of this disease is required to improve the outcomes of these patients.

HP120

Unbiased molecular analysis of MPL reveals novel disease associations in myeloid malignancy

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Aim: Activating *MPL* variants are primarily associated with myeloproliferative neoplasms (MPNs). Most molecular studies to date have focussed on W515 variants and exon 10 of *MPL* in MPN. We aimed to perform an unbiased assessment of variants across the entire coding region of *MPL* and across all myeloid malignancies to comprehensively understand the landscape of *MPL* variants.

Method: All *MPL* coding exons were assessed by unique molecular index-corrected NGS (along with 79 other genes recurrently mutated in haematological malignancy) in consecutive samples referred for diagnostic testing and correlated with clinicopathological features.

Results: *MPL* variants were identified in 105/4403 of patients assessed. Of these variants, 85/111 were assumed to be of somatic origin and included (i) typical W515 and S505 codon variants (n=53) (ii) exon 4 variants (predominantly S204P n=3) and (iii) exon 12 variants (predominantly Y591D, n=11). Two novel stop loss variants were also detected. In addition, we identified 16 variants of assumed germline origin including R102P (n=4) either representing carrier status for congenital amegakaryocytic thrombocytopenia or the emerging phenotype of thrombocytosis associated with loss of function *MPL* variants. Strikingly, whilst the majority (82%) of exon 10/exon 4 variants were observed in MPN, the majority of exon 12 variants (72%) were observed in non-MPN contexts (e.g. MDS/MPN, MDS, AML) ($p<0.00001$) and enriched for *ZRSR2* and *TET2* co-mutation. *MPL/JAK2* or *MPL/CALR* co-mutation was identified in 11 patients. Six patients carried multiple *MPL* variants, with 11/17 co-mutated involving exon 10 variants in an MPN context. Co-mutation of any gene was detected in 96% of exon 12 variants compared to 66% of exon 10 variants.

Conclusion: Our unbiased assessment of *MPL* variants in this large cohort has revealed multiple novel findings including undescribed somatic *MPL* variants, an expanding role of LOF *MPL* variants and an enrichment in exon 12 mutations in non-MPN context.

HP121

Endomitosis mayhem! Aurora kinase and GATA-1 dysregulation in Megakaryocytes of Myeloproliferative Neoplasms.

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Aim: Myeloproliferative neoplasms (MPN) are chronic myeloid malignancies characterised by megakaryocytic hyperplasia with morphologic atypia. Abnormalities in megakaryocyte endomitosis arise in MPN and their transformation to myelofibrosis (MF). Aurora kinase A (AURKA) and B (AURKB) initiate megakaryocyte endomitosis and polyploidisation, while GATA-1 facilitates their maturation; disruptions of these pathways promote haematologic malignancies. We investigated the proteomic expression of AURKA, AURKB and GATA-1 in megakaryocytes to assess their dysregulation in MPN and transformation to MF.

Method: Archival, bone marrow trephine biopsies were obtained from 212 MPN patients and 304 normal controls (PathWest Laboratory Medicine, WA). MPN subtype, *JAK2/CALR/MPL* mutation status and platelet count were obtained for each case. Megakaryocytes were identified by CD61 immunostaining, with concurrent double immunostaining of AURKA, AURKB and GATA-1 biomarkers. The megakaryocyte percent positivity for each biomarker was assessed by light microscopy and evaluated according to MPN entity and mutation status using Kruskal-Wallis ANOVA and post hoc Dunn's tests. Expression levels were also compared with platelet counts (Spearman's correlation).

Results: AURKA positivity was greater in MPN (15.3%) than controls (6.4%, $p<0.0001$), and was highest in MF (17.6%). In contrast, GATA-1 levels were suppressed in MPN (73.1%) relative to controls (79.4%, $p<0.0001$), and lowest in MF (70.3%). GATA-1 expression showed a weak, positive correlation with platelet count, most notably among ET cases ($r=0.26$, $p=0.03$). AURKB expression did not vary between MPN entities or controls. *JAK2/CALR/MPL* mutation status did not affect any the megakaryocytic expression of any biomarker.

Conclusion: Pathobiological abnormalities in megakaryocytes may drive MF in MPN. AURKA overexpression and downregulation of GATA-1 may disrupt normal megakaryocyte endomitosis in MPN, and could be involved in their transformation to MF. These perturbations may induce pro-survival signals, driving megakaryocytic hyperplasia, excess polyploidisation and morphologic atypia in MF. Since AURKA was upregulated in MPN megakaryocytes, the use of AURKA inhibitors may represent an attractive therapeutic option.

HP122

Clinicopathological effects of Concurrent Myeloid Mutations detected via Next-Generation Sequencing in JAK2 positive Chronic Myeloid Neoplasms: a single centre experience.

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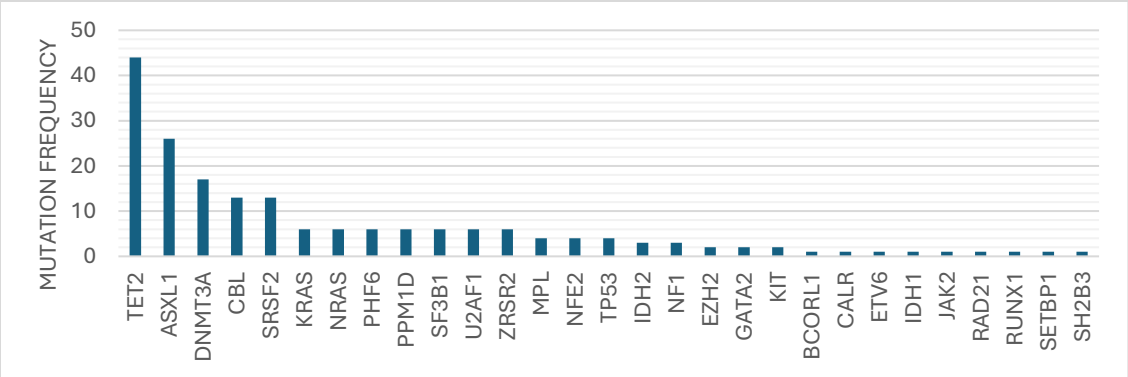
Aim: To determine if additional myeloid mutations are associated with clinicopathological differences in JAK2 mutated CMNs. To determine if molecular profiling of JAK2 mutated myeloproliferative neoplasms (MPNs) via NGS can assist with disease diagnosis or prognostication.

Method: Patients with a JAK2 mutation detected on myeloid NGS performed at a public hospital pathology service between June 2020 and December 2023 were reviewed. The NGS panel included all genes recommended by the ALLG subcommittee for MPNs and other genes involved in JAK-STAT signalling. Patients with chronic myeloid leukaemia or acute myeloid leukaemia were excluded. P-values were calculated using Microsoft Excel to perform ANOVA and the Chi-Square test.

Results: 126 patients were included. 74 patients (58.7%) had ≥ one additional myeloid mutation. A higher proportion of myelofibrosis (both primary and secondary) was seen in patients with any additional mutations compared to no additional myeloid mutations (26.9% compared to 61.9% for two additional mutations, $p < 0.001$). The mean age of JAK2 only patients was 58.2 years, one additional mutation 64.8 years and two additional mutations 74.3 years ($p < 0.001$). The mean haemoglobin of JAK2 only CMNs was 140 g/L, one additional mutation 127 g/L and two additional mutations 111 g/L ($p < 0.001$). The presence of at least one additional mutation was associated with a higher mean monocyte count; 0.59 x 10^9/L for no other mutations, 0.64 x 10^9/L for one additional mutation and 0.83 x 10^9/L for two additional mutations ($p < 0.001$). There was no statistically significant difference between JAK2 variant allele frequencies, total white cell count or platelet count between the 5 groups.

Conclusion: Additional mutations in epigenetic regulation genes are relatively common in JAK2 positive CMNs, and are associated with increasing age, a lower haemoglobin level, a higher monocyte count and myelofibrosis (both primary and secondary).

Figure 1: Total mutation frequency in all JAK2 mutated patients with ≥ 1 additional myeloid mutation (74 patients).



Myeloma

HP123

Myeloma-Associated Hemophagocytic Lymphohistiocytosis - A Case Study and Therapeutic Breakthrough with Anakinra

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Introduction: Hemophagocytic lymphohistiocytosis (HLH) is an immune syndrome with excessive inflammation and tissue destruction. HLH has only been only rarely described in association with multiple myeloma (MM) and results in high mortality. Anakinra, an interleukin-1 antagonist, has been used in secondary HLH in adults given safety and efficacy in limited studies. We report a unique case of anakinra successfully used for MM-associated HLH.

Case Presentation: A 78-year-old male suffered fatiguability, weight loss and anorexia. Assessment revealed hypercalcemia (4.20 mmol/L), acute kidney injury (creatinine 178 µmol/L), hyperferritinaemia, anaemia (Hb 104 g/L), and thrombocytopenia (platelets 81 x 10^9/L). There was widespread lytic disease and an IgA kappa paraprotein (12.3 g/L). MM was confirmed on bone marrow biopsy (R-ISS stage III). He was treated with cyclophosphamide, bortezomib, and dexamethasone. Hypercalcemia responded to intravenous fluids and pamidronate.

Although the paraprotein responded, severe pancytopenia ensued. The patient required near daily platelets and packed cells, despite withdrawal of cyclophosphamide. Ferritin reached 35,475 µg/L, and he developed bilateral pitting oedema and ascites. Echocardiography demonstrated severe systolic dysfunction despite no prior cardiac history. Suspecting HLH, further tests revealed bone marrow hemophagocytic activity, reduced NK cell function, elevated EBV DNA PCR (1030 copies/mL), and increased soluble CD25 (1583 pg/ml).

A decision was made to administer anakinra 100 mg subcutaneous daily, IVIG 1gm/kg for two days and dexamethasone 10mg/m^2 daily. HLH responded well and the patient was discharged. Three weeks later, there was near normalisation of FBC parameters with decreasing ferritin (2,790 µg/L). Anakinra was withdrawn and dexamethasone tapered. At six months, the patient is ambulatory, with myeloma in VGPR.

Conclusion: Our reported case highlights a rare and challenging diagnosis of MM-associated HLH. Successful treatment of our patient with anakinra illustrates a novel therapeutic option and raises the provocative question of the role of a chemotherapy-free approach to MM-associated HLH.

Table 1: Clinical, laboratory, and radiological features supporting HLH diagnosis according to HLH-2004 trial:

Criteria	Patient values	HLH-2004 reference values
Temperature	39.3°C	≥38.5°C
Spleen size	10.4 cm (Normal spleen)	Splenomegaly
Hemoglobin	71 g/L	<90 g/L
Platelets	6000/microL	<100,000/microL
Neutrophils	1000/microL	<1000/microL
Fibrinogen	100 mg/dL	<150 mg/dL
Fasting triglycerides	25.2 mg/dL	>265 mg/dL
Hemophagocytosis	Yes (bone marrow)	Hemophagocytosis in bone marrow, spleen, lymph node, or liver
NK cell activity	Reduced compared to the control	Low or absent NK cell activity
Ferritin	35,475 ng/mL	>500 ng/mL
sCD25 (soluble IL-2 receptor)	1583pg/ml	> 2 SD from the mean, mean=533pg/ml (242-1043)

NK=Natural killer, sCD25= Soluble CD25, SD=Standard Deviation.

HP124

B- Cell marker expression in (11;14) translocated multiple myeloma patients

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Multiple myeloma (MM) is a plasma cell neoplasia characterised by clonal proliferation of plasma cells that acquire genetic changes during B cell development.[1] The translocation of chromosomes 11 and 14 (t(11;14)), is a primary cytogenetic abnormality found in approximated 16% to 24% of patients with MM. Several studies have shown T(11;14) myeloma patients display an overexpression of B-cell associated genes and this subtype of myeloma often is associated with increased BCL-2 expression.

This aim of this study was to investigate expression of the B cell markers (PAX 5 and CD20) in the malignant plasma cell infiltrate in a cohort of patients with MM harbouring the t(11;14), and compare this expression to the patients not harbouring this translocation. In addition, we also explored the expression of BCL-2 and cyclin D1 in the malignant plasma cells in both cohorts. All markers were assessed using immunohistochemistry on bone marrow trephines done at diagnosis of myeloma.

A retrospective review of patients identified through medical records, found four patients with t(11;14) myeloma. We compared these patients to four patients without the translocation. These 5 patients had various chromosomal aberrations including gain of 1q, loss of TP53, deletions of 1p, t(14;16).

In the t(11;14) cohort, only one patient expressed CD20 in the myeloma infiltrate, however 3 out of 4 patients expressed PAX5, all expressed BCL-2 and cyclin D1. In contrast, in the non t(11;14) cohort, there was no expression of CD20, PAX 5 or CyclinD1 in all 4 patients. However, the malignant infiltrate in the non t(11;14) did express BCl-2 in all 4 patients. Overall, t(11;14) MM have a tendency for increased B cell marker expression but BCL-2 expression does not seem to be specific to the t(11;14) cohort.

Additional patients are being added to this study and will be presented on the poster presentation

HP125

POEMS Syndrome: A diagnostic conundrum with an excellent treatment outcome

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POEMS syndrome is a rare, chronic, disabling multisystem disorder characterized by peripheral neuropathy, organomegaly, endocrinopathy, skin changes and monoclonal plasma cells disorder. Its pathogenesis, while poorly understood, is associated with an overproduction of pro-inflammatory cytokines including vascular endothelial growth factor (VEGF). VEGF elevation is a major criteria for diagnosis and linked with pulmonary hypertension (PH).

We describe the case of a 55-year-old male who presented with lower leg weakness and numbness in the inner calf. He was diagnosed with chronic inflammatory demyelinating polyneuropathy and treated with IVIG infusions. His neuropathy worsened over three years, ultimately leading to bedridden stage. He had frequent admissions to hospital with dyspnoea and reduced exercise tolerance.

Serum electrophoresis revealed a low level IgA paraprotein of 2g/l and serum free light chains showed raised free lambda light chain at 125mg/l with normal ratio. This prompted evaluation for POEMS syndrome. He met both the mandatory criteria (polyneuropathy and monoclonal plasma cell proliferation) and had significantly elevated VEGF levels of 6800 ng/l(62-707 ng/l) satisfying one major criteria and several minor criteria (splenomegaly, peripheral oedema, pleural effusion, papilloedema, prominent skin involvement with acrocyanosis and subclinical hypothyroidism and hypogonadism). Bone marrow biopsy was unremarkable. Transthoracic echocardiogram showed normal ejection fraction, increased right ventricle pressures and elevated pulmonary artery pressures. He was treated with lenalidomide in combination with steroids leading to dramatic improvement in his mobility and decline in lambda light chain and VEGF levels. This response was consolidated with autologous stem cell transplant.

This case highlights the relevance of pulmonary hypertension in the diagnosis of this rare paraneoplastic condition with a reasonably good treatment outcome. POEMS should be considered when patients present with polyneuropathy unresponsive to treatment, along with plasma cell dyscrasia.

HP126

A case of severely debilitating inflammatory demyelinating polyneuropathy following bortezomib therapy for multiple myeloma

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Bortezomib is a proteasome inhibitor which is used as a cornerstone for multiple myeloma therapy both in the upfront and relapsed setting [1]. It has been well documented that bortezomib can be associated with a length-dependent, sensory axonal neuropathy. However, cases of inflammatory demyelinating neuropathy associated with bortezomib are extremely rare [2].

We report the case of a 68-year-old man treated for newly diagnosed multiple myeloma with Bortezomib who developed a severely debilitating progressive ascending sensory neuropathy. He presented with bilateral lower limb sensory loss after his first cycle of Bortezomib with subacute progression to multifocal upper limb motor and sensory weakness resulting in significant functional impairment.

Investigations including nerve conduction studies and neuromuscular ultrasound demonstrated slowed conduction velocities and prolonged F wave latencies as well as median and ulnar nerve enlargement respectively. These findings were consistent with a chronic inflammatory demyelinating polyneuropathy. Additional supportive findings include a sural nerve biopsy demonstrating mild reduction in myelinated fibres and active axonal degeneration with epineurial inflammation. Bortezomib was ceased and intravenous immunoglobulin therapy and high dose methylprednisone were commenced, which resulted in improvement in his symptoms.

This case highlights that inflammatory demyelinating polyneuropathy is a rare but possible complication of Bortezomib therapy which warrants consideration and further investigation with electrodiagnostic studies, lumbar puncture, and MRI of the nerve roots and plexuses. Increasing recognition is pivotal for prompt diagnosis and management of this potentially debilitating but treatable condition.

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HP127

An individualised bone-targeted exercise intervention for people with multiple myeloma: Study protocol of the MyeEx-Impact randomised controlled trial

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Aim: Focal bone lesions are one of the strongest independent predictors of poor prognosis for people with multiple myeloma (MM). Preclinical evidence has shown mechanical load-induced changes in bone cell activity through bone-targeted exercises can delay osteolytic bone metastases. Whether bone-targeted exercises can improve bone health in people with MM, where bone pain, lesions, and fractures are common, requires investigation. This trial aims to determine the effect of bone-targeted exercises on the bone health of people with MM.

Method: People with MM (n=78) will be randomised to an exercise (EX) or control (CON) group. The EX group will perform two supervised and one unsupervised session of individualised, bone-targeted exercise training weekly for 9 months. The CON group will continue receiving standard care and maintain their current physical activity levels. Primary (bone density and microarchitecture) and secondary (bone pain, quality of life, fatigue, physical function, psychological constructs, gut microbiome, disease response, and biomarkers of bone health, immune function, and disease progression) outcomes will be assessed at baseline, 3-, and 9-months. Adverse events, attendance, and adherence will be monitored and cost-effectiveness analysis performed. Linear mixed models will examine group by time differences for all variables of interest. Data will be analysed on an intention-to-treat basis. Semi-structured interviews will be conducted and coded to determine the experiences of participants and the perceived benefits and barriers of the intervention.

Conclusion: The findings of this study will identify whether bone-targeted exercise is safe, feasible, and can improve bone health in people with MM. Furthermore, this study will provide evidence of the effects of bone-targeted exercise on common MM- and treatment-related side-effects, as well as the potential mechanisms underpinning these effects. Collectively, this novel study will identify the potential role of exercise as an adjuvant therapy for the management of bone and psychosocial health for people with MM.

HP128

t(4;14) IGH::FGFR3 can be detected in circulating plasma cells by imaging flow cytometry

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Background: Translocations involving the *IGH* locus (14q32) are usually detected by fluorescence *in situ* hybridisation (FISH) on aspirated bone marrow. “Immuno-flowFISH” is a new flow cytometric method that can identify FISH abnormalities in immunophenotyped plasma cells in suspension to a level of 10^{-5}.

Aim: We investigated whether immuno-flowFISH could detect t(4;14) *IGH::FGFR3* in circulating plasma cells in myeloma.

Method: Blood mononuclear cells from 13 patients with myeloma were incubated with monoclonal antibodies CD38-BV605 and CD138-BV480 to identify plasma cells. After fixation and permeabilisation, DNA was denatured, FISH probes to *FGFR3*-Tamra (R) (4p16) and *IGH*-Fluorescein (G) (14q32) were added and hybridised overnight. Nuclei were counterstained (SYTOX) and cells acquired on an Amnis® ImagestreamX Mk II imaging flow cytometer. Data was analysed (IDEAS software) and FISH signals within the nuclei of CD38/CD138-positive cells quantified and digital images assessed.

Results: Between 45,976 and 328,249 cells were analysed of which 0.01-0.63% were CD38/CD138-positive. The t(4;14) translocation was identified in 2/13 cases. In one (0.01% plasma cells), 20% of cells had the balanced t(4;14) *IGH::FGFR3* FISH pattern (1R1G2F) and 60% 1R1G1F pattern indicating loss of a fusion signal from one derivative chromosome. The second case (0.63% plasma cells) showed multiple populations with 1R0G2F (30%), 1R1G1F (20%), 1R0G1F (12%), 0R0G2F (12%) and 1R1G3F (1%). There were 2 cases with numerical abnormalities of *IGH* and nine with normal diploid FISH signals for both probes.

Conclusion: Immuno-flowFISH was able to detect t(4;14) *IGH::FGFR3* in circulating plasma cells in 2 cases of myeloma, even when they made up only 0.01% of leucocytes. Both the balanced translocation and other defects (i.e. gains and losses of fusion signals and individual gene loci) could be detected. This highlights the sensitivity and specificity of immuno-flowFISH and detecting t(4;14) with clonal heterogeneity using blood-based testing.

HP129

Biallelic deletion of 1p32 in newly-diagnosed Multiple Myeloma (NDMM) patients associated with inferior outcomes: a report from the Myeloma and Related Diseases Registry (MRDR)

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Aim: Cytogenetic abnormalities involving chromosome 1 namely 1q21+ (gain and amplification) and del(1p32) are seen in 30% and 10% of NDMM respectively with the former incorporated into the second revision of the International Staging System. The prognostic impact of del(1p32) is still unclear in the era of modern frontline MM treatment (Lenalidomide + Bortezomib +/- Daratumumab).

Method: We retrospectively reviewed newly diagnosed MM patients from the MRDR across 2 Australian states and included patients who had FISH or SNP microarray testing for 1q21+ and del(1p32). High-risk cytogenetic abnormality (HRCA) was defined by the presence of del(17p), t(4;14), or t(14;16). We used Kaplan-Meier methods to compare PFS and OS in patients with and without del(1p32). Multivariate analysis (MVA) adjusted for other concurrent HRCA and 1q+.

Results: Of 607 patients included, 96 (16%) had del(1p32) (89 with monoallelic loss, 7 with biallelic loss). Median follow up was 22 months[m] (IQR 12-37). No differences in age, gender, year of diagnosis were seen. Patients with del(1p32) had higher rates of ISS-3 disease, concurrent HRCA and 1q+. Median PFS was shorter in patients with del(1p32) vs those without (21.4m vs 34.6m, HR 1.53; p=0.024). OS was inferior in patients with del(1p32) (3 year OS 57% vs 78%, HR 1.65; p=0.046). However on MVA, both lost significance after adjustment for HRCA and 1q+. Patients with biallelic loss of del(1p32) had significantly shorter PFS vs those with monoallelic loss (13.3 vs 21.4m, p=0.009). On MVA, median OS in patients with biallelic del(1p32) loss was significantly shorter vs those without del(1p32) (21.9m vs NR, HR 3.64; p=0.02).

Conclusion: The presence of del(1p32) is associated with high ISS and cytogenetic risk disease in NDMM. Although del(1p32) has been an independent prognostic factor in the era of modern therapies, we have failed to demonstrate this in our data set except in cases with biallelic loss which portends to dire survival outcomes.

HP130

Phospholipid composition drives ferroptosis sensitivity in Multiple Myeloma

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Aim: The aim of this project is to determine whether ferroptosis could be a valuable therapeutic strategy for Multiple Myeloma (MM). Ferroptosis is a recently characterised form of iron-dependent regulated cell death, characterised by the accumulation of oxidised membrane polyunsaturated phospholipids to lethal levels [1].

Method: A phospholipidomic analysis was conducted on 5 MM and 5 DLBCL cell lines using liquid chromatography mass spectrometry (LC-MS). MM cells were cultured with exogenous phosphatidylethanolamine lipids, ± the GPX4 inhibitor, RSL3. Cell viability was assessed using Annexin-V/propidium iodide staining and flow cytometry and changes in cell morphology assessed using an Incucyte live cell imaging system. The synthetic antioxidant, liproxstatin-1, was used to confirm ferroptosis-mediated cell death.

Results: Lipidomic analyses revealed that MM cells contain a significantly higher proportion of phospholipids containing monounsaturated fatty acids (MUFA) than DLBCL cells (34.5% higher). In contrast, DLBCL cells were found to contain significantly higher levels of PUFAs than MM cells (38.5% higher). Increasing the proportion of PUFAs in MM cells by addition of exogenous lipids induced spontaneous, dose-dependent cell death and sensitised the cells to RSL3 (Figure 1). Cell death was inhibited by liproxstatin-1, confirming ferroptosis as the mechanism of cell death. Increasing the proportion of MUFA in MM cells increased their resistance to the GPX4 inhibitor RSL3, comparable to liproxstatin-1.

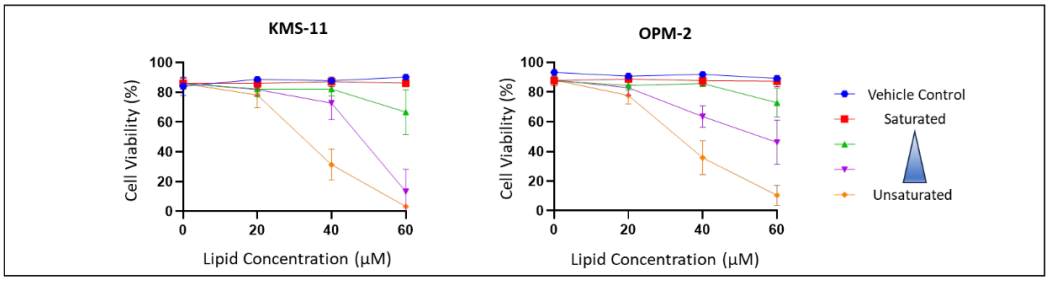

Figure 1. Ferroptotic cell death of KMS-11 (left) and OPM-2 (right) MM cells was dependant on the concentration saturation of the lipids added.

Conclusion: Our findings demonstrate a strong correlation between lipid composition and the sensitivity of MM and DLBCL cells to ferroptosis. Modulating the phospholipid profile of MM cells using exogenous lipids can both sensitise or desensitize MM cells to ferroptosis via GPX4 inhibition. Increasing the PUFA content of MM cells may represent a novel strategy for harnessing ferroptosis as a therapeutic approach in MM, particularly for patients with disease that is resistant to apoptosis-dependent regimens.

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HP131

Lenalidomide, bortezomib and dexamethasone (RVd) in patients with transplant eligible newly diagnosed multiple myeloma (TE NDMM): final analysis of the NSW Harmonisation study

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Aim: RVd induction is therapy standard of care for TE NDMM. Following the Pharmaceutical Benefits Scheme (PBS) listing, we proposed the harmonisation of RVd therapy in NSW. Dosing as per the GRIFFIN study protocol(1) was selected as there was a preference for a published regimen. We aimed to evaluate real world outcomes for this patient group.

Method: TE NDMM patients from nine NSW sites were registered into a REDCap database. Data was prospectively collected including disease characteristics, induction, transplant, consolidation and treatment response. Progression free (PFS) and overall survival (OS) were analysed using the Kaplan-Meier method.

Results: 173 patients were registered, 104 (60%) were male with a median age of 62 (range 38-74). At data cut-off, 168 patients had completed induction with a median of 4 cycles (range 1-9). Treatment was prematurely ceased in 13 (8%) due to toxicity. Dose modifications occurred most frequently with bortezomib (19%). Peripheral neuropathy was seen in 69 (42%) during induction, including 20 (12%) grade 2 and 2 (1%) grade 3 events. Hospitalisation occurred in 49 (29%) patients, mainly due to infection (18). 147/165 patients proceeded to mobilisation. High dose cyclophosphamide with filgrastim was utilised in 70%, and unplanned plerixafor reported in 12%. Mean CD34+ cell count was 9.17×10^6/kg with 3 patients collecting $< 2 \times 10^6$/kg. 139 (87%) proceeded to transplant. Consolidation was administered in 50%, at a median of 2 cycles (range, 0-4). At D+100, 106/138 (83%) achieved a response of $\geq$ VGPR. At a median follow up of 25 months, 2-year OS was 96% (Figure 1) and 2-year PFS 83% (Figure 2).

Conclusion: Harmonised RVd treatment was deliverable in the TE NDMM population with high rates of mobilisation. Peripheral neuropathy was a primary non-haematologic toxicity and hospitalisations frequent. In our real world population, treatment response rates and overall survival were comparable to reported trial outcomes(2).

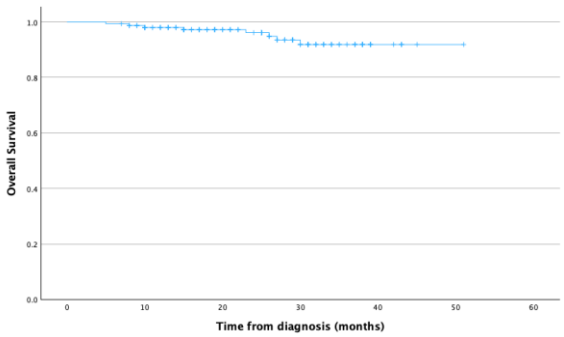

Figure 1 Overall survival

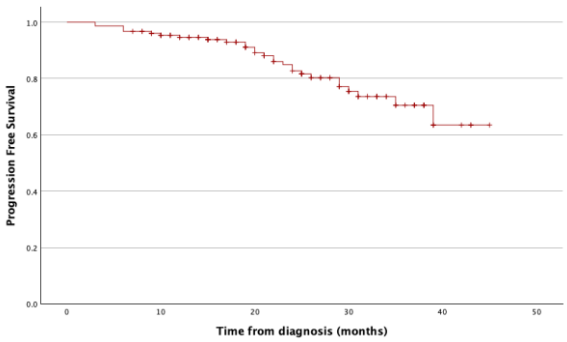

Figure 2 Progression free survival

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HP132

What determines initiation of immunoglobulin therapy in multiple myeloma patients? A longitudinal study using real-world administrative data

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Aim: To investigate factors that influence clinicians' decisions to initiate immunoglobulin (Ig) treatment in patients with multiple myeloma (MM).

Method: Patients' hospital admissions, including Ig therapy, were tracked from diagnosis until death or data cut-off date for patients diagnosed with MM in Victoria, Australia from 2007 to 2021. Non-parametric survival analysis using Kaplan-Meier method and Cox proportional hazard models were conducted to understand the role of previous serious infections and chemotherapy on the decision to initiate Ig.

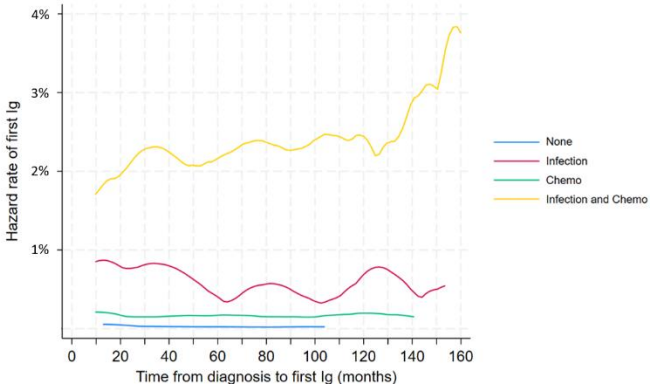
Results: Of all 10405 MM patients who started Ig (n=1492), 54% had experienced one or two infections within the last six months and 70% were undergoing chemotherapy by the time of first Ig.

Survival analysis revealed a higher likelihood of starting Ig when patients had infections or chemotherapy in the previous six months (8 out of 1000 per patient-month) compared to the time without such events (1 out of 1000 per patient-month). The initiation rate was the highest when both events occurred simultaneously, at 20 out of 1000 patients started Ig per month, with a marked upward trend over time (Figure 1).

A Cox regression highlighted that infection has a greater impact than chemotherapy in explaining clinicians' decision to initiate Ig, especially if it occurred within the previous month compared to earlier months. The duration of chemotherapy also impacted Ig initiation, and the effect varied depending on infection timings. When patients had been continuously undertaking chemotherapy for a longer period, the impact of infections on IVIg initiation rate was further strengthened.

Conclusion: This study identifies a positive association between infections/chemotherapy occurring in the previous six months and the likelihood of initiating Ig. Infections within the previous month exert the strongest effect on Ig initiation rate, alongside an interaction effect between infections and chemotherapy. These data support further research into understanding the optimal timing of initiating Ig.

Figure 1. Rate of initiating Ig in all MM patients



HP133

Clinical Trial versus Real-World Data: Comparison of Outcomes of Older Patients with Relapsed/Refractory Multiple Myeloma

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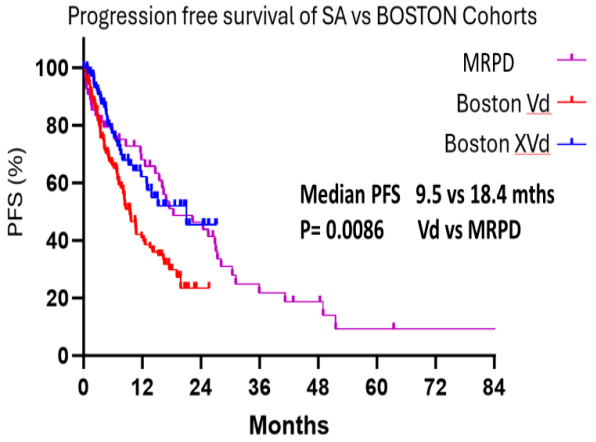
Aim: Randomised Controlled Trials (RCTs) provide gold standard evidence for safety and efficacy of new therapies. However, real-world data (RWD) is critical to review implementation of new therapies. RWD guides the optimal use of these therapies in under-represented populations in clinical trials, such as the elderly, and in patients with co-morbidities. Here, we report outcomes of a contemporaneous cohort of relapsed / refractory myeloma (RRMM) patients from South Australia (SA) and compared them to those treated in the BOSTON study, a phase 3, prospective RCT comparing the triplet Selinexor, bortezomib and dexamethasone (XVd) with Bortezomib and Dexamethasone (Vd).

Method: Patients with RRMM who had 1-3 prior lines of therapy (LOT) were identified from the SA Myeloma and Related Paraproteinaemias Database (MRPD). Data from patients enrolled in the BOSTON study were obtained for analysis. Baseline characteristics were summarised (ECOG, ISS, High risk cytogenetics and prior LOT). Differences in categorical and continuous variables were compared using Fisher's Exact-test and t-test respectively. Overall survival (OS) and progression free survival (PFS) were analysed using Kapler-Meier methods and compared using a log-rank test between groups.

Results: 55 SA patients were compared to 129 patients from BOSTON Vd arm. There were statistically significant differences seen with SA patients demonstrating higher ISS stage but having fewer lines of prior therapy which usually included ASCT. Whilst the SA cohort appeared to have superior PFS as compared with the BOSTON Vd patients (median PFS 18.4 vs 9.5 months, p=0.0086), there was no difference in the OS. PFS and OS were also similar in MRPD vs BOSTON XVd patients.

Baseline characteristics		BOSTON Vd (n=129)	SAMMD (n=55)	P value
AGE (median [IQR])		71 [67, 77]	72[69, 77]	0.088
ISS (%)	1	52 (40.3)	11 (21.1)	0.04
	2	57 (44.2)	29 (55.8)	
	3	20 (15.5)	12 (23.1)	
ECOG (%)	0	40 (31.0)	36 (69.2)	<0.001
	1	77 (59.7)	14 (27.0)	
	2	12 (9.3)	5 (9.6)	
HRCG risk (%)	NO	65 (50.4)	42 (76.4)	0.0011
	YES	64 (49.6)	13 (23.6)	
Prior LOT (%)	1	69 (53.5)	40 (72.7)	<0.001
	2	36 (27.9)	15 (27.2)	
	3	24 (18.6)		
Prior ASCT (%)	NO	105 (81.4)	7 (12.7)	<0.001
	YES	24 (18.6)	48 (87.3)	

Conclusion: This study highlighted the strength of using real-world evidence to complement RCTs, which will be important to inform future clinical practice, for relevance of newer therapies to patients excluded from RCTs.



HP134

Identifying an early response milestone to predict progression-free survival in relapsed/refractory multiple myeloma patients treated with carfilzomib

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Aim: Carfilzomib with dexamethasone is a backbone treatment for multiple myeloma. In relapsed/refractory multiple myeloma (RRMM), 77% of patients achieve a partial response and the median progression-free survival (PFS) is 18.7 months[1]. Depth of response without a specified timepoint has previously been shown to predict PFS[2]. This study aims to identify an optimal response milestone that is predictive of PFS, enabling therapy modifications prior to the development of progressive disease.

Method: This is a retrospective review of 94 RRMM patients treated with Carfilzomib/Dexamethasone in a single centre between 2016 to 2024. Clinical documentation and laboratory data were reviewed via MOSAIQ and eMR databases to determine patient characteristics, disease characteristics, and response. Log-rank analyses of Kaplan-Meier survival curves were performed using IBM SPSS Statistics.

Results: Preliminary analysis of 33 patients treated between August 2016 and May 2024 found a median PFS of 196 days (IQR 82.5-441.5). Very good partial response or better at cycle four significantly predicted greater PFS (n = 7/32; p = 0.013), with a median difference of 322 days (461 days v 139 days). Partial response or better at cycle four significantly predicted greater PFS (n = 20/32; p < 0.001), with a median difference of 330 days (410 days v 80 days). A 50% reduction in the difference of involved versus uninvolved serum free light chains regardless of M protein at cycle four compared to baseline was significantly associated with greater PFS (p < 0.001).

Conclusion: Failure to achieve partial response at cycle four of carfilzomib-based therapy may be a useful indicator of poor prognosis and a prompt for consideration of treatment modification.

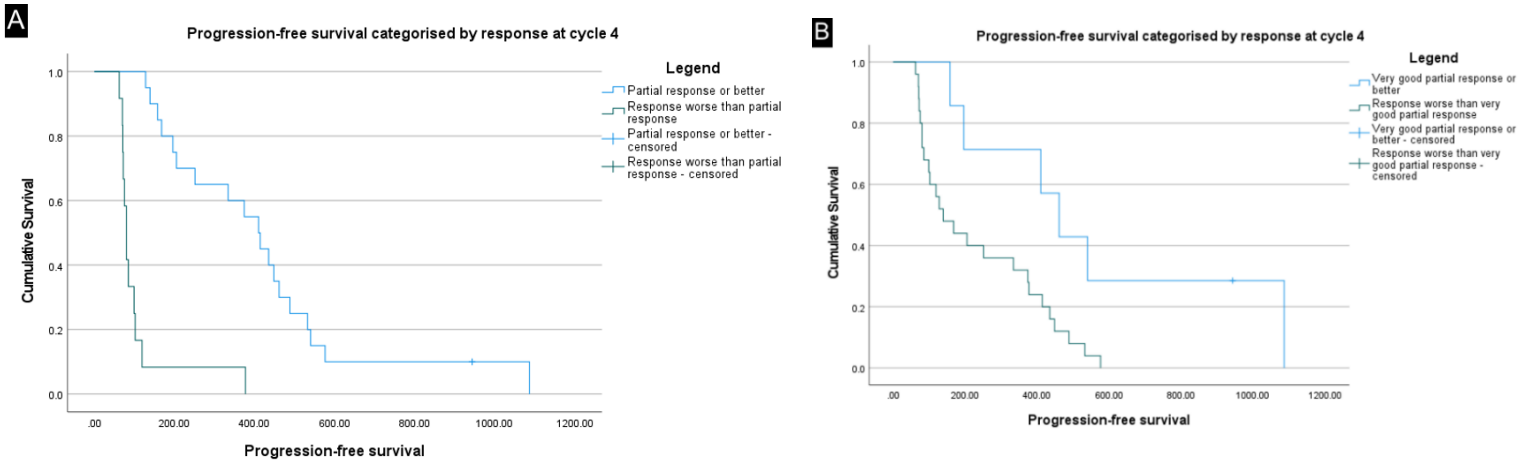

Figure 1: Kaplan-Meier plot of progression-free survival in relapsed/refractory multiple myeloma patients treated with carfilzomib/dexamethasone based on response at cycle 4 (A: Partial response or better; B: Very good partial response or better)

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HP135

Limiting Lenalidomide Exposure and Rescue Plerixafor can eliminate Haematopoietic stem cell (HPC) first collection failure in Bortezomib, Lenalidomide and dexamethasone (VRD) treated and transplant eligible Plasma cell Myeloma (MM) patients.

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Aim: A retrospective analysis to assess the timing of HPC collection prior to greater than 6-weeks of lenalidomide with or without the use of rescue plerixafor reduces primary HPC collection failures in MM.

Method: MM first attempt autologous HPC mobilisation were eligible included(n=111). Three sub-groups were assessed to compare HPC collection outcomes: Group 1-Pharmaceutical benefit scheme (PBS) plerixafor and >6-weeks weeks lenalidomide(n=45), Group2-Lenalidomide <6-weeks (n=29, PBS plerixafor and Group 3-Lenalidomide exposure <6-week, rescue plerixafor (n=37). Mobilisation was filgrastim 10mcg/kg 4 nights and pre-count day 5, cyclophosphamide mobilisation was at clinician discretion. In group 3, plerixafor was added if CD34 was <14x 10^6/L or the estimated first day CD34 yield was less than half the total target. In groups 1 and 2, no plerixafor rescue was used. Inability to proceed to apheresis or collection of <2-3x10^6/kg defined collection failure in all groups. Medians of demographic data and collection outcomes were compared using Kruskal-Wallis and group proportions with Fisher Exact test contingency tables.

Results: The 3 groups were comparable for demographic data, prior radiotherapy, response and collection targets. Cyclophosphamide for HPC mobilisation was more frequent in Groups 1 and 2 (p0.008). Primary HPC mobilisation failure was higher in group 1, 19/25, compared to group 2, 4/25 failures, (p0.011). The combination of rescue plerixafor and limiting lenalidomide exposure (group 3) reduced collection failures to zero (4/24 in group 2 vs 0/37 failures in group 3, p0.033). Median collection days were lower in group 3, at 1 day compared to group 2 (1.5 days) and group 1 (2 days) respectively, p0.0273. CD34 pre-counts on day 1 of collection were higher in group 3, 49x10^6/L compared to 29 x10^6/L in group 2 and 19x10^6/L in group 1, p0.00. Total CD34 yield was higher with plerixafor rescue(group3), than group 2 or 1, (7.44x10^6/kg, 6.04x10^6/kg, 5.18x10^6/kg respectively), p0.0019.

Conclusion: The combination lenalidomide exposure <6-weeks and the use of rescue plerixafor can eliminate HPC primary collection failure in MM, minimising collection days and treatment delays.

HP136

ALLG MM26/D1/AMN009 Novel Combinations for Orphan Myeloma (NORM) Platform Study

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[1]Department of Haematology, St Vincent's Hospital, Sydney, [2]Garvan Institute of Medical Research, [3]School of Clinical Medicine, UNSW Medicine and Health, [4]School of Translational Medicine, Monash University, [5]Department of Clinical Haematology, The Alfred Hospital, [6]Princess Alexandra Hospital, [7]Royal Adelaide Hospital, [8]Samsung Cancer Centre, [9]Taiwan National University Hospital, [10]Royal Prince Alfred Hospital, [11]Central Clinical School, Faculty of Medicine and Health, University of Sydney, [12]Concord Clinical School, Faculty of Medicine and Health, University of Sydney, [13]Concord Repatriation General Hospital, [14]St Vincent's Hospital, [15]National University of Singapore, [16]University of Melbourne

Aim: In multiple myeloma (MM), patients with non-measurable disease, renal impairment, extramedullary myeloma (EMM) or central nervous system (CNS) involvement are frequently excluded from clinical trials. We have established a multi-arm platform trial to explore novel agents in these patient groups.

Method: The NORM platform is recruiting patients with relapsed/refractory MM (RRMM) who meet the definition of one of the following strata: renal impairment (CrCl <30ml/min) (stratum A); non-measurable disease (stratum B); EMM (stratum C) and CNS disease (stratum D). Novel therapies can be trialled across one or more strata.

The primary objective is to determine efficacy of the novel agent/s in each stratum, defined as the proportion of patients who achieve ≥partial response (IMWG), at any time up to cycle 4. In stratum B, PET will be used for response assessment[1]. In stratum D, primary CNS lymphoma response criteria will be utilised[2]. Secondary endpoints include progression free and overall survival, safety and quality of life.

In each stratum, efficacy will be investigated using a dual-criteria, Bayesian, Proof-of-Concept (PoC) approach with a minimally informative prior for the response rate.
The first treatment domain is selinexor, pomalidomide and dexamethasone (SPd)[3]. Forty patients will be recruited into Strata A, B and C and twenty into Stratum D. PoC for efficacy of SPd in a stratum will be claimed if 2 criteria are met: Stratum A or B, observed ORR ≥40% and posterior probability (PP) that the true ORR is ≥30%, given the data, is ≥0.90 and in stratum C or D, observed ORR ≥30% and PP(true ORR ≥20% | data) ≥ 0.90.

Results: Accrual ongoing.

Conclusion: The PoC platform study design allows rapid assessment of novel therapeutic regimens, using one master protocol, in patient populations typically excluded from clinical trials. We aim to demonstrate efficacy and safety of these agents in these subgroups of MM patients.

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HP137

Biomarker correlates of response to Ciltacabtagene Autoleucel (cilta-cel) in patients with Relapsed or Refractory multiple myeloma (RRMM) from CARTITUDE-1, a Phase 1b/2 open-label study, at the ~3 year follow-up

Montes de Oca R[1], Wang F[2], Hao M[2], Smirnov D[1], Zhao H[1], Gormley M[1], Chang S[1], Zudaire E[1], Foulk B[1], Patel J[1], Wu D[1], Davis C[1], Boominathan R[1], Zhu J[3], Lau O[1], Calara-Nielsen K[1], Rajpurohit Y[1], Madduri D[4], Jagannath S[5], Lin Y[6], Cohen A[7], Plaks V[1]

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Aim: Cilta-cel demonstrated outstanding ORR (97.9%) and duration of response (DOR) in patients with RRMM after ≥4 prior lines of therapy; however, relapse still occurs. Biomarkers associated with durable response and acquired resistance remain undetermined. We present updated correlative data from CARTITUDE-1.

Method: At the ~3 year follow-up (October 2022 data cutoff), 97 patients had received a single infusion of cilta-cel (median 0.71 $x10^6$ cells/kg [range 0.52 $x10^6$–0.94 $x10^6$]). Drug product (DP), baseline and on-treatment whole blood and bone marrow samples were analysed by methods including flow cytometry, MSD immunoassays, Cellular Indexing of Transcriptomes and Epitopes by Sequencing (CITE-seq) and TCR sequencing.

Results: In CARTITUDE-1, the DP contained both transduced and non-transduced T cells; the CAR+ fraction had an approximate 1:1 central memory/effector memory T-cell (T_{cm}/T_{em}) ratio pre-infusion (median 33% and 37%, respectively).

Median DOR[a]	33.9 months (95% CI 25.5–NE)	
Median PFS[a]	34.9 months (95% CI 25.2–NE)	
DP Median transduction efficiency	16% (range 5–32%)	
DP CD4:CD8 ratio	**Median frequency of CAR+CD4+**	**Median frequency of CAR+CD8+**
	12% (range 2–28%)	6% (range 2–20%)
Median CAR+ T cell peak concentration (C_{max}) post-infusion	C_{max} 730 cells/µL (range 3–13805 cells/µL); reached between days 12–14 post-infusion	
Median CAR+ T cell persistence (T_{last}) in circulation	100 days (range 20–912 days)	
Proportion of cells with a T_{cm} phenotype at C_{max}	**CAR+CD4+**	**CAR+CD8+**
	Median 95% (range 62–99.5%)	Median 96% (range 33–99.7%)

NE, not estimable. [a]Lin Y et al, ASCO 2023.

High ORR and DOR were achieved despite variable CAR-T cell expansion and lack of detectable CAR-T cell persistence over time. CD4:CD8 ratio (based on % of CAR+ cells) at C_{max} was 0.29, demonstrating CAR+CD8+ T cell preferential expansion, further, there was a predominant T_{cm} phenotype. CITE-seq analyses showed DP characteristics such as high CD8+ stem-like and low CD4+ Treg-like phenotypes in the CAR+ T cell compartment associated with longer PFS. B-cell maturation antigen (BCMA) expression on bone marrow plasma cells was prevalent, highly variable and did not associate with best response or PFS. High ORRs were observed in patients with high-risk cytogenetics, high tumour burden, or baseline

plasmacytomas. Patient-intrinsic characteristics associated with inflammation (CRP, ferritin, neutrophils, pro-inflammatory cytokines) correlated with shorter PFS.

Conclusion: Correlative analyses suggest an emerging DP and PK profile, plus baseline patient-intrinsic and disease characteristics to understand cilta-cel's outstanding efficacy. These investigations help identify markers of response to cilta-cel and may lead to CAR-T cell design or manufacturing strategies that enhance DP characteristics and thus clinical efficacy.

HP138

Retrospective Observational study of the Incidence and Rate of acquisition of High-risk secondary Cytogenetic Abnormalities in Relapsed multiple myeloma at a state-wide Cytogenetics servi

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Aim: Recent publications[1,2,3] have demonstrated poor responses to standard myeloma therapy, poorer prognosis, and shortened progression-free-survival in patients with one or multiple of del1p, gain/amp1q and/or del17p. This study aims to assess the incidence and rate of acquisition of these lesions.

Method: Retrospective observational study of patients with biopsy-proven relapsed plasma cell myeloma who had cytogenetic testing sent to a state-based reference laboratory for analysis between 01/09/2020-01/09/2023. IGH break-apart, and if indicated, dual fusion FISH probe testing was performed on all new diagnosis specimens, whilst CDKN2C/CKS1B and TP53/NF1 dual colour FISH probe testing was performed on both new diagnosis and relapse specimens. 110 patients had this testing performed twice or more. Quantification of incidence, rates, and clone sizes of abnormalities was performed, together with statistical analysis of TBT using two-sample, two-tail unequal variance T-testing.

Results:

	Incidence (n / %)		TBT (mean, median, IQR1-3) months	TBT P-value: N vs _ (α 0.05)	Clone size (mean +/- SD)
Total		110 / 100.00%	36.4, 33.3, 27.6 (21.5-49.1)		
Normal		37 / 33.6%	34.8, 32.4, 26.5 (20.7-47.1)		
*Del1p	AD	14 / 12.7%	44.2, 41.8, 21.3 (36.3-57.6)	0.07	76.0 +/- 26.1
	NAR	5 / 4.5%	45.1, 47.2, 30.8 (20.9-51.7)	0.49	62.6 +/- 34.9
*Gain1q	AD	49 / 44.5%	35.1, 33.3, 27.1 (22.2-49.3)	0.94	69.3 +/- 25.4
	NAR	11 / 10.0%	33.4, 22.0, 27.0 (19.0-46.0)	0.97	33.4 +/- 23.0
*Amp1q	AD	2 / 1.8%	32.1, 32.1, 4.7 (29.8-34.5)	0.69	85.5 +/- 2.1
	NAR	2 / 1.8%	51.3, 51.3, 18.0 (42.3-60.3)	0.53	59.5 +/- 53.0
*Del17p	AD	12 / 10.9%	38.7, 36.5, 25.6 (24.6-50.2)	0.21	63.3 +/- 30.5
	NAR	10 / 9.1%	48.8, 50.0, 29.0 (36.9-65.9)	0.07	71.4 +/- 26.0
*Including this abnormality					
Del1p / Gain1q	AD	8 / 7.3%	42.4, 41.8, 27.7 (32.2-59.8)	0.29	84.4 +/- 15.1 / 84.0 +/- 7.3

Del1p / Del17p	AD	4 / 3.6%	47.2, 43.3, 17.2 (36.7-53.9)	0.18	73.0 +/- 33.8 / 69.8 +/- 31.6
Gain1q / Del17p	AD	6 / 5.5%	29.1, 26.5, 21.8 (17.2-39.0)	0.44	66.5 +/- 25.9 / 50.2 +/- 30.6
AD – at diagnosis, N – normal, NAR – new at relapse, SD – standard deviation, TBT – time between tests					

Conclusion: Gain1q, del1p, del17p and amp1q were all seen at diagnosis, in decreasing frequencies, respectively. These lesions were also newly detected at relapse, with gain1q and del17p the most commonly acquired. There was no statistically significant TBT comparing normal patients and those with any of the high-risk abnormalities. Further analysis of the patient subgroups and correlation with their treatment history may elucidate why patients with high-risk findings had similar time between tests with their unaffected counterparts.

HP139

Real-world treatment duration to front line multiple myeloma therapies in transplant ineligible Australian patients.

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[1]Johnson & Johnson, [2]Model Solutions Pty Ltd

Aim: Lenalidomide-dexamethasone (Rd) was reimbursed in Australia on the Pharmaceutical Benefits Scheme (PBS) for the treatment of newly diagnosed transplant ineligible multiple myeloma (ND TIMM) in February 2017 and was followed by bortezomib-lenalidomide-dexamethasone (VRd) in June 2020. There are limited other treatment options available for ND TIMM patients. The objective of this study was to determine if the addition of newer options, such as VRd, onto the PBS has improved treatment duration in ND TIMM patients.

Method: This was a retrospective observational study of real-world evidence from Australia using the randomly selected 10% PBS dataset. We evaluated the treatment duration of patients starting VRd (n=153) and Rd (n=109) treatments in TI NDMM patients for the period June 2020 to January 2024 using the Kaplan-Meier (KM) method. The Cox proportional hazard models were used to assess differences, along with restricted mean survival time where appropriate, adjusting for age and gender.

Results: Australian TI NDMM patients receiving VRd (median 14 months) at first-line (1L) did not show a statistically significant (p=0.13) difference in treatment duration compared to those receiving Rd (median 11 months). This is further supported by a restricted mean survival analysis at Month 43 (p=0.42) which does not require the proportional hazard assumption.

Conclusion: These results show that in the real-world setting, Australian TI NDMM patients receiving VRd show the same duration on treatment compared to patients receiving Rd, reflective of what was observed in the elderly population (65+ years) in the SWOG S0777 clinical trial[1]. As treatment duration is strongly correlated with improved outcomes and survival[2], this result may highlight an unmet clinical need in this Australian population, especially considering that new and more effective therapies are available in other markets.

References:

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HP140

Evolving real-world treatment duration outcomes at first relapse in Australian patients with multiple myeloma.

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Aim: There is no standard algorithm for the treatment of patients with relapsed and/or refractory multiple myeloma (RRMM), and although new treatments have recently been made available on the Pharmaceutical Benefits Scheme (PBS) for Australian patients, there is limited data on how these have influenced clinical outcomes and other measures related to efficacy such as treatment duration. The aim of this study was to examine weather there has been an improvement in second-line (2L) treatment duration in Australian MM patients since daratumumab-bortezomib-dexamethasone (DVd) was listed on the PBS.

Method: This was a retrospective observational study of real-world evidence from Australia using the randomly selected 10% PBS dataset. We evaluated the treatment duration of patients receiving any 2L MM therapy available on the PBS during two timepoints: from January 2018 to December 2020 and from January 2021 (when DVd became available on the PBS) to December 2023, using the Kaplan-Meier method. The Cox proportional hazard model was used to assess differences, adjusting for age, gender, first-line (1L) therapy received, early progression from 1L therapy (<18 months), and lenalidomide refractory status.

Results: Patients receiving 2L MM treatments from January 2021-December 2023 showed a significant risk reduction ($p<0.001$) in treatment discontinuation (57% unadjusted, 62% adjusted) vs the period January 2018-December 2020. The median treatment duration was 2.5-fold longer for these patients (14 months) compared to 5.6 months.

Conclusion: These results show that in the real-world, Australian RRMM patients who have received treatments between January 2021 to December 2023, when DVd was made available on the PBS, have a longer duration on treatment compared to those who received treatments between January 2018 to December 2020. As treatment duration is strongly correlated with improved outcomes and survival[1], this result indicates that new therapies are having a positive impact on real-world indicators of efficacy in Australian RRMM patients.

References:

[1]Hari P, Romanus D, Palumbo A, et al. Prolonged Duration of Therapy Is Associated With Improved Survival in Patients Treated for Relapsed/Refractory Multiple Myeloma in Routine Clinical Care in the United States. Clin Lymphoma Myeloma Leuk. 2018;18(2):152-160. doi:10.1016/j.clml.2017.12.012

HP141

The use of Mass Spectrometry in the diagnosis and monitoring of plasma cell dyscrasia

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Background: Paraprotein detection by electrophoresis, immunofixation and free light chain assays is the gold standard in diagnosis and monitoring of plasma cell dyscrasia. However, these methods have limitations in analytical sensitivity, interference from endogenous and exogenous proteins, and cannot characterise post-translational modifications. Mass spectrometry methods have been shown to overcome these issues. However, additional work and optimisation are needed to implement these methods in the diagnostic laboratory.

Aim: To demonstrate the clinical utility of mass spectrometry methods in plasma cell dyscrasia.

Method: Serum samples of myeloma patients, miscellaneous subjects (MGUS, lymphoid malignancies, nonmalignant disorders), and healthy controls were collected prospectively. Pre and post treatment samples of myeloma patients were collected. Results have been compared with protein electrophoresis and serum free light chain assays.

Results:

Case 1: MGUS IgA kappa
Free-lite assay : serum free kappa 104.00 mg/L, free lambda 8.98 mg/L
N-Latex assay : serum free kappa 72.70 mg/L, free lambda 14,600.00 mg/L

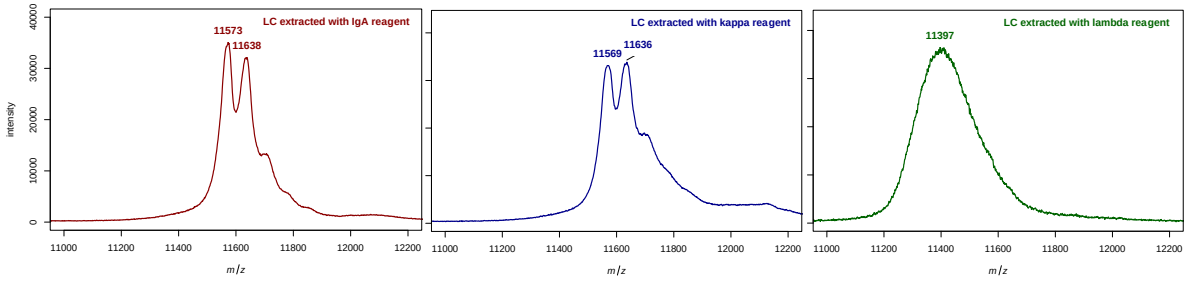

Figure 1: MS is useful in discerning the discrepancy between N latex and free lite assays. Serum free lambda is spuriously high due to interference. There is no monoclonal lambda light chain.

Conclusion: MS is more sensitive and specific than conventional laboratory methods for monoclonal gammopathy. It improves the diagnostic accuracy of paraproteinaemia and is useful in detecting oligo secretory, non-secretory disease and minimal residual disease. It resolves interference issues encountered by standard protein electrophoresis and free light chain assays.

HP142

Optimising blood cancer care by developing tools to evaluate adherence to Optimal Care Pathways

Chauhan A[1], Janowski W[2], Boshier C[2], Milliken V[2], Reardon B[2], Simpson J[3], Smith M[4], Pinto C[4], Shaw W[4], Enjeti A[2], Harrison R[1]

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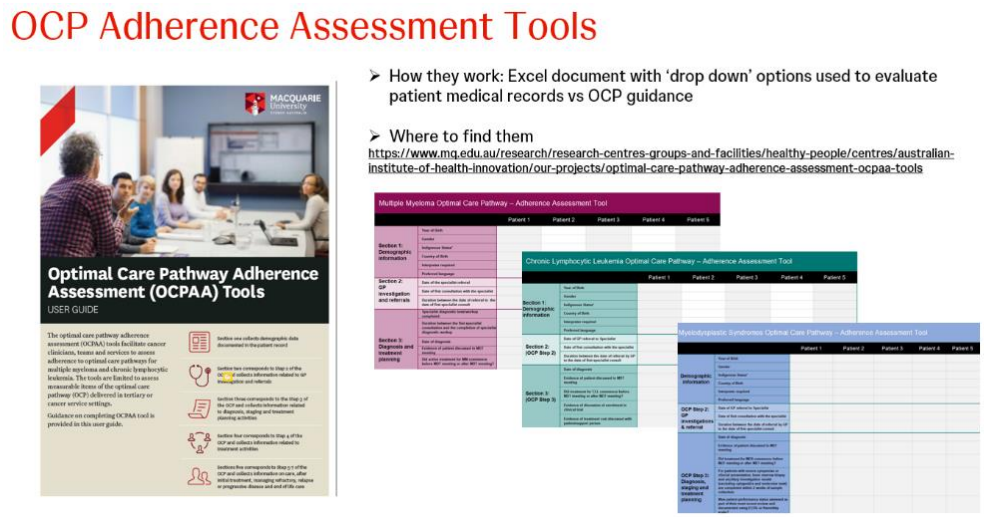
Aim: Optimal Care Pathways (OCPs) have been embedded in the Australian Cancer Plan as national standards of consistent, safe, high-quality, and evidence-based care[1]. Adherence to OCPs can support consistent delivery of best practice care to patients with cancer[2,3]. The aim of this project was to develop the OCP Adherence Assessment Tool (OCPAAT) for three blood cancer types so haematology teams can assess adherence to OCP recommendations.

Method: A team-based approach in partnership with various stakeholders (health service managers, cancer therapy providers, academics and health professionals) was used to develop the three OCPAATs. A multistage iterative process was employed that consisted of a desktop review, identification of items for inclusion and expert group consensus through series of surveys and meetings to determine the items for inclusion in the Tools.

Results: The chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS) and multiple myeloma (MM) OCPAAT (Figure 1) have been published, with a user guide, on the Australian Institute of Health Innovation (AIHI) website. The Tools have been evaluated in one cancer service to determine their practical application. User feedback indicates the Tools are easy to use and can assist in identifying variations from OCP recommendations and areas for improvement.

Conclusion: The OCP Adherence Assessment Tools for CLL, MDS and MM provide cancer services with a mechanism to identify areas for improvement. The next steps for the Tools are to validate their use across different cancer services. The process to develop these Tools can be used to develop OCP Adherence Assessment Tools for other cancer types.

Figure:



HP143

Cardiac Plasmacytoma: A rare manifestation of multiple myeloma

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Cardiac plasmacytoma is an extremely rare heart tumour that may arise as a primary cardiac lesion (solitary extramedullary plasmacytoma), or as a secondary manifestation of multiple myeloma. We report a case of biopsy proven cardiac plasmacytoma in the context of newly diagnosed multiple myeloma.
Case report:

Our patient is a 73-year-old woman who was diagnosed with monoclonal gammopathy of undetermined significance (MGUS) at 48 years of age. After over 2 decades of stability there was a sudden increase in both her IgG lambda paraprotein and her lambda free light chains prompting further investigations. A CT skeletal survey showed no evidence of myeloma-related bone disease but reported a mass lesion involving her heart. Further imaging demonstrated a bulky mass centred at the right atrium extending superiorly up to the cavoatrial junction and inferiorly into the IVC, as well as a pericardial effusion. A biopsy of the mass established the diagnosis of a lambda-positive plasma cell neoplasm. Her bone marrow biopsy confirmed the diagnosis of multiple myeloma demonstrating an infiltrate of lambda-positive plasma cells (31%). FISH studies demonstrated the presence of several high risk abnormalities [gain of 1q, TP53 deletion, t(14;16)]. She commenced therapy with lenalidomide, bortezomib and dexamethasone which resulted in a rapid improvement in her paraprotein, the cardiac mass and her pericardial effusion.

Conclusion: A review of the literature regarding cardiac involvement by plasma cell neoplasms reveals that the majority of cases (67%) have a history of a plasma cell dyscrasia with primary plasmacytomas accounting for only 12% of the cases. Cardiac plasmacytomas demonstrate a predilection for the right atrium (42%) and patients typically present with dyspnoea, orthopnoea and chest pain due to a pericardial effusion (>80%) with some reports describing cardiac tamponade, heart failure and pleural effusions at diagnosis. Most reports describe a poor prognosis with over half of the patients dying with 15 months of diagnosis.
References:

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HP144

Real world retrospective analysis of Daratumumab therapy for relapsed or refractory multiple myeloma

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Monoclonal antibody therapy is a key component of management in relapsed or refractory multiple myeloma (RRMM). Daratumumab is a key component of therapy that is available as 2nd line therapy under the current PBS schedule. We performed a retrospective review at a single tertiary centre of Daratumumab use in RRMM in order to report PFS and OS in a real-world setting from 2018 to 2023.

Results: Baseline characteristics are summarised in table 1. There were a total 53 patients. 58% had 1 prior line of therapy, 44% had prior autologous stem cell transplantation. Adverse cytogenetics as defined by IMWG[1] were present in 59% of cases. 75%(40) received daratumumab as combination therapy, majority in combination with bortezomib and dexamethasone(65%, 34). Response rates are summarised in table 2 with a combined overall response rate of 35%. Median PFS was 13 months(Figure 1A). There was no difference in PFS for those with high risk cytogenetics(HR 2.28,95% CI0.98to5.29, p=0.055). PFS was significantly longer in those who had only 1 prior line of therapy(HR 4.29, 95% CI1.94to9.47, p=<0.001) with median PFS not reached(Figure 1C). Median OS in all patients was 27 months(Figure 1B). OS was significantly lower in those who had high risk cytogenetics (HR 2.8, CI 95% 1.0to7.8, p=0.049) as well as in those who had only 1 prior line of therapy (HR 10.79, 95% CI3.12to37.27, p=<0.001)(Figure 1D). There was no difference in PFS or OS in patients who had received prior autologous stem cell transplantation.

Discussion: Comparison to previously published data of DVd in RRMM, our cohort had a higher median age(74 compared with 64), lower number of patients with prior autologous stem cell transplant(44% versus 95%) and higher number of high risk cytogenetics(54% versus 22%). PFS was lower in cohort(13 months versus 16.5 months) as well as combined response rate(63% versus 35%).[1]

Table 1: Baseline Characteristics

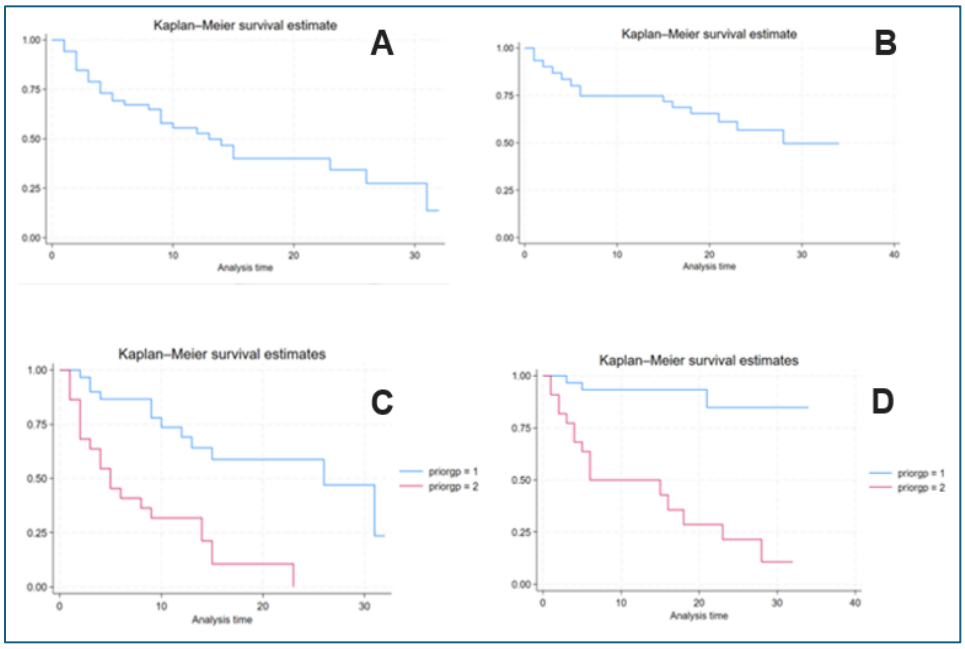
Age (median)	**74 (41 to 74)**
Gender (female)	19 (37%)
Prior lines	
1	30 (58%)
2	9 (17%)
3	7 (13%)
4	2 (4%)
5	4 (8%)
Disease	
IgA kappa/lambda	8 (15%)
IgG kappa/lambda	24 (46%)
Plasma cell leukaemia	2 (4%)
Plasmacytoma/non-secretory	1 (2%)
Light chain	17 (33%)
Cytogenetics: IMWG High Risk +1q, t(14:16), t(14:20), t(4:14), del17p	29 (59%)
Autologous stem cell transplant	23 (44%)
Prior Treatment	
Lenalidomide	19 (37%)
Bortezomib	43 (83%)

Table 2: Response Rates

CR	VGPR	PR	Stable	Progressive
10% (5)	25% (13)	42.3% (22)	2% (1)	23% (12)
35% Combined response				

Conclusion: Further data is needed in real world settings to better evaluate daratumumab, particularly with newer studies using it in the upfront setting triplet and quadruplet combinations.

Figure 1: (A) Median PFS (13 months); (B) Median OS (27 months); (C) PFS and (D) OS for those who had 1 prior line of therapy versus >1



References: (1) Mateos MV, Sonneveld P, Hungria V, Nooka AK, Estell JA, Barreto W, Corradini P, Min CK, Medvedova E, Weisel K, Chiu C, Schecter JM, Amin H, Qin X, Ukropec J, Kobos R, Spencer A. Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Patients With Previously Treated Multiple Myeloma: Three-year Follow-up of CASTOR. Clin Lymphoma Myeloma Leuk. 2020 Aug;20(8):509-518.

HP145

Outcomes with Selinexor, Bortezomib and dexamethasone (SVd) in patients with relapsed refractory multiple myeloma (RRMM): Regional subgroup analysis of the Phase 3 BOSTON trial

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Aim: To understand outcomes of SVd treatment in patients from countries with similar standards of care (Regions 1-3; R1-3), with reference to Region 4 (R4) and the intention-to-treat (ITT) population.

Region	Countries
1	Canada & Unites States
2	Australia, Austria, Belgium, France, Germany, Israel, Italy, Spain & United Kingdom
3	Czech Republic, Greece, Hungary & Poland
4	Bulgaria, India, Romania, Russian Federation, Serbia & Ukraine.

Table: Countries included in the BOSTON trial

Method: A retrospective, post-hoc, subgroup analysis of the SVd cohort in R1-3 was conducted to assess differences in outcomes across subgroups with reference to R4 and the ITT population.

Results: 263 pts from R1-3 were randomized in the BOSTON trial:126 to SVd, 137 to bortezomib and dexamethasone (Vd). The overall treatment effect for SVd vs. Vd in R1-3 was consistent with the ITT population, with a favourable trend: Hazard Ratio of 0.54 for progression free survival (PFS) and odds ratio (OR) of 2.29 for overall response rate (ORR), in reference to a HR of 0.70 and OR of 1.96 for the ITT population, respectively. There were some differences in baseline characteristics, prior treatments and selinexor exposure observed for SVd pts across regions.

Efficacy in the SVd cohort from R1-3 included an ORR of 78% and a mPFS of 16.6m (Figure). The mPFS in clinically relevant subpopulations from R1-3 receiving SVd was 21.0m in ≥65 years of age and 12.2m in lenalidomide-refractory. The overall adverse event profile for the SVd cohort in R1-3 was also consistent with the overall population, but there was a higher incidence of sepsis and new onset cataracts in R4.

Conclusion: Results are reflective of a diverse and global RRMM population. This analysis highlights the importance of better understanding regional differences and the potential impact on clinical outcomes, and supports the need for patient education, close monitoring, supportive care and dose modifications to ensure optimal outcomes.

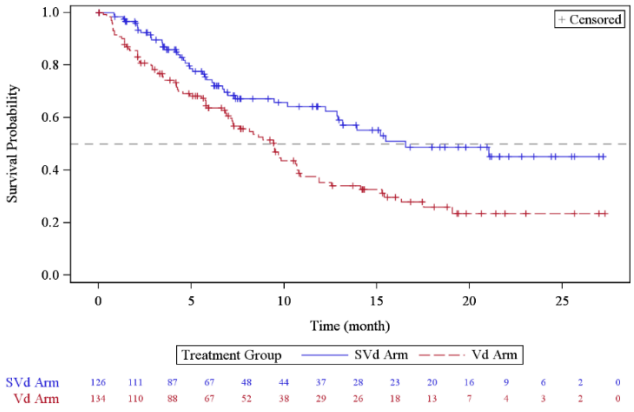

Figure: Region 1-3 PFS Kaplan Meier Curves, SVd vs Vd

HP146

Patient-reported outcomes (PROs) in the CARTITUDE-4 study of ciltacabtagene autoleucel (cilta-cel) vs standard of care (SoC) in patients with lenalidomide refractory multiple myeloma (MM) after 1–3 lines of therapy

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Aim: In the Phase 3 CARTITUDE-4 trial (NCT04181827), cilta-cel significantly improved PFS (hazard ratio [HR], 0.26; P<0.0001) and increased the rate and depth of response vs SoC. Here, we present adjusted comparisons of PROs.

Method: 419 patients with lenalidomide-refractory MM and treated with 1–3 prior lines of therapy were randomised (intent-to-treat [ITT]) to receive cilta-cel (n=208) or SoC (n=211). All patients were administered the EORTC QLQ-C30, EQ-5D-5L, and MySIm-Q until disease progression. PRO compliance was calculated as the number of patients who provided PROs divided by the number expected. Mixed-model for repeated measures analyses were performed on the ITT population to analyse changes from baseline for each arm (including baseline PRO score and prognostic characteristics as covariates to adjust for confounders). Time to symptom worsening (clinically meaningful increase [≥0.5 standard deviation of pooled baseline values] with no reduction in MM symptoms) was assessed using the Kaplan-Meier method.

Results: 99 cilta-cel patients and 66 SoC patients had baseline and 12-month PRO assessments, representing data prior to progression (clinical cut-off November 1, 2022). PRO compliance was 100% at baseline, decreasing to 74% and 81% in cilta-cel and SoC patients at month 12, respectively. Patients reported improved functioning and symptom reduction from baseline with cilta-cel, while PRO scores in the SoC arm trended towards worsening or lower degrees of improvement from baseline for most domains (**Table**). On the MySIm-Q total symptom scale, the median time until MM symptom worsening with cilta-cel was 23.7 months (95% CI, 22.1–not estimable) and 18.9 months (95% CI, 16.8–not estimable) with SoC (HR, 0.42).

Table: Least squares (LS) mean of change from baseline to month 12 in PROs

Mean change (95% CI)			Cilta-cel (n=99)	SoC (n=66)
EORTC QLQ-C30	**Global health status**		10.1 (7.0, 13.1)[a]	–1.5 (–5.3, 2.3)
	Functional scales	Cognitive	0.5 (–2.4, 3.5)	–7.5 (–11.2, –3.9)
		Emotional	9.5 (6.6, 12.5)	2.2 (–1.3, 5.7)
		Physical	6.5 (3.8, 9.1)	–2.1 (–5.0, 0.7)
		Role	7.7 (3.7, 11.7)	–1.7 (–6.3, 2.9)
		Social	6.1 (2.1, 10.0)	–0.1 (–4.2, 4.0)
	Symptom scales	Fatigue	–9.1 (–12.4, –5.8)	2.8 (–1.4, 7.0)
		Nausea/vomiting	–1.2 (–3.1, 0.7)	0.6 (–1.4, 2.7)
		Pain score	–10.2 (–14.0, –6.5)[a]	–3.9 (–7.9, 0.2)
EQ-5D-5L	Visual analogue scale (VAS)		8.0 (5.2, 10.7)[a]	1.4 (–1.9, 4.7)[b]
MySIm-Q	Total symptom subscale		–1.8 (–0.27, –0.10)	0.17 (0.06, 0.27)[b]
	Total impact subscale		–0.41 (–0.53, –0.29)	0.01 (–0.13, 0.14)[b]

A higher score indicates better health on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30; 100-point scale) global health status and functional scales and the EuroQoL 5-Dimension 5-Level (EQ-5D-5L VAS; a self-rated health score; 100-point scale); a >0 point change in score from baseline indicates improvement. A higher score on the Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q; 5-point scale) or EORTC QLQ-C30 symptom scales indicates greater symptom severity, and a higher score on the MySIm-Q impact scale indicates greater impact of the symptom (fatigue, nausea/vomiting, pain); a <0 point change from baseline indicates improvement. [a]Change from baseline to month 12 exceeds threshold for clinically meaningful improvement (EORTC QLQ-C30 ≥10 points; EQ-5D-5L VAS ≥7 points; MySIm-Q total symptom subscale ≥0.32 points [not estimable for total impacts subscale]). [b]In SoC arm, n=64 for EQ-5D-5L and MySIm-Q assessments.

Conclusion: Patients demonstrated clinically meaningful improvements from baseline in health-related quality of life and disease-specific symptoms after a single cilta-cel infusion. These results strengthen the potential for cilta-cel to be a new SoC for patients with lenalidomide-refractory MM after first relapse.

HP147

Subcutaneous daratumumab (DARA SC) + bortezomib/lenalidomide/dexamethasone (VRd) in transplant-eligible (TE) patients (pts) with newly diagnosed multiple myeloma (NDMM): analysis of minimal residual disease (MRD) in the PERSEUS trial

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Aim: In the phase 3 PERSEUS study primary analysis, DARA SC + VRd (D-VRd) induction/consolidation (ind/consol) and D-R maintenance improved PFS and increased depth of response (complete response or better [≥CR] and MRD negativity [neg]) compared to VRd ind/consol and R maintenance for TE NDMM. Here, we report further results on deepening of response during maintenance.

Method: TE NDMM pts were randomised 1:1 to D-VRd or VRd (Table 1). MRD-neg rate (clonoSEQ®) was defined as the proportion of ITT pts who achieved both ≥CR and MRD neg.

Table 1

D-VRd	Randomised 1:1	Up to six 28-day cycles (4 pre-ASCT ind, 2 post-ASCT consol) of VRd (V 1.3 mg/m^2 SC on Days [D] 1, 4, 8, 11; R 25 mg PO on D 1-21; d 40 mg PO/IV on D 1-4, 9-12) followed by R maintenance (10 mg PO on D 1-28 until progressive disease [PD])	DARA SC (DARA 1,800 mg + recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; Halozyme]) QW in Cycles 1–2, Q2W in Cycles 3–6, and Q4W during maintenance until PD
VRd			

Results: In the 709 pts randomised (D-VRd, n=355; VRd, n=354), responses deepened over time and were higher with D-VRd vs VRd (≥CR end of consol: 44.5% vs 34.7%; P=0.0078 and overall: 87.9% vs 70.1%; P<0.0001; MRD-neg at 12, 24, and 36 mo all P<0.0001; Table 2). Sustained MRD-neg rates for ≥12 mo were higher for D-VRd vs VRd (10^{-5}: 64.8% vs 29.7%; P<0.0001; 10^{-6}: 47.3% vs 18.6%; P<0.0001); results were consistent across prespecified clinically relevant subgroups. Significantly more pts who were MRD positive at end of consol achieved MRD neg during maintenance with D-VRd vs VRd at 10^{-5} (68.8% vs 52.7%; P=0.0330) and 10^{-6} (62.3% vs 31.0%; P<0.0001) and sustained MRD neg for ≥12 mo at 10^{-5} (44.2% vs 22.6%; P=0.0028) and 10^{-6} (34.4% vs 12.7%; P<0.0001). End of consol and overall MRD neg at both 10^{-5} and 10^{-6} were associated with improved PFS. Additional data on response rates in different study phases and sustained MRD neg will be presented.

Table 2

Rates of MRD neg up to: (months after Cycle 1 Day 1)	**10^{-5}**			**10^{-6}**		
	D-VRd (n = 355)	**VRd (n = 354)**	**P**	**D-VRd (n = 355)**	**VRd (n = 354)**	**P**
12 mo	65.1%	38.7%	< 0.0001	43.9%	20.9%	< 0.0001
24 mo	72.1%	44.9%	< 0.0001	57.7%	27.4%	< 0.0001
36 mo	74.6%	46.9%	< 0.0001	63.9%	30.8%	< 0.0001

Conclusion: During maintenance, a greater proportion of MRD-positive pts achieved MRD neg with D-R vs R. The higher rates of deep (10^{-6}) and sustained MRD neg achieved with D-VRd ind/consol and D-R maintenance vs VRd ind/consol and R maintenance translated to a clinically meaningful benefit of improved PFS.

HP148

Fatal case of drug induced enterocolitis associated with bortezomib and lenalidomide.

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Here we describe a fatal case of severe enterocolitis with colopathy histological pattern associated with newly commenced bortezomib and lenalidomide.

Case: A 63 year old man with new diagnosis IgA kappa plasma cell myeloma ISS stage II with K/L ratio 84.5 commenced standard first-line therapy for transplant eligible candidates comprising lenalidomide 25mg D1-14 of 28, bortezomib 1.3mg/m^2 D1, 4, 8, 11 and dexamethasone 20mg twice weekly (VRd). He received concurrent radiotherapy to the bilateral sacroiliac joint and left hip for painful lytic lesions (20Gy in 5 daily fractions on VRd C1D4-D8).

On Cycle 1 Day 18, he was hospitalised with severe abdominal pain and profuse non-bloody diarrhoea (CTCAE Grade 4). There was no evidence of infection on stool or systemic culture. Sigmoidoscopy demonstrated severe colitis with deep ulceration, absent vascularity and friability in the proximal rectum and distal sigmoid. Sigmoid biopsy histology showed an apoptotic colopathy pattern of injury consistent with drug-induced enterocolitis. His symptoms were non-responsive to chemotherapy cessation and methylprednisolone and thereafter only partially responsive to biologic agents Infliximab and vedolizumab. He subsequently developed multiple severe opportunistic infections including recurrent klebsiella bacteremia and pulmonary aspergillosis which precluded further immunosuppression or surgical management. He died just four months after commencing myeloma therapy. Notably, myeloma had responded very well to the first cycle of VRd therapy with normalisation of the K/L ratio 0.95.

Discussion: This is the first described episode of fatal drug-induced enterocolitis associated with bortezomib or lenalidomide. Case reports have described milder patterns of bowel injury including haemorrhagic colitis, ischaemic colitis and non-specific mucositis [1-5] or caused by infections such as Clostridium Difficile or cytomegalovirus [6-8]. There is also a contested association between the radiosensitising effect of bortezomib and increased radiation induced intestinal toxicity, which has been described in two case studies [9-12].

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HP149

Eligibility requirements in clinical trials for relapsed refractory multiple myeloma: systematic bias against patients with limited access to CD38 monoclonal antibody treatment in standard of care

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Aim: Access to novel therapeutics in multiple myeloma (MM) varies around the world. In Australia, the CD38 monoclonal antibody Daratumumab is only available publicly in second-line, meaning a higher proportion of relapsed/refractory (RRMM) patients are CD38 antibody-naïve compared with other jurisdictions. We sought to review trial eligibility criteria in RRMM, to assess the impact this restriction has on patient care.

Methods: Actively enrolling prospective drug studies were identified through clinicalgov.org on 1/4/24, of which, 182 were included.

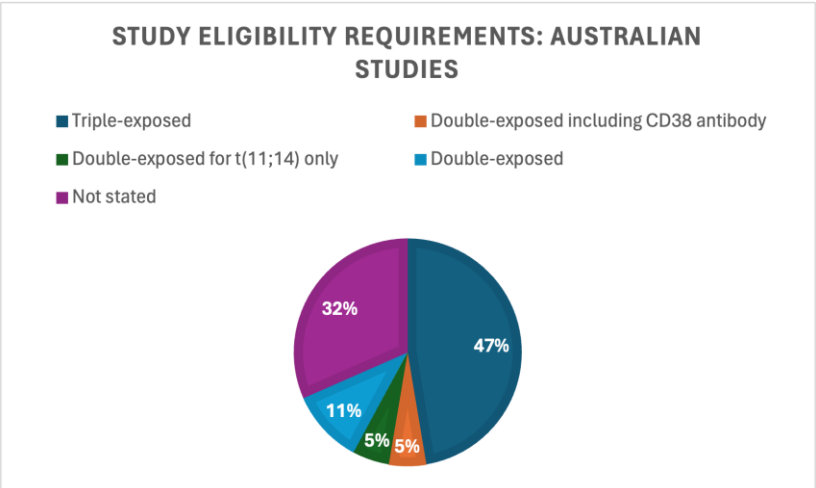
Results: 179 were phase I/II studies (93.4%), 12 were phase III (6.6%), 100 (54.9%) were industry-sponsored and 82 (45.1%) investigator-initiated. 28.6% assessed BCMA-directed therapy, 35.3% a cellular therapy and 18.7% a T-cell engager.

139 studies, or cohorts, stated whether patients needed to be 'double-exposed' (predominantly to a proteosome inhibitor (PI) and immunomodulatory agent (IMiD)), or 'triple-exposed', to a PI, IMiD and CD38 antibody. Of these, 86 (61.9%) and 53 (38.1%) required triple and double-class exposure respectively. The requirement for triple-exposed disease was not associated with industry sponsorship (OR 1.51 [95% CI 0.75-3.02]), whereas studies running in China only, were significantly less likely to require triple-exposure compared with other locations (OR 0.11 [95% CI 0.04-0.28], p<0.0001).

17% of studies were active in Australia. Of these 31 studies (38 arms), 18 were available only to triple-exposed patients, and of the 8 in which double-class exposure was documented, 2 studies required prior CD38 antibody treatment, and 2, the presence of translocation(11;14). Therefore, only 4 clinical trials would accept patients who had only received a PI or IMiD without specific cytogenetic aberrations. These were all phase III, industry-sponsored, multinational studies.

Conclusion: A significant proportion of studies in RRMM require triple-class exposed disease and prior CD38-antibody treatment. This significantly limits access to novel therapeutic agents in Australia. Broadening trial access represents an unmet need in global MM care.

Figure 1. Eligibility requirements for RRMM studies in Australia



HP150

Carfilzomib and influenza A induced thrombotic microangiopathy successfully treated with therapeutic plasma exchange and eculizumab: a case report

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Background: Thrombotic microangiopathies (TMA) encompass a group of syndromes that are characterised by the presence of microangiopathic haemolytic anaemia (MAHA), thrombocytopenia and microvascular ischaemic organ damage or the presence of microthrombi on histopathology. Multiple myeloma itself, proteasome inhibitors (PIs), autologous stem cell transplantation and infectious complications during treatment have all been implicated in the development of TMAs. The pathogenesis of these syndromes in multiple myeloma patients, is broadly categorised into ADAMTS13 deficiency or excessive alternative complement pathway activation.(1) The recognition of complement dysregulation as pathogenic in carfilzomib-induced TMA, has led to its successful treatment with eculizumab, a C5 complement inhibitor. These findings are described in several published case reports.(1-9)

Case presentation: Herein we report a case of TMA with acute onset MAHA, thrombocytopenia, renal dysfunction and confusion in a multiple myeloma patient treated with carfilzomib and belantamab mafodotin with concurrent influenza A infection. Myeloma restaging confirmed complete response, ADAMTS13 level was normal, Shiga toxin was negative and completement C3 and C4 levels were normal. Prompt initiation of plasmapheresis while awaiting ADAMTS13 results and eculizumab supply provided temporising improvement, avoided renal deterioration and the need for haemodialysis. Eculizumab therapy (900mg intravenously weekly for 4 weeks) led to rapid and sustained improvement in all clinical and biochemical parameters. Additionally, a concurrent secondary haemophagocytic lymphohistiocytosis (HLH) resolved. The patient remains without TMA relapse 9 months following completion of four weeks eculizumab therapy and cessation of carfilzomib but continuation of belantamab mafodotin.

Conclusion: Our case report adds to the sparse literature of carfilzomib-induced TMA successfully treated with eculizumab. We demonstrate a durable sustained remission post cessation of the proteasome inhibitor but continuation of belantamab mafodotin monotherapy. Further research is warranted to better understand the complex interplay of this rare, but life threating complication of a common disease and therapeutic modality.

HP151

Aggressive Multiple Myeloma in 12-year-old Girl

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Introduction: We described a case of 12-year-old girl diagnosed with multiple myeloma (MM) IgG kappa, treated with chemotherapy followed by allogeneic stem cell transplantation (AlloSCT) as consolidation.

Case report: A 12-year-old girl, presented with fever and back pain for 4 days. There was right eye proptosis. There was no lymphadenopathy nor hepatosplenomegaly.

Full blood count showed Haemoglobin 7.6 g/dL, platelet 118 $x10^9$/L and white blood cell 7.7 $x10^9$/L. Renal profile was normal, but there was hypercalcemia with corrected calcium 3.08mmol/L. MRI spine showed compression fractures of C3, C5, C6, T7, T8, L4 and L5. CT orbit showed right orbital mass (4.8x3.9x1.6cm) which was proven to be plasmacytoma. Serum protein electrophoresis showed IgG kappa paraproteinemia of 89.3g/L. Serum free light chain showed kappa: 339mg/L, lambda: 26mg/L with kappa/lambda ratio: 12.71. Serum ß2-microglobulin was 1.5mg/dL.

She was diagnosed with MM IgG Kappa, ISS stage I. She was started on chemotherapy V-CHP (velcade-cyclophosphamide-doxorubicin-prednisolone) and monthly pamidronate. After 4 cycles of chemotherapy, her right eye lesion resolved and she achieved partial response.

She underwent matched sibling AlloSCT with reduced-intensity conditioning (RIC) using Fludarabine-Melphalan and Graft-Versus-Host Disease (GVHD) prophylaxis with cyclosporin and mycophenolate. Her transplant was uneventful. She achieved very good partial response at 1-year post-transplant. She was given pre-emptive donor lymphocytes infusion (DLI) at 1-year post-transplant and lenalidomide maintenance for 3 years post-transplant. Currently, she remains well at 3 years post-transplant with no evidence of relapse and no GVHD.

Discussion: We opted for upfront RIC AlloSCT for her as consolidation in MM treatment with the intent that she can be cured from the disease. Pre-emptive DLI was given to boost the donor immune system, together with lenalidomide maintenance to further improve the chance of long-term remission for her.

Conclusion: AlloSCT appears as a promising consolidation therapy for young patients with MM to achieve cure.

Non-malig

HP152

Multiple myeloma patients demonstrate haemostatic imbalances and thrombin generation may be an effective tool in guiding thromboprophylaxis.

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Background: Myeloma patients are associated with an increased risk of thrombosis and bleeding, due to the complex interplay of patient, disease biology and treatment related factors Conventional coagulation assays have limited utility in assessing the overall haemostatic balance. We hypothesize that thrombin generation has utility in guiding thromboprophylaxis in this cohort of patients.

Aim: To assess the changes in thrombin generation parameters in newly diagnosed multiple myeloma patients at diagnosis and post induction chemotherapy.

Methodology: Thrombin generation was assessed in 12 newly diagnosed multiple myeloma patients at diagnosis and post induction chemotherapy using PPP. Thrombin generation studies were carried out using a commercially available kinetic fluorogenic substrate method (calibrated automated thrombogram – CAT). Results were expressed in terms of mean +/-SD, and paired *t*-test using GraphPad-Prism Software)

Results: Our results showed changes in TG parameters in MM subjects, shortening ttPeak (p-value <0.001), and lengthening of lag time, and endogenous thrombin potential (ETP) and peak height (each p-value of <0.001) were lower in MM subjects compared to local reference range.[1] TG parameters remained statistically unchanged from the time of diagnosis to post-induction therapy. One patient who developed thrombosis demonstrated high ETP and shortening of lag time.

Conclusion: Our results suggest that newly diagnosed myeloma patients exhibit a haemostatic imbalance with increase rate in thrombus formation but overall hypocoagulable state. Thrombin generation may have utility in assessing the effectiveness of thromboprophylaxis and may be predictive in thrombotic risk. This study may translate into larger future studies to confirm these qualitative findings with implications on VTE prophylaxis and prevention of bleeding complications.

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HP153

A three-year review of the RCPAQAP ESR EQA

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Aim: A 3-year data review of the RCPAQAP ESR program was conducted to monitor method biases and as part of ongoing monitoring of the appropriateness of analytic performance specification (APS) limits.

Method: The RCPAQAP ESR external quality assessment (EQA) program involves two surveys a year and two samples per survey. Participants are required to submit a quantitative value for each stabilised whole blood sample and return the qualitative interpretation, either normal or raised, for that value based on their laboratory reference range.
Three years of survey sample data (12 data sets) were extracted, categorised, and analysed according to the analytical performance specifications. The all methods median and the method/instrument group medians were compared to evaluate method biases. The percentage concordance for the interpretative results for each sample was calculated and compared against assessment criteria (>80 % within acceptable limits or expected target).

Results: The interpretive results showed a consistently high consensus for each survey sample (>90%). Looking at the quantitative values, method biases were evident in some method groups. This manifested as some samples having quantitative results falling outside the 'all method' APS limits but within APS for their peer group. On average, 8.9% (p-value=0.01) more results were acceptable when comparing all methods acceptable ranges to method group APS limits. Designated "normal" or "raised" samples were within the expected qualitative consensus; however, some participants were marked as outside of APS limits for the associated quantitative results.

Conclusion: The interpretative results are consistently reported to a high standard when looking at the overall results despite method biases. Some quantitative data is not meeting the >80% acceptance criteria of APS limits some of the time. This may be an indication to widen the current APS limits for the ESR EQA program.

HP154

Retrospective study of fertility and pregnancy outcomes in patients with transfusion dependent haemoglobinopathy

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Aim: To report patient characteristics and pregnancy outcomes in men and women with transfusion-dependent (TD)-haemoglobinopathy.

Method: Local registry of patients with TD-haemoglobinopathy at a tertiary centre between 1991-2023 was reviewed. Maternal and fetal outcomes were extracted from electronic medical records (1991-2023); and available pregnancy outcomes reported (after 2001).

Results: Overall, 22 pregnancies (≥20 weeks) were analysed from 16 women (1991-2003). Of these pregnancies, 20/22 (90.9%) were carried by women with TD-thalassaemia (TDT) and two with TD-sickle cell disease (SCD). One woman had non-TD beta-thalassaemia who became TD post-pregnancy. All women required blood transfusions during pregnancy.

Twelve pregnancies (54.5%) required assisted reproduction. There were two multiple pregnancies – one set of twins and one woman with quadruplets from ovarian stimulation; fetal reduction led to twins with subsequent single intrauterine demise. All pregnancies resulted in live births (23 babies).

Pregnancy outcomes were available for 16 pregnancies (11 women, two multiple pregnancies, 17 live births). Pre-existing comorbidities included: hypopituitarism (4/16; 25%), cardiovascular disease (3/16; 18.8%), kidney disease (2/16, 12.5%) and diabetes (2/16, 12.5%). Pregnancy complications included: gestational diabetes (4/16, 25%), preeclampsia (2/16, 12.5%), gestational hypertension (1/16, 6.3%), and postpartum haemorrhage (6/15 or 40%).

Of the live births within this cohort, 12/17 (70.6%) were born via caesarean and five vaginally (29.4%). Seven babies were born preterm (41.2%) with 5/15 (33.3%) requiring special/neonatal intensive care. Five babies (29.4%) weighed <2500 grams (median 2875, IQR 2100-3080). The registry included 14 men (13 with beta-thalassaemia and one with SCD/beta-thalassaemia) who had 30 children. Three pregnancies required reproductive assistance.

Conclusion: While acknowledging significant risks, all pregnancies (≥20 weeks) in women with TD-haemoglobinopathy resulted in live births. Of the men with TD-haemoglobinopathy who had children, <5% required reproductive assistance. These data add to the limited available evidence and highlight the need for collaborative research to guide evidence-based practice.

HP155

Bivalirudin experience in Neonates and Children with Complex Anticoagulation

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Aim: Bivalirudin, a direct thrombin inhibitor, provides stable and predictable anticoagulation independent of antithrombin. Previous studies have shown stability benefits in patients at risk of thrombosis and bleeding complications e.g., extracorporeal membrane oxygenation (ECMO) or ventricular assist devices (VAD).[1,2] Despite lacking paediatric guidelines, bivalirudin is increasingly used in children with complex anticoagulation needs or when anticoagulation with unfractionated heparin is not successful.[3,4] At our institution, bivalirudin was historically used in rare cases of proven heparin-induced thrombocytopaenia (HIT). However, with growing evidence for its safety and efficacy,[5-7] there is a shift towards bivalirudin in specific cohorts, primarily VAD patients. As paediatric dosing information remains limited,[8] we reviewed our local experience.

Method: Retrospective review of neonates and paediatric patients (< 19 years of age) at a quaternary paediatric centre, who received bivalirudin between 1 January 2016 and 1 May 2024. Bivalirudin was delivered as a continuous infusion at a standard starting dose (0.3mg/kg/hr) based on international literature,[9] with no pre-infusion bolus.

Study data collated included: demographic characteristics, weight, minimum/maximum bivalirudin doses (mg/kg/hr), primary indication, target APTT and adverse events. Multiple linear regression was carried out using ordinary least squares method.

Results: Bivalirudin was used in 38 patients, indications including VAD 24/38 (63.2%), ECMO 11/38 (28.9%) and other 3/38 (7.9% - 2 renal dialysis, 1 HIT). 25/38 (65.8%) were male, median age 1.82 years (IQR 0.41 - 6.05) and median weight 10.0kg (IQR 5.82 – 18.5). Average minimum dose 0.138mg/kg/hr (SD = 0.095), and average maximum dose 0.602mg/kg/hr (SD = 0.416). Multiple linear regression analysis suggested no significant linear relationship between the minimum/maximum doses and predictors (age, sex, weight).

Conclusion: Our data suggests wide variability in dosing requirements in neonates and children, and that a lower bivalirudin starting dose (~0.1mg/kg/h) may be more appropriate. Multi-centre prospective studies on bivalirudin pharmacokinetics and pharmacodynamics in neonates and children are needed.

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HP156

Delayed onset Immune thrombocytopenia secondary to Alemtuzumab in a patient with relapsing-remitting multiple sclerosis: a case report.

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Background Multiple sclerosis is an immune-mediated inflammatory demyelinating condition of the central nervous system often presenting in young adults(1). Disease modifying therapies are often initiated early to mitigate the long-term risk of disease progression. Alemtuzumab a humanized monoclonal antibody induces depletion of CD52-expressing cells, and is employed in patients with highly active relapsing-remitting multiple sclerosis (RRMS) (2). I describe a case of Alemtuzumab-associated immune thrombocytopenia (ITP).

Case Report A 45-year-old woman presented with isolated moderate-severe thrombocytopenia, ranging from 39x10^9/L to 63x10^9/L, alongside a normal full blood count in November 2022. She had been asymptomatic with no recent infections and lacked clinical or laboratory indications of connective tissue disorders or lymphoproliferative disorders. Notably, she had received her annual influenza vaccine in April 2024. Bone marrow examination revealed adequate trilineage haematopoiesis.

Her medical history included relapsing-remitting multiple sclerosis, diagnosed in 2013 following an episode of optic neuritis. Due to high radiological and symptomatic burden, she commenced Glatiramer therapy in 2013. Disease progression necessitated high-dose pulse methylprednisolone in 2014 followed by two annual courses of Alemtuzumab in 2015 and 2016. Subsequently, she achieved clinical remission, with ongoing radiologically quiescent disease activity.

Discussion Alemtuzumab is a potent therapy for high-risk multiple sclerosis (MS), however it poses risk of a delayed immune thrombocytopenia. Pivotal trials report incidence rates of ITP post alemtuzumab exposure ranging 2.0% to 3.3% over a median of 6.1 years in patients with MS (3), This significantly surpasses the background rate of primary ITP observed in adults, of 3.3 cases per 100,000 adults annually (4). Patients typically exhibit favourable responses to frontline corticosteroids and temporising intravenous immunoglobulin. Escalation to second-line treatments, rituximab and splenectomy for sustained efficacy are rare but are effective (3). Additionally, thrombopoietin receptor agonists have demonstrated efficacy in Alemtuzumab associated ITP (5). Encouragingly, analyses of limited patient cohorts indicate that the occurrence of ITP did not exert negative impacts on the clinical outcomes in patients with MS(3).

In conclusion, this case underscores the need for vigilant monitoring of haematological complications in MS patients treated with alemtuzumab.

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HP157

IgA mediated Evans Syndrome

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Background: Evans syndrome is a rare condition of autoimmune haemolytic anaemia (AIHA) and immune thrombocytopenic purpura (ITP), with or without autoimmune neutropenia (1). Most often, primary Evans syndrome is associated with warm autoimmune haemolytic anaemia which is IgG associated. IgA antibody mediated warm AIHA is rare, IgA mediated Evans syndrome is not described in the literature (2). We report a case of IgA-mediated Evans syndrome with an excellent response to steroids and rituximab.

Case: A 66-year-old female presented with severe thrombocytopenia (Platelets $1x10^9$/L) manifesting as petechial rash, wet purpura and gastrointestinal haemorrhage. She had a background history of acute ITP treated 9 years previously with rituximab after a suboptimal response to steroids and IVIG.

She was re-treated with IVIG and Prednisolone 1mg/Kg with good effect. During the wean of prednisolone at 25mg, she developed acute onset anaemia with dyspnoea and palpitations. Her haemolytic screen showed elevated unconjugated bilirubin (51), LDH (934), low Haptoglobin (0.02), however the DAT was negative for both IgG and C3d. Blood film demonstrated spherocytes and polychromasia. Extended DAT was positive for IgA antibodies. Workup for lymphoproliferative disorders (bone marrow examination, protein electrophoresis, flow cytometry and PET scan) was negative. Increase in prednisolone back to 1mg/kg was unsuccessful. She received Rituximab 375mg/m^2 weekly for 4 weeks with good response and was successfully weaned off prednisolone. She remains in remission 5 years post rituximab.

Conclusion: IgA antibodies should be considered in patients with IgG DAT and C3d DAT negative Evans syndrome. Rituximab may provide durable remissions in steroid-refractory cases.

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HP158

Updated results from the Australian and New Zealand Thrombotic Microangiopathies Registry

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Aim: To describe updated patient data from the ANZ TMA registry, which collects and analyses data on all TMAs at participating sites in Australia and New Zealand.

Method: Analysis of TMA registry data from 2009 to 2024.

Results: Patient demographics of different types TMA are presented in Table 1. The most common hospital-assigned diagnosis was immune thrombotic thrombocytopenic purpura (iTTP, n=164). The clinical features, diagnoses and treatments of iTTP are presented in Table 2. Mortality was 6.5% during initial admission, and 11.4% at 12-months, with 13.5% relapse rate during this period.

Table 1 Demographic of TMA patients in the TMA registry (n = 408)

	Total	iTTP	cTTP	aHUS	HUS (adult)	HUS (children)	Pregnancy-associated	Cancer-associated	Other	Uncategorized
N (%)†	408	164 (40%)	4 (1%)	75 (18.5%)	4 (1%)	5 (1%)	36 (9%)	2 (0.5%)	21 (5%)	97 (24%)
Female‡	271 (67%)	112 (68%)	3 (75%)	44 (60%)	2 (50%)	3 (60%)	36 (100%)	0 (0%)	12 (57%)	59 (61%)
Age of first presentation median (IQR)	38 (26-53)	43 (30-54)	44 (34-54)	27 (8-38)	50 (30-65)	1.5 (NA)	30 (25-33)	44 (34-54)	44 24-54)	50 (33-62)

† % of all patients. ‡ % of category

Table 2 Clinical features, diagnostic and treatment of iTTP patients	
Autoimmune disease	14 (8.5%)
HIV	4 (2.4%)
Active malignancy	2 (1.2%)
ADAMTS13 activity test	156/162 (96.3%)
ADAMTS13 activity (%) (median, IQR)	1 (1,2)
ADAMTS13 antibody testing performed	69/127 (54.3%)
Plasma exchange	132/138 (95.6%)
Plasma infusion	31/118 (26.3%)
Rituximab	72/133 (54.1%)
Cyclophosphamide	9/126 (7.1%)
Caplacizumab	7/48 (14.6%)
Vincristine	2/126 (1.4%)

Conclusion: Characteristics of TMA patients in the registry appear similar to those of other international cohorts. ADAMTS13 activity testing is now widely used for diagnosing iTTP; however, ADAMTS13 antibody testing was limited. Patient recruitment and follow-up data in the registry will be helpful to understand local TMA practices and outcomes in this rare disease.

HP159

A novel case of inherited haemolytic anaemia due to digenic heterozygous variants in EPB42 and RHAG

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Aim: We report a family study involving two brothers diagnosed with mild non-immune compensated haemolysis and co-inherited heterozygous variants in erythrocyte membrane protein band 4.2 (EPB42) and Rh-associated glycoprotein (RHAG). Homozygous or compound heterozygous variants in EPB42 and RHAG are associated with haemolysis due to hereditary spherocytosis and Rh-deficiency syndrome respectively, but have not previously been reported in combination. We functionally assessed red blood cells to examine possible mechanical and/or structural deficiencies. We propose that the haemolytic phenotype is due to co-inheritance of these variants.

Method: We describe the genotype-phenotype correlation of co-inherited heterozygous variants in EPB42 and RHAG with haemolysis in this family. Segregation testing was performed in immediate family members by sequencing of EPB42 and RHAG genes, haemolysis markers, and blood film morphology. The two brothers and a clinically-unaffected sister proceeded to eosin-5-maleimide binding, functional studies of red cells including osmotic fragility, osmotic gradient ektacytometry, cellular deformability, aggregation, and cell membrane proteomics and glycomics.

Results: Two brothers presented clinically with intermittent jaundice. Investigations were consistent with mild well-compensated Coombs-negative extravascular haemolysis. After excluding other causes, genetic testing revealed heterozygous variants in EBP42 and RHAG. Segregation studies in this family confirm that these variants are inherited, and are phenotypically recessive in isolation.

Eosin-5-maleimide binding was equivocal. Osmotic fragility and osmotic gradient ektacytometry was consistent with osmotically fragile, dehydrated RBC with abnormal surface area-to-volume ratio. Intriguingly, red cells from only one of the brothers were highly sensitive to “sublethal” mechanical stress.

Protein 4.2 and RhAG are components of the ankyrin/band 3 complex, which is essential for the structural integrity of the red cell membrane. We propose a double-hit mechanism of haemolysis due to disruption of the ankyrin/band 3 complex. Further investigations including proteomics and glycomics are underway, which may add to our understanding of the mechanisms of haemolysis in this family.

Conclusion: This is the first case reporting haemolysis due to co-inheritance of heterozygous variants in EPB42 and RHAG.

HP160

A Rare Cause of Polycythaemia: Chronic Carbon Monoxide Poisoning Secondary to Shisha-pipe

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Aim: To describe a rare cause of polycythaemia.

Method: Case report

Results: A 42-year-old male IT professional was referred to haematology clinic due to polycythaemia. Medical history includes Crohn's disease, perianal abscess, discectomy and inguinal hernia, taking sertraline. Social history included shisha-pipe smoking five times per week.

Symptoms included fatigue, brain 'fog', irritability and headaches. Erythromelalgia was found to be affecting the patient's whole body. Nil lymphadenopathy or hepatosplenomegaly. Baseline investigations revealed a haemoglobin of 205g/L, a red cell count of 6.74 x 10^12/L, and a haematocrit of 0.62. Symptomatic venesection was performed and patient commenced on aspirin pending further investigations.

Repeat full blood count confirmed haemoglobin 190 – 200g/L. EPO level was normal. Investigations for secondary polycythaemia included pulmonary function tests (normal) and sleep study (moderate airway obstruction). A 3-month trial of CPAP did not alter the patient's haemoglobin. Subsequent investigations included JAK2 mutation (negative) and bone marrow biopsy did not demonstrate definitive features of myeloproliferative disorders or fibrosis. VBG was performed revealing a carboxyhaemoglobin saturation of 32.4%.

Patient was treated with high flow oxygen therapy in the emergency department for 6 hours with normalisation of carboxyhaemoglobin levels. Toxicology follow-up confirmed Shisha smoking as the culprit cause for carbon monoxide poisoning.

Discussion: Evidence suggests the popularity of shisha smoking has been increasing in Western countries such as Australia. Despite beliefs that shisha is healthier than other forms of smoking, it presents serious health risks. Chronic exposure can cause dangerous levels of carbon monoxide without altered conscious state.
Conclusion: This case highlights an atypical cause of secondary polycythaemia. Chronic carbon monoxide poisoning may be difficult to detect and clinicians should consider testing carboxyhaemoglobin levels in patients with unexplained polycythaemia and a smoking history.

HP161

Mycoplasma Pneumoniae causing Severe cold agglutinin syndrome in a 17-year-old woman without features of a respiratory illness.

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[1]Mater

A previously well 17-year-old presented to our institution with 4-6 weeks of lethargy and pale complexion. On assessment they were febrile at 38.8 °c with normal respiratory rate and oxygen saturations. There were no clinical features suggestive of an infection and no acrocyanosis.

Pathology revealed severe anemia with a haemoglobin of 46g/L (120-160g/L) with a normal neutrophil and platelet count. The mean corpuscular volume was elevated at 117fL (80-98). Blood film demonstrated cold agglutinins, moderate polychromasia and tear drop cells.

Haemolysis screen demonstrated an elevated LDH of 793 U/L (120-250), elevated Bilirubin of 45 umol/L (<20) and an undetectable Haptoglobin of <0.20 g/L (0.25-1.80). Direct anti-globulin test was positive for both IgG and C3D. Cold agglutinin titres were positive at 1:512 and confirmed with thermal amplitude testing. Donath-Landsteiner antibody was negative.

Extensive testing was performed to identify a cause of the cold agglutinin haemolysis. Despite the polymerase chain reaction for *M. pneumoniae* from a pharyngeal swab being negative, the elevated serum *M. pneumoniae* antibody titres of 1:320 (<1:64) were felt to represent a clinically significant infection. Interestingly, there were no symptoms of recent respiratory tract infection and there was no radiological evidence of either recent or current pneumonia. Computed tomography imaging did not show any signs of a lymphoproliferative disorder and peripheral blood flow cytometry did not reveal a clonal population.

She was transfused with 2 units of warmed blood. Her post transfusion haemoglobin was 79 (g/L) and no further were required. She commenced on Doxycycline 100mg twice daily for treatment of *M.pneumoniae* infection.

This case demonstrates that severe haemolytic anaemia secondary to *M. pneumoniae* infection is not always associated with significant respiratory symptoms or radiological findings. Furthermore, our patient was only 17-years-old and cold agglutinin syndrome more commonly affects older individuals.

HP162

QUAntitative Novel Testing method for Fibrinogen studY: Laboratory validation study of novel point of care qLabs FIB system for fibrinogen testing within a Tertiary trauma centre.

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Aim: This study evaluated the analytical performance of the novel qLab FIB system. It validated the accuracy and precision of fibrinogen results obtained from the qLab Fib system, compared to standard of care fibrinogen testing via Clauss assay.

Method: Data was collected on 101 patients who had routine coagulation studies performed, in the inpatient and outpatient setting. Fibrinogen levels were performed on the qLab FIB device and Fibrinogen Clauss assay on the Stago STA R Max analyser. Subgroups included patients on anticoagulation; warfarin (n=10), unfractionated heparin (n=10), low molecular weight heparin (n=10), dabigatran (n=2) and other direct oral anticoagulants (apixaban/rivaroxaban) (n=10), known hypofibrinogenaemia (<1.1g/L) (n=10) and known anaemia (Hb <75 g/L) (n=10), as well as assessment of underfilled citrated tubes (n=10), dilutional effect (n=3) and controls (n=24). Precision testing was performed on low (n=1) and normal (n=1) fibrinogen values with ten repetitions. Bland & Altman and Passing Bablok distribution analysis were used for statistical analysis.

Results: The results show strong correlation of fibrinogen results between qLab FIB system and Clauss assay for patients with hypofibrinogenaemia, anaemia and on anticoagulation. The correlation coefficient was 0.952 with an intercept of -0.04 and slope of 0.97 (n=124) between the reported qLab FIB device values of 1.0g/L and 4.0g/L. There was acceptable concordance between qLab FIB device values <1.0g/L with all five samples and reasonable concordance with values >4.0g/L with eight out of ten samples being concordant. One sample failed to show concordance, however this patient had known congenital dysfibrinogenemia.

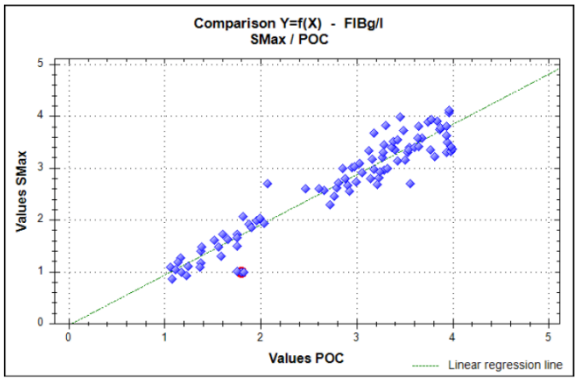

Figure 1 - Passing Bablok regression

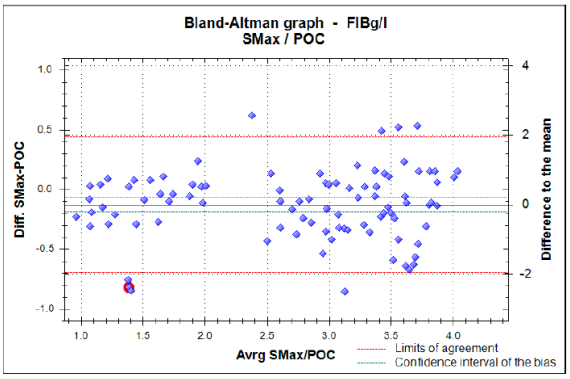

Figure 2 -Bland and Altman analysis

Conclusion: The qLabs FIB system provides an accurate point of care measurement of fibrinogen, with strong correlation to standard Fibrinogen Clauss assays. The clinical application of the qLab FIB system is being evaluated as part of this study in the trauma and critically ill setting in massive haemorrhage.

HP163

Haemoglobin I-Toulouse: A rare haemoglobinopathy

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Hb I-Toulouse is a rare haemoglobin variant produced secondary to lysine to glutamic acid substitution at position 67 in beta globin. This leads to a change in the ionic bond between lysine in position 67 of beta-globin and the propionic chain of haem. The alteration causes instability of the haemoglobin associated with mild haemolytic anaemia and increased methemoglobin levels. Hb I-Toulouse causing low oxygen saturations (SpO2) has only been previously reported once in the literature in a family affecting the father and son, which was discovered on haemoglobinopathy studies also performed at our institution. In this case we report the third case of an adult presenting with persistently low SpO2 and found to have the Haemoglobin variant I-Toulouse.

The patient was a 66-year-old female who presented with acute gangrenous cholecystitis requiring urgent surgery. She was noted to have a persistently low SpO2 during this admission and review of prior admissions identified long standing reduction in SpO2 of 88-92%. The patient had low levels of methemoglobin identified on repeated venous and arterial blood gases at a level of 1.6-3.3%. On review of the patients' medical records there was no history of documented episodes of oxidative haemolysis. The suspicion for an underlying hemoglobin variant occurred after the resolution of hypoxia post red blood cell transfusion post operatively due to multifactorial anaemia.

Cases of Hb I-Toulouse are rare with only 7 cases previously reported in the literature. To our knowledge this is the third case reported of Hb I-Toulouse presenting with low oxygen saturations.

HP164

A rare case of a Chest wall Pseudotumour in a patient with Severe Haemophilia A and high titre inhibitor managed with Emicizumab

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Haemophilic pseudotumours are a rare complication of severe haemophilia, characterized by a progressive cystic swelling that commonly occurs in muscles or bones and have also been reported in the lung, abdomen, and the nasal cavity. Surgical excision under haemostatic cover is generally considered standard of care. Management of patients with pseudotumours continues to pose a significant challenge.

We report a rare case of a migrant patient with severe Haemophilia A who presented to our institution for the first time at the age of 47 with chest wall swelling which was found to be secondary to a massive pseudotumour arising from the left 3rd rib which was abutting the left ventricle. The patient's previous treatment of his haemophilia (rare on-demand therapy) meant that he was well within 20 exposure days on arrival in Australia and upon initiation of recombinant factor VIII therapy promptly developed a high titre inhibitor. Inhibitor eradication was attempted with immune tolerance induction (ITI) therapy but was ceased after just 5 months due to significant venous access difficulties, PICC line related thromboses and recognition of thoracic outlet obstruction limiting further PICC attempts. During ITI the patient continued to experience recurrent bleeding into the pseudotumour requiring intermittent rFVIIa therapy and the inhibitor titre continued to rise (peak titre 2867 Bethesda units). Surgical removal of the pseudotumour was discussed at length, however the patient and family declined this very high-risk procedure.

The patient was commenced on Emicizumab prophylaxis. After commencement of emicizumab the patient experienced no further reported bleeds into the pseudotumour. After 3 years of close follow up with yearly CT imaging of the chest, the pseudotumour remains stable in size and the patient is asymptomatic.

This case report further contributes to the limited literature around impact of emicizumab prophylaxis in patients with haemophiliac pseudotumours.
No conflicts of interest to disclose.

HP165

Successful treatment of Refractory Immune Thrombotic Thrombocytopenic Purpura associated with Plasma cell dyscrasia following Daratumumab-based therapy and Autologous stem cell transplant– a case report.

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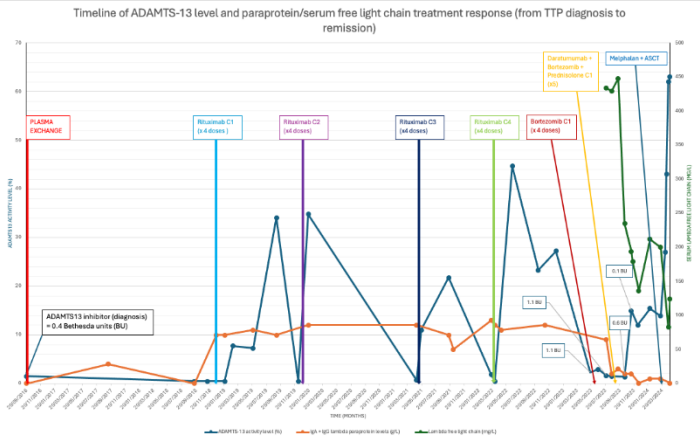
Background: The treatment of relapsed refractory immune thrombotic thrombocytopenic purpura (R/R iTTP) is challenging. Salvage therapies are usually limited to additional cycles of rituximab, while other immunosuppression strategies including bortezomib, cyclophosphamide or splenectomy are associated with limited evidence. Recent reports have highlighted the evolving role of daratumumab. Cases of autoimmune disorders with haematological manifestations (e.g., autoimmune haemolytic anaemia) have been reported in multiple myeloma (MM) with resolution observed after initiation of MM therapy, including haematopoietic stem cell transplantation (HSCT). To our knowledge, we present only the second case of R/R iTTP associated with plasma cell dyscrasia and complete ADAMTS-13 remission following HSCT.

Results: We present the case of a 47-year-old man with multiply relapsed iTTP over the past eight years with progressive shortening periods of treatment-free clinical remission (CR) despite multiple cycles of rituximab and bortezomib monotherapy. Workup for treatment-refractoriness revealed both IgG and IgA lambda paraproteinemia and a bone marrow biopsy consistent with monoclonal gammopathy of undetermined significance (MGUS) in the absence of myeloma-defining events.

Given severe ADAMTS-13 deficiency (<1.5%), the patient received five cycles of salvage anti-myeloma therapy (daratumumab, bortezomib and prednisolone) and achieved a very good partial response (VGPR) with >90% reduction in paraproteins, >50% reduction in serum free lambda light chains (SFLC), a ten-fold increase in ADAMTS-13 activity (15.0%) and eradication of ADAMTS-13 inhibitor (0.1 BU). The patient proceeded to autologous HSCT with melphalan conditioning with a day+28 post autograft ADAMTS-13 activity level showing complete remission (62.0%) and reduction in SFLC (>50% from pre-ASCT).

Conclusion: This case study illustrates the link between immune dysregulation and plasma cell dyscrasia manifesting as multiply R/R iTTP and highlights the therapeutic efficacy of a novel consolidative strategy of daratumumab based therapy and HSCT.



HP166

Localised Cerebral light-chain Amyloidosis: A rare cause of cerebral amyloid deposition.

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Background: Localised cerebral AL amyloidosis (CA) is the rarest form of cerebral amyloid-related disease. It is characterised as a slow-growing localised mass of amyloid light-chain deposition with no evidence of systemic disease and is not typically associated with a clonal B-cell population. CA have a distinct radiographic appearance on magnetic resonance (MR) imaging. They usually present as a singular lesion, but cases with multi-focal lesions have been reported.

Case Presentations:

Case One

A forty-five-year-old female was referred with three months of progressive left-sided upper-motor-neurone features. MR brain demonstrated a right frontoparietal nodular irregular area of enhancement with an additional satellite focus in the left parietal region.

Brain biopsy demonstrated nodular deposits of amyloid, with positive congo-red staining. Liquid chromatography tandem mass spectrometry (LC-MS/MS) confirmed the presence of immunoglobulin lambda light-chain amyloid. No evidence of systemic amyloidosis was present on investigations. Surgical excision was not feasible and because of concern about progressive neurological symptoms the patient underwent stereotactic fractionated radiotherapy to biparietal lesions. After two years follow up, the lesions remain radiologically stable, and the patient has residual left upper limb spasticity.

Case Two

An eighty-year-old female presenting with recurring symptoms of visual hallucinations, vertigo and myoclonic jerks was found to have a right parietal lesion on MR brain. Biopsy of the lesion demonstrated amyloid deposition with lambda restricted B-cells. LC-MS/MS was performed which was consistent with a diagnosis of lambda light-chain amyloidosis. There was no evidence of systemic disease on work up. Due to the increasing size of the lesion on serial imaging, the patient underwent surgical excision and had residual left sided homonoymous hemianopia post-operatively. Surveillance imaging did not demonstrate residual or recurrence of disease.

Conclusion: CA are usually slow-growing, with low risk of recurrence or dissemination. Given the localised nature of the lesion, they are potentially curable with surgical resection. Radiotherapy can be considered for locations not amenable to a surgical approach to reduce symptomatic progression.

HP167

Latrogenic Amyloidosis resulting from Peptide drug administration.

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Most cases of localised amyloidosis are light-chain type, however, several peptide drugs are also amyloidogenic. Here we describe two cases of insulin amyloidosis (AIns) and one anakinra-associated (AIL1RAP) amyloidosis.

Cases:

1. A twenty-five-year-old female with Rabson-Mendenhall syndrome; an inhertited condition resulting in severe insulin resistance, presented with rapid weight loss and peripheral neuropathy. Prominent bilateral inguinal lymph nodes were biopsied demonstrating complete nodal replacement by amyloid deposition. Typing was confirmed by insulin immunohistochemistry (IHC) and laser capture tandem mass spectrometry (LC MS/MS) demonstrating a peptide profile consistent with AIns. Assessment for systemic amyloidosis was confounded due to end organ complications of severe diabetes. In this case, AIns detected at sites distant to administration could represent subcutaneous insulin migration to draining lymph nodes or formation of amyloid systemically due to circulating high insulin levels. Due to the necessity of ongoing high insulin therapy and lack of available therapies for treatment of AIns the patient was observed.

2. A seventy-one-year-old male with a history of type-1 diabetes mellitus was referred with a slow-growing left deltoid subcutaneous mass at a site of regular insulin injections. Biopsy demonstrated amyloid deposition which was positive on insulin IHC staining, confirming a diagnosis of AIns. There was no evidence of systemic organ involvement. Given the localised nature of this case, management was recommendation of injection site rotation.

3. A sixty-year-old female with Muckel-Wells Syndrome treated with anakinra, an interleukin-1 (IL-1) inhibitor subcutaneously for over 10 years presented with multiple enlarging abdominal subcutaneous masses. Biopsy showed nodular amyloid deposition; LC MS/MS confirmed AIL1RAP(anakinra-related)-amyloidosis. Systemic assessment did not demonstrate organ involvement. There have been case reports suggesting the presence of systemic organ involvement with AIL1RAP. Given this, the recommendation of switching to an alternative anti-IL-1 therapy was made.

Conclusion:

These cases demonstrate a rare complication of iatrogenic amyloidoidis from peptide drugs which are potentially amyloidogenic. Where possible, change in injection site, reduction in dose of peptide drug or change in treatment can be considered to reduce disease progression.

HP168

Expanding the pharmacist role: Evaluation of pharmacist led interventions within an anticoagulant stewardship service at a large tertiary multisite Hospital

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[1]Monash Health

Background: Anticoagulants are known for their high-risk nature and potential for significant morbidity and mortality. An ACS service was implemented in November 2022. The service adopts a collaborative model where specialist pharmacists play a key role in making independent recommendations, thereby alleviating consult burden and saving haematologists' time. Patients are identified in two ways: direct clinician referral or via a novel electronic dashboard; that allows real-time proactive screening for patients at-risk of anticoagulant-related harm.

Aim: To outline the activities of specialist ACS pharmacists and determine the benefits of pharmacy-led interventions

Method: Descriptive summary and prospective audit of pharmacist-led interventions (defined as clinical recommendation provided to treating teams) and estimated time-saving (based on average time per intervention) from November 2022 to January 2024. Patients deemed as 'high-risk' were identified by expert consensus (*see table 1)*

Results: Of a total of 2,449 interventions, 622 (25%) were independent pharmacist interventions (Figure.1). Of these, 468 were identified by direct referral and 154 through dashboard. High-risk interventions accounted for 111 incidents, with 91% (101) being identified via dashboard. Over half of these high-risk interventions involved duplicate prescribing of anticoagulants (Figure.2). Acceptance rates of interventions were high (89%), with 96% being actioned within 24 hours. Approximately 142 hours of haematologist time (~2.5 hours/week) was redirected to a pharmacist, thereby freeing up haematologist time to be reallocated to alternative priorities, ensuring optimal use of resource.

Conclusion: Pharmacist-led interventions, as part of an ACS service, have high acceptance rates from teams. Upskilling pharmacists in anticoagulation allows them to independently review patients, leading to enhanced patient-care and potential cost-savings in healthcare.

Table 1. Electronic Dashboard filter criteria and high risk categories

- ≥2 anticoagulants concurrently charted *(high risk- excluding warfarin/enoxaparin bridging)*
- Platelet count <50x10^9/L + on anticoagulants/antiplatelet *(high risk)*
- eGFR <40mL/min and on therapeutic anticoagulation *(high risk when eGFR <30 mL/min)*
- INR >4.0
- aPTT >100 seconds
- Anti-Xa level *(high risk if level >1.5 units/L, or within therapeutic range at non-peak timing)*
- Weight >130kg
- Non-standard anticoagulants (e.g. bivalirudin, heparin)

Figure 1. Types of interventions

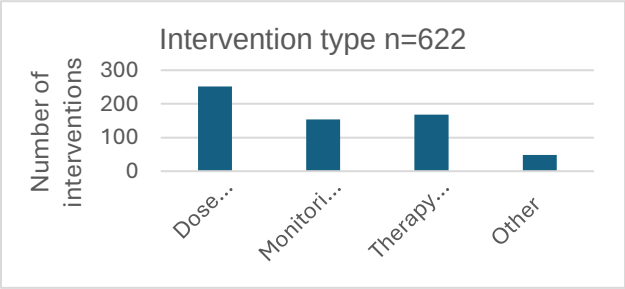
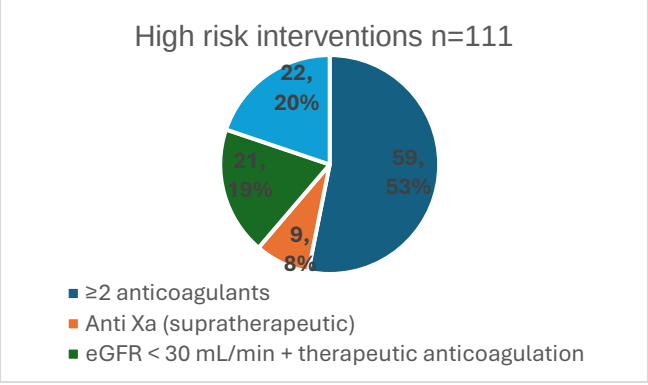


Figure 2. Types of high-risk interventions



HP169

Haemoglobin Howden - a case report of a rare haemoglobinopathy

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[1]Gold Coast University Hospital

Background: Polycythemia is characterized by an increase in red cell blood count and can be divided into primary causes, originating in the bone marrow, or secondary causes, with stimuli that often lead to increased erythropoietin. Rarely, polycythemia can be due to abnormal or high affinity haemoglobin (Hb), which results in decreased oxygen supply to tissues and consequent increased marrow red cell production. The ultimate production of functional red blood cells relies on the composition of both heme and globin chains, alongside the relationship between these globin chains.

Case report: In this report we discuss the case of a 77 year old man referred for an essentially lifelong history of asymptomatic polycythaemia. No obvious secondary cause had been found. A prior bone marrow biopsy was normal. He had no history of thrombosis, but was on therapeutic anticoagulation for atrial fibrillation. With us he was found to have a low p50. Haemoglobin capillary electrophoresis and high-performance liquid chromatography was normal, however beta-globin gene sequencing demonstrated a heterozygous variant of the c.62T>C p.(Val21Ala) in the HBB gene. This is consistent with a high affinity haemoglobinopathy, Haemoglobin Howden. He continued on his anticoagulation, with a plan to venesect to a haematocrit of <0.6 or for symptoms, and to send away for family studies. Given the rarity of this disease, the clinical framework of how to monitor and act on it is not clearly defined.

HP170

Efficacy and safety is maintained in adult patients with paroxysmal nocturnal haemoglobinuria receiving pegcetacoplan for up to 3 years.

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Aim: To report on the longest continuous clinical trial data set for pegcetacoplan by conducting an integrated analysis of 2 phase 3 trials and the open label extension (OLE).

Method: Patients received pegcetacoplan 1080mg subcutaneously twice weekly initially, with dose escalations to three times weekly permitted thereafter. Efficacy was evaluated from baseline by haemoglobin, lactate dehydrogenase (LDH), absolute reticulocyte count (ARC), indirect bilirubin, FACIT-Fatigue scores, and transfusion avoidance. Safety was evaluated by the incidence of adverse and serious adverse events (AEs & SAEs) over 3 years.

Results: 114/133 patients enrolled in the OLE. Prior to initiating pegcetacoplan, 75% patients required transfusions and mean (SD) Hb levels in C5i experienced and treatment-naïve patients were 8.95 (1.09) g/dL and 9.27 (1.44) g/dL respectively. Improvements in mean haemoglobin, ARC and indirect bilirubin observed in PEGASUS and PRINCE were maintained during the OLE. LDH stabilised below the upper limit of normal (226U/L). FACIT-Fatigue scores improved and were maintained near the general population norm (43.6). Annual transfusion avoidance ranged from 71%-86%. 52% of C5i-experienced patients & 67% of treatment naïve patients were transfusion free for up to 3 years and 2.5 years respectively.

Most patients had an AE. SAEs occurred in 50.0% of patients, 4.5% patients had an SAE deemed related to pegcetacoplan. 17 patients discontinued due to an AE. 9 discontinued due to haemolytic disorder (7 within 1 year of initiation). Four deaths and three thrombotic events occurred, considered unrelated to pegcetacoplan. No cases of meningitis were reported, and no new safety findings were identified.

Conclusion: Pegcetacoplan showed sustained efficacy and safety for up to 3 years in C5i-experienced patients and up to 2.5 years in C5i-naive patients, with significant reductions in transfusion burden and no new safety concerns.

HP171

Paroxysmal cold haemoglobinuria: a chilling case of acute renal failure

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Introduction: Paroxysmal cold haemoglobinuria (PCH) is a rare form of intravascular complement-mediated haemolysis secondary to a biphasic, polyclonal IgG antibody that targets the P-antigen on red blood cells. It is more common in children. Patients classically present with haemoglobinuria, jaundice and fever. Acute renal failure necessitating dialysis has only been described three times in the literature.

Case Details: A 64-year-old man presented with 48-hours of fevers, myalgia, abdominal pain and haemoglobinuria following a coryzal illness two weeks prior. Haemoglobin at presentation was 105g/L, with a rapid decline to 79g/L over six hours. Haemolysis screen was positive with hyperbilirubinaemia (91µmol/L), high lactate dehydrogenase (2354U/L), undetectable haptoglobin and strongly positive direct antiglobulin test for C3d. Reticulocyte count was inappropriately normal ($42x10^9$/L). He had severe acute kidney injury (creatinine 506µmol/L). ADAMTS13 level was normal. Testing for cold agglutinins was negative. Donath-Landsteiner antibody testing was positive, confirming PCH. An extensive infectious screen was negative. The patient's haemolysis rapidly stabilised with supportive care including environmental warming, with normalisation of bilirubin and haptoglobin over 48 hours. He required only two units of packed red blood cells. No steroids, intravenous immunoglobulin, or plasmapheresis were required. However, the patient's renal function continued to deteriorate and he developed uraemic encephalopathy necessitating haemodialysis. There were concerns that haemolysis alone might not explain such significant kidney injury. Glomerulonephritis screen was negative and renal biopsy confirmed acute tubular necrosis secondary to haemolysis with occasional injured tubules showing intraluminal red cell fragmentation. The patient was managed with a warmed haemodialysis circuit and made a complete renal recovery after two weeks.

Conclusion: This case demonstrates acute renal failure as a rare presentation of PCH. The management of PCH is largely supportive. Environmental warming is critical in arresting the pathogenic driver autoantibody. Furthermore, even in cases of acute renal failure due to haemolysis, complete renal recovery is possible.

HP172

A rare case of lymphocytic-variant hypereosinophilic syndrome presenting with neurological manifestations

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Background: Lymphocytic variant hypereosinophilic syndrome (L-HES) is a rare haematological disorder characterized by persistent eosinophilia and associated end-organ damage,[1] mediated by aberrant T-lymphocytes producing eosinophil-stimulating cytokines.[2] Neurological symptoms associated with L-HES are uncommon and can present a diagnostic challenge.[2,3]

Case Presentation: We discuss the case of a 68-year-old male presenting with truncal ataxia, limb weakness and unsteady gait. Initial investigations revealed marked eosinophilia ($5.75x10^9$/L) and an unremarkable non-contrast CT brain. During his admission, he developed progressive limb weakness and hypertonia, new bulbar symptoms and worsening encephalopathy. MRI brain demonstrated watershed ischaemia, a typical pattern seen in L-HES.[4] This culminated in an intensive care admission for low GCS requiring intubation where he was commenced on IV pulse methylprednisolone at a dose of 1g/day for 3 days followed by lower dose steroids and hydroxyurea. The diagnosis of L-HES was made on the basis of typical radiological changes, eosinophilia and two small aberrant T cell populations on flow cytometry of a bone marrow aspirate. Further treatment with pegylated interferon-alpha and mepolizumab was commenced and the patient's peripheral eosinophilia and encephalopathy gradually improved. Despite this, he had a terminal aspiration event and was transitioned to comfort cares.

Conclusion: This case underscores the importance of considering L-HES in patients with neurological symptoms and marked eosinophilia. However, neurological involvement of HES is rare and only described in case reports.[4] This may cause diagnostic uncertainty. Timely initiation of targeted therapy may prevent irreversible neurological damage in these patients. Ongoing publication and presentation of case reports such as this can aid in improving awareness.

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HP173

Thrombotic Thrombocytopenic Purpura with concurrent Evans Syndrome

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Introduction: Thrombotic Thrombocytopenic Purpura (TTP) is characterized with microangiopathic hemolytic anemia (MAHA) with negative Coombs test. In rare cases where Coombs test was positive, this would suggest simultaneous occurrence of TTP with Evans syndrome. Here, we described a case of relapse immune-TTP (iTTP) with concurrent Evans syndrome.

Case Report: A 17-year-old lady initially presented with dizziness and was found to have thrombocytopenia (platelet $8x10^9$/L), hemolytic anemia (Hemoglobin 5g/dL), and 5% schistocytes in the peripheral smear, in keeping with MAHA. There was no renal impairment nor coagulopathy. She was diagnosed with TTP and immediately started on plasmapheresis and high-dose steroids. ADAMTS13 level was 2% with inhibitor level of 48U/ml. However, Coombs test was positive (anti-IgG 1+ with pan-agglutination). Her disease responded well after 6 courses of plasmapheresis and discharged with tapering dose of steroid. Her disease relapsed after 5 months. Investigation showed hemolytic anemia (Hemoglobin 9g/dL), thrombocytopenia (platelet $11x10^9$/L), 2% schistocytes in the peripheral smear. She was treated as relapsed TTP and urgent plasmapheresis and high dose steroid were started. Her counts achieved response after 5 cycles of plasmapheresis. Again, Coombs test came back positive (anti-IgG 1+ with pan-agglutination). ADAMTS13 level was absent with inhibitor level of 41U/ml. In view of early relapse and concurrent Evans syndrome in this case, she was given Azathioprine as immunosuppressant.

Discussion: The concurrent Evans syndrome could be the reason for our patient to relapse in a short time. Patient with iTTP and Evans syndrome should be monitored closely during follow up with ADAMTS13 level to assess the risk of relapse. Ideally, this patient will require monitoring ADAMTS13 activity every 3–6 months. If ADAMTS13 activity decreases to < 10%, rituximab may be considered for preventing clinical relapse.

Conclusion: Concurrent TTP and Evans syndrome may need long term immunosuppressant to prevent clinical relapse.

HP174

Weathering a Storm in Hemophagocytic Lymphohistiocytosis driven by EBV infection

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We described a case of EBV-driven hemophagocytic lymphohistiocytosis (HLH), which responded well with HLH-94 protocol and virostatic agent.

Case: A 25-year-old lady, with no known medical illness, presented with unresolving fever for 5 days. Clinically there was splenomegaly. Full blood count showed pancytopenia (white blood cell $0.9x10^9$/L, Haemoglobin 7.7g/dL, Platelet $32x10^9$/L). There were hyperferritinemia (14,873 ng/mL), hypofibrinogenemia (1.09g/L) and transaminitis. Bone marrow aspirate and trephine biopsy showed hemophagocytosis with no evidence of leukemia, lymphoma and malignancy. EBV viral load was raised with 740,100 copies/mil, while blood culture, ANA, Hepatitis B, C and HIV were negative. She was diagnosed with EBV-driven HLH and was commenced on HLH-94 protocol with etoposide and steroid. She was also given Rituximab and intravenous immunoglobulin. Ganciclovir was given for 24 days until clearance of EBV viral load. She responded well with the treatment with resolution of fever, splenomegaly and cytopenia. She completed 24 weeks of protocol HLH-94. Currently, her condition remains stable at 2 months completion of protocol HLH-94.

Discussion: The diagnosis of HLH is always challenging as described in our patient who was presented with unresolving fever. Her presentation mimics infectious and autoimmune conditions. High clinical suspicion and rapid recognition for HLH are mandated in unresolving fever, splenomegaly, pancytopenia and extremely high ferritin. In our patient, HLH-94 protocol was initiated promptly within 1 week of presentation. Rituximab was added in the treatment of our patient to deplete EBV-harboring B cells. EBV viral load is useful to guide the duration of ganciclovir treatment and monitor the response to treatment. Patients with persistently high EBV viral load may eventually require allogeneic stem cell transplant as a cure of the disease.

Conclusion: High clinical suspicion and rapid recognition for HLH are important as prompt treatment of HLH may prevent irreversible organ damage and mortality.

HP175

Haemolysis and haemodialysis an un-fava-rable condition

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Introduction: Glucose 6-phosphate dehydrogenase (G6PD) deficiency is one of the most common inherited enzymopathies in the world. Many of the cases presenting with acute haemolytic anaemia tend to have a rapid recovery and acute renal failure is a rare, reported complication (1). We present an interesting case of a 9-year-old boy with acute haemolytic anaemia secondary to G6PD deficiency with a complex and prolonged hospital course.

Case report: Our patient presented with lethargy, jaundice and dark urine following consumption of dried and roasted fava beans. He had an acute normocytic anaemia of 79 g/L with a reticulocyte count of 117 x10^9/L and an unconjugated bilirubin of 87 umol/L. His blood film features were consistent with oxidative haemolysis. His G6PD assay result was low at 1.5IU/gHb. He had a normal renal function on admission which rapidly deteriorated with associated anuria resistant to fluid therapy within 24 hrs of his admission with a peak creatinine of 640 umol/L. Haemodialysis was required for 2 weeks before his urine output returned and his acute kidney injury resolved. A renal biopsy was performed due to unexpected ongoing haemodialysis requirement and was consistent with haemolysis associated cast nephropathy.

Conclusion: Haemolysis associated haemoglobin cast nephropathy is a rare complication of G6PD deficiency. It is an important complication to recognise as despite the need for haemodialysis and significant morbidity, the prognosis is favourable (2). The literature on this condition in paediatrics is limited. It is thought to occur particularly in cases where the haemolysis is brisk and massive (3). Particular attention to early fluid management and serial urine monitoring are important considerations in patients presenting with acute haemolysis secondary to G6PD deficiency. Evidence of severe or brisk haemolysis such as methemoglobinemia should be signals for careful fluid management, lower transfusion support threshold and vigilance to prevent significant renal injury.

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HP176

Clinical parameters of patients referred for isolated neutropenia with Duffy null phenotype: A single centre, retrospective review

Zammar G

Aim: To characterize the clinical parameters of patients referred for isolated neutropenia who were found to express the Duffy null phenotype and subsequent diagnosis of Duffy Associated Neutrophil Count.

Method: A single centre, retrospective review of adult patients (18 years and over) referred to a tertiary hospital for further investigation of isolated neutropenia between June 2023 and February 2024. Patient demographics, co-morbidities, ethnicity, medications, laboratory results and final diagnosis was obtained from electronic database and chart review. Data was collated and analysed using descriptive statistics.

Results: A total of 34 patients (35% male) were identified with a median age of 43 years (IQR 31, 61). The median neutrophil count was 1.42 x 10^9/L (IQR 0.74, 1.80). Ten patients (29.4%) referred for isolated neutropenia were subsequently found to have another cytopenia's. 10 patients (29.4%) had confirmed Duffy null status with all 10 patient's reporting African heritage (Table 1). Of those with confirmed Duffy null status, there was no history of recurrent infections, constitutional symptoms or other cause of isolated neutropenia.

Of those who did not express Duffy Null phenotype (n=24), three patients (12.5%) were found to have a primary hematological disorder including AML, CLL and CCUS and all were anaemic and had abnormal blood film morphology. Other causes of neutropenia included auto-immune (29.1%), cyclical (8.4%), congenital (4.2%) and iatrogenic (4.2%). Ten patients (41.6%) had no cause of neutropenia identified or had spontaneous resolution of their neutropenia.

Conclusion: Duffy Associated Neutrophil Count was the most common cause of referred isolated neutropenia. Initial investigations could be limited to assessing Duffy null status in asymptomatic patients of

African heritage.

Table 1: Patient Demographics

	Duffy Null phenotype (n=10)	Duffy positive phenotype (n=24)	Entire Cohort (n=34)	Statistics
Age years (median, IQR)	38.5 (32.25, 44.5)	45.5 (30.75, 65)	43 (31.0, 61.8)	
Male Sex (n, % of column)	2 (20)	9 (24)	12 (35.3)	
Ethnicity (n, % of column) • African • European • Asian • White • Unknown	 10 (100) 0 (0) 0 (0) 0 (0) 0 (0)	 0 (0) 4 (16.6) 3 (12.5) 9 (37.5) 8 (3.3)	 10 (29.4) 4 (11.8) 3 (8.8) 9 (26.4) 8 (23.6)	

Haemoglobin g/L (mean, SD)	130 (12.4)	129 (13.8)	129 (13.6)	Mann Whitney U Z=0, p=1.0
Number anaemic (% of column)	0 (0)	5 (20.8)	5 (14.7)	
Total White Cell Count x 10^9/L (median, IQR)	3.41 (2.78, 3.69)	3.08 (2.61, 3.82)	3.21 (2.66, 3.75)	Mann Whitney U Z=-0.26, p=0.794
Neutrophil Count x 10^9/L (median, IQR)	1.66 (0.98, 1.66)	1.15 (0.67, 1.53)	1.42 (0.74, 1.80)	Mann Whitney U Z= -0.718, p=0.47
Number neutropenic (% of column)	9 (90)	21 (87.5)	30 (88.2)	X^2=0.04, df=1, p=0.84
Platelet Count x 10^9/L (mean, SD)	185 (53.7)	210 (49.6)	198 (58.6)	Mann Whitney U Z=-4.40 p=<0.0001
Number thrombocytopenic (% of column)	3 (30)	3 (12.5)	6 (17.6)	X^2=1.5, df=1, p=0.22

Supportive Care

HP177

Immunoglobulin therapy in chronic lymphocytic leukaemia: results from a state-wide data linkage study

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Aim: To explore immunoglobulin (Ig) treatment patterns and the association with infections in patients with chronic lymphocytic leukaemia (CLL).

Method: Retrospective data-linkage longitudinal study using the Victorian Admitted Episodes Data, Victorian Cancer Registry and Victorian Death Index. Our cohort included patients diagnosed with CLL and admitted to hospital from 2007 to 2021, excluding those who had a stem cell transplant. Kaplan-Meier survival analysis was used to estimate survival outcomes.

Results: We included 8704 patients with CLL, of whom 1231 (14.1%) had received Ig in hospital during their follow-up. Patients treated with Ig were followed-up for longer compared to Ig-naïve patients (mean years: 6.6 vs. 4.2), and a higher proportion of Ig-treated patients had at least one hospitalisation in the year before diagnosis (84.3% vs 52.4%).

The median time to death was 110 months (9.17 years). From Year 1 to Year 8, the proportion of patients receiving Ig decreased from 12.6% to 8.9%, the proportion of patients experiencing infection-related hospitalisations decreased from 28.6% to 10.3% and those undergoing chemotherapy from 21.2% to 8.1%.

Of patients initiating Ig, the median time to stop treatment was 12 months (cessation was defined as more than 3 months since their last Ig). Of those who stopped Ig, the median time to restart was 14 months. After the first Ig, the rate of infection-related hospitalisations per month was significantly higher in patients who did not receive Ig in the previous month compared to those who continued Ig treatment (Figure 1).

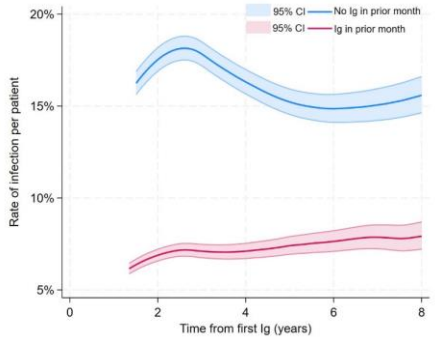

Figure 1. Rate of infection-related hospital admissions in CLL patients treated with Ig

Conclusion:
Approximately 14% of all patients with CLL received Ig, with the proportion remaining relatively constant over time. Patients who continued Ig treatment experienced fewer infection-related hospitalisations compared to those who stopped. Further research is needed to fully understand the patterns of Ig use and its effectiveness.

HP178

Haematological Malignancies During Pregnancy: A Systematic Review of Necessary Services in the Australian Context

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Background: Haematological malignancies diagnosed during pregnancy are rare events with increasing incidence, that pose unique therapeutic, social, and ethical challenges for the treating team, the patient and their family. Symptoms of pregnancy can obscure the underlying malignancy, often delaying diagnosis. Currently, there are no established guidelines regarding the appropriate referral pathways, recommended resources and services for the management of pregnant patients diagnosed with a haematological malignancy.

Objective: To conduct a systematic review of the literature to identify the essential multidisciplinary team members required for the optimal care of pregnant patients with haematological malignancies. This data will then be used to evaluate the capabilities of Australian health networks to provide this coordinated care.

Methods: A systematic review of the literature in MEDLINE and SCOPUS databases was conducted. Eligible studies focused on pregnant patients diagnosed with haematological malignancies in Australia while exploring multidisciplinary care models and specialist teams involved, and the services utilised during the management of these patients. Data obtained from the systematic review was then used to generate the map of Australian hospitals that can service this patient demographic.

Results: It was found that the multidisciplinary team members involved in the care of perinatal women include clinicians from haematology, maternal-fetal medicine (MFM), anaesthetics, midwifery, ICU, psychology and social work. Service utilisation by patients included haematology and maternity, intensive care, tertiary imaging, operating theatre, pharmacy and dedicated perinatal mental health services. Utilising these data, a total of 25 hospitals in Australia were identified as having the potential capability to manage these patients.

Conclusions: This study provided an overview of the necessary healthcare practitioners, services and hospitals available that can manage pregnant patients with a haematological malignancy in Australia. Future research should focus on determining ideal treatment regimens and timing of therapy throughout gestation, as well as establishing a national patient registry and implementing an optimal cancer care plan and frameworks for best practice care. Furthermore, establishing a centralised referral pathway leveraging telehealth will allow expedient, multidisciplinary action as well as equity in access to all women across Australia.

HP179

Myeloma Australia and Myeloma Research Laboratory: insights from laboratory tours by the myeloma community

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Since 2009 Myeloma Australia (MA) and the Myeloma Research Laboratory (MRL), University of Adelaide have conducted annual laboratory tours for people and their families affected by myeloma, aiming to increase understanding of local myeloma research, through a personalised experience.

Over 15 years, the MA support nurse worked with MRL staff, coordinating groups of 10-20 participants to tour facilities at the South Australian Health & Medical Research Institute (SAHMRI), hosted by PhD students and postdoctoral researchers.

Tours aim to provide an immersive experience, with participants viewing laboratory techniques, engaging with scientists, and gaining insights into ongoing local cancer research projects. Tours include interactive presentations, hands-on demonstrations, Q&A sessions and informal discussions over morning tea between researchers and participants. To understand the tours' effectiveness, participants and researchers were each invited to complete a short qualitative survey using Survey Monkey, before and after a tour held in February 2024.

100% of participants rated the tour as very good or excellent, meeting their expectations. They reported an increased understanding of cancer research and treatment development, and it provided hope for improved treatments. Meeting the disease under the microscope was reported as a powerful experience.

Researchers reported the tours were very valuable in advancing their research (71%), increased their understanding of the patient experience (100%) and enhanced their communication skills from explaining complex science in simpler terms (88%). Postdoctoral researchers highlighted potential opportunities for consumer involvement in grant applications and clinical studies (83%) and has resulted in a high response from the MA SA myeloma community to study recruitment. PhD students reported positive impacts on their training and development (100%).

Clearly the tours are valued by everyone involved. They are an important link between this myeloma specific support organisation, scientists working in the myeloma field and the people living with this chronic blood cancer.

HP180

In-hospital daily step count pattern in adults following autologous haematopoietic stem cell transplant

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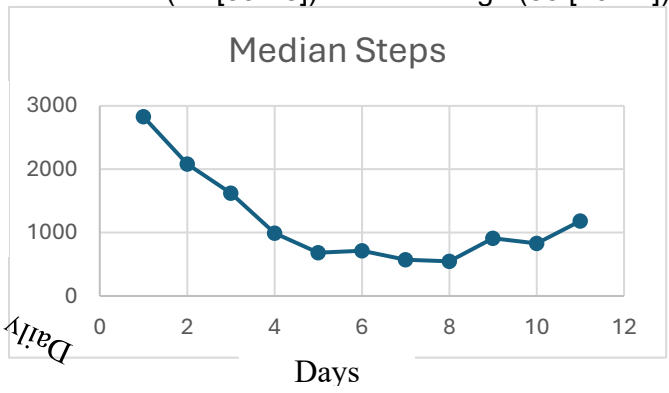
Aim: There is a paucity of data on in-hospital physical activity levels in people with haematological malignancies following elective autologous haematopoietic stem cell transplant (ASCT). Our aim was to describe in-hospital daily step count in this population as well as changes in functional performance and fatigue from hospital admission to discharge.

Method: Observational study on 18 adults (mean age: 60 ± 12 yr; 6 [33%] female) with multiple myeloma or lymphoma admitted for an ASCT at Sir Charles Gairdner Hospital, Western Australia. On hospital admission, prior to transplant, as well as on hospital discharge, measures were taken of 10-metre walk speed (10MWS) and fatigue (FACIT-Fatigue questionnaire). From day 1 following ASCT, participants were asked to wear a physical activity device (StepWatch) for 24 hours/day for 14 days or until discharge. Daily steps were recorded by the StepWatch. The Wilcoxon test was used to compare median daily steps between Day 1 post-transplant to the day with the lowest daily step count, as well as changes in 10MWS and fatigue between admission and discharge.

Results: Median [interquartile range] time to neutrophil >1.0 post-transplant was 11 days [10-15]. Median daily steps reduced by 80.6% from Day 1 post-transplant (2,828 steps [1514-3800]) to the lowest point post-transplant (Day 8; 547 steps [380-1834]), p<0.001 (see figure). Fatigue worsened between admission (42 [39-48]) and discharge (33 [26-42]), with no change in 10MWS.



Conclusion: Adults admitted for autologous stem cell transplant have a significant reduction in physical activity during their acute ward stay and worsening of fatigue. This may indicate longer term follow-up of physical activity levels and fatigue should be recommended for this population.

HP181

Subcutaneous Immunoglobulin (SCIg) anytime, anywhere!

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Aim: Mid North Coast Cancer Institute (MNCCI) Port Macquarie NSW, detected rapid increases with Intravenous Immunoglobulin (IVIg), occasions rising from 339 in 2021 to 625 in 2023. This 4-hour appointment every 4-weeks occurred continual changing of dates and times, consequently impacting our patient's quality of life (QOL). A Quality Improvement Project (QIP) evaluated our current cancer care provision and efficiency of resources for Immunoglobulin. Aimed at transitioning IVIg to SCIg therapies, enabling patients and MNCCI staff to work collaboratively to empower our Haematology patients to self-management therapies. Subsequently, our patients gained greater control of their treatment and autonomy by self-administering their SCIg, anywhere and anytime, thus enhancing one's QOL.

Method

Locale: MNCCI Immunoglobulin patients

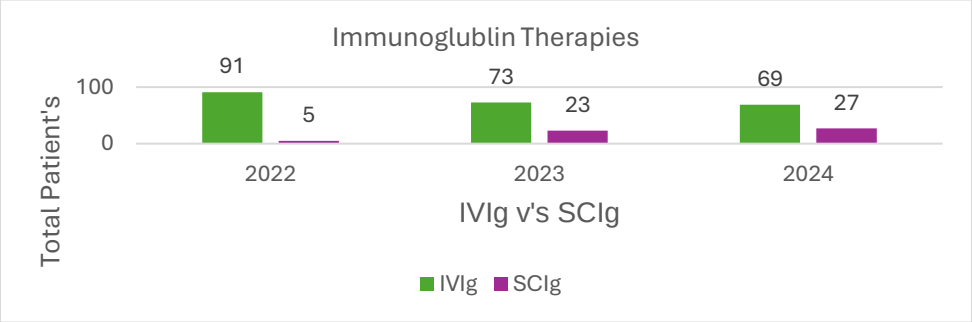
Sample size: 96 patients, receiving Immunoglobulin replacement therapies

Principal test(s) performed
Provide education sessions to all IVIg patients on the ease and benefits of SCIg

Identification of patients	with difficulties around cannulations
	with good physical dexterity
	with lengthy travel times or pays for transport

Statistical analysis
Retrospective data analysis, analysing Mosaiq reports for all Immunoglobulin replacement therapies

Results: 28% transitioned to SCIg.



Challenges
Fearing self-managing own treatment
Fearing self-needling
Lacking the dexerity required for the administration technique

Loses

Reasons returned back to IVIg	2 patients	lacked the dexterity for administration
	1 patient	formed an abscess
	1 patient	failed to gain steady serum IGg level

Quick wins

Patients love it
Suited patients with young families
Patients' anxiety levels decreased around multiple cannulations
Improve patients lifestyle

- increases more time at home and freedom to have lengthy holidays
- less time traveling to appointments plus decreasing the financial cost of paid transport
- decreases wait times and lengthy appointments in health care establishments especially during COVID

Conclusion

28% of our immunoglobulin replacement therapy patients have transitioned to SCIg. Ongoing future direction of Immunoglobulin replacement therapies is with early education on the benefits and ease of SCIg. Empowerment and autonomy gained for our SCIg patients, via self-managing their care anywhere and anytime. Consequently, the QIP has reduced the occasions of services for the MNCCI and decreasing the time our patients spend in health care establishments.

HP182

The HSCT-BIOME Study: A Hybrid phase 0/I trial evaluating oral capsule faecal microbiota transplantation for preventing HSCT-associated complications

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Aim: Changes in the gut microbiota during haematopoietic stem cell transplantation (HSCT) is increasingly linked to the development of severe complications. Faecal microbiota transplantation (FMT), a method of delivering a healthy gut microbiota to a recipient, offers potential in promoting gut microbiota stability and improving HSCT outcomes. The HSCT-BIOME study is designed to determine the tolerability and safety of orally-administered, encapsulated FMT in HSCT recipients, and test its ability to reduce the incidence/severity of complications.

Method: Peri-HSCT FMT (i.e. FMT delivered before and after HSCT) will be administered to eligible participants (adults undergoing autologous HSCT for a haematological malignancy) over two courses, with the second starting when ANC>0.8 (Figure 1). Following an open-label, safety run in (N=5), peri-HSCT FMT will be evaluated for its efficacy in N=51 participants randomised 2:1 to FMT or placebo. The primary outcome is the proportion of participants that develop severe gastrointestinal toxicity - defined as 4 consecutive days of the diarrhea (Bristol Stool Chart 6+) at a frequency of twice daily - within 3 weeks of HSCT. Safety is defined as the incidence of treatment-emergent adverse events (TE-AEs). Tolerability is defined as the incidence of TE-AEs and adherence to FMT.

Results: The trial is anticipated to start in late 2024, with results available 18 months after completion.

Conclusion: FMT is a promising HSCT adjunct to mitigate complications; however, its clinical utility is limited to narrow indications i.e. treatment-resistant/refractory GvHD. Our goal is to develop a protocol that is feasible to administer and offers an extended duration of microbial support both before and after HSCT. Through peri-HSCT FMT delivery, avoiding only periods of severe immunosuppression (ANC<0.8), we hope to demonstrate that FMT can be safely administered to HSCT recipients and reduce the personal, clinical and economic burden of HSCT complications.

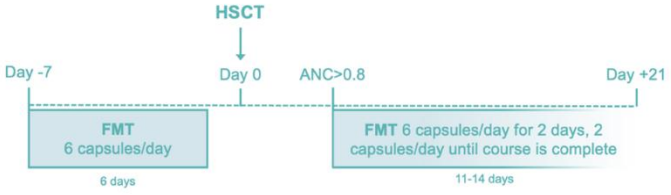

Figure 1 - Schedule of peri-HSCT FMT delivery

HP183

Matching stem cells and gut microbes: a pilot preclinical study on donor-matched faecal microbiota transplantation for Graft versus Host Disease

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Aim: Faecal microbiota transplantation (FMT) is increasingly recognised as a viable therapy for GvHD, inducing remission in ~40% of cases. However, FMT for GvHD has only been investigated with 3rd party (donor) FMT which fails to recognise the intimate relationship that exists between the immune system and microbiota within an individual. Hence, in the setting of allogeneic-HSCT, we hypothesise matching stem cell and fecal donors, i.e. "donor-matching", will optimise the compatibility between donor-derived immune cells and the unique microbiome it is primed for, thereby improving FMT's efficacy for GvHD. This pilot study aimed to explore the effect of donor-matched FMT in a preclinical model of GvHD.

Method: A MHC-matched, minor-histocompatibility antigen mismatched model of GvHD (LP/J [H2kb] → C57BL/6 [H2kb]) using busulfan and cyclophosphamide conditioning was established in N=10 male C57BL/6 mice (Riesner 2016). C57BL/6 mice were confirmed for engraftment and monitored for GvHD before randomisation into experimental groups; saline/control (n=3), 3rd-party FMT (n=3), donor-matched FMT (n=4). Caecal contents from stem cell donor LP/J mice or unrelated C57BL/6 mice were used to prepare FMT for the donor-matched and 3rd-party FMTs, respectively. 3× 200ul FMT was administered to GvHD positive mice via oral gavage. Mice were followed for 3 weeks post FMT (+54 days post allo-HSCT). Key outcomes for GvHD were change in body weight and GvHD score.

Results: Donor-matched FMT induced a significant increase in body weight 18 days after compared to control mice (P=0.03, 95% CI [0.5918, 13.33]) and 3rd party-FMT mice (P=0.02, 95% CI [-14.06, -1.326]). This was in parallel to a significant decrease in GvHD clinical scores compared to saline/control mice (P= 0.03, 95% CI [-3.756, -0.1610]).

Conclusion: Donor-matched FMT appears to be more effective in controlling murine GvHD compared to 3rd party (donor) FMT. Although promising, cautious interpretation is required given preliminary nature of data.

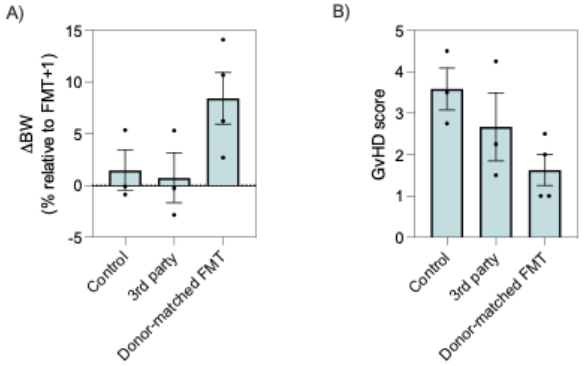

Figure 1: Percentage weight change and GvHD scores in N=10 GvHD positive mice treated with saline/control (n=3), 3rd party-FMT (n=3), donor-matched FMT (n=4). **(A)** Percentage weight increase in donor-matched FMT mice (baseline corrected to +1 day after FMT) at 18 days after FMT (FMT+18) is significantly greater than control mice (P= 0.03, 95% CI of 0.5918 to 13.33) and 3rd party-FMT mice (P=0.02, 95% CI of -14.06 to -1.326). **(B)** Donor-matched mice showed decreased GvHD clinical scores compared to saline/control mice at FMT+18 (P= 0.03, 95% CI of -3.756 to -0.1610). **FMT administerd when GvHD score 3+ (with skin symptoms).**

HP184

A Retrospective review of the Assessment and Publication Rate of Health-related quality of Life outcomes in Investigator initiated Clinical trials sponsored by the Australasian Leukaemia and Lymphoma Group (ALLG)

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Background: Inclusion of health-related quality of life (HR-QOL) outcomes is a best-practice standard in modern clinical trial design, but in as many as 50-75% of trials where HR-QOL is collected, QOL results are not reported (1). Identification of the reasons for non-publication of HR-QOL will improve meaningful use of HR-QOL measures and reduce research waste.

Aim: To assess the reporting of HR-QOL data from ALLG clinical trials for which the primary efficacy results are published. To describe factors associated with unreported HR-QOL results.

Method: We retrospectively reviewed ALLG clinical trials (1993-2023) in which HR-QOL data was collected a trial endpoint. We searched PubMed to identify trials with published results and for these reviewed whether HR-QOL results were also published. Trials that closed early were excluded from this analysis. Factors associated with HR-QOL publication were evaluated.

Results: A total of 111 ALLG trials (1993-2023) were reviewed. In 66 (59%), HR-QOL data were collected. Of these, 19 (28%) had a publication eligible for analysis. HR-QOL outcomes were reported in 5/19 (26%) published trials. In three trials, HR-QOL results were reported together with the primary efficacy results while in two trials HR-QOL results were published in a subsequent separate paper. For one trial, efficacy and HR-QOL results were presented in abstract form in the same year (Table 1). The most commonly used tool was the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (54%).

		HR-QOL non-published n=14	HR-QOL published n =5
Trial design			
Randomised	Yes	7/14	4/5
Disease group			
	Acute Leukaemia/MDS	3	2
	NHL / Hodgkin	5	2
	MM	3	1
	CML/CLL	4	-
Trial era (first patient enrolled)			
	Before 2010	6	3

	2011-2020	4	2

Table 1 – Summary of HR-QOL publication rate in ALLG Trials

Conclusion: We found 26% of ALLG clinical trials with published results reported HR-QOL data. In this small data set, there was no apparent association between HR-QOL publication and disease type or trial era. Our findings are in keeping with international experience and highlight the need for further work to identify reasons behind the low publication rate and identify areas of improvement.

Reference: 1) Marandino L, Trastu F, Ghisoni E, Lombardi P, Mariniello A, Reale ML, et al. Time trends in health-related quality of life assessment and reporting within publications of oncology randomised phase III trials: a meta-research study. BMJ Oncology. 2023;2(1):e000021.

HP185

More than blood count recovery - identifying and responding to the spiritual needs of patients with acute myeloid leukaemia.

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Aim: To identify the spiritual needs of patients with AML

Method: This research was undertaken in a 180 bed acute care tertiary teaching hospital. The haematology unit is an 18 bed inpatient unit with outpatient clinics and services. The spiritual care model at this facility is a person-centered model with spiritual care staff integrated into the interdisciplinary team.

A retrospective audit of pastoral care entries was undertaken with a review of 70 documented pastoral visits. The data was coded in accordance with WHO Spiritual Care Coding for pastoral care interventions. An interpretative phenomenological thematic analysis methodology was then used with two major themes emerging - Illness experience for individuals with AML, and the patient's spiritual needs during the illness experience.

Results: Identified gaps in current clinical practice pathways, highlighting the importance of spiritual care in patient care, and the expertise a spiritual care practitioner can bring to the interdisciplinary team. 95% of individuals took up the opportunity to engage in a pastoral visit with a pastoral practitioner during their hospitalization. Identified the spiritual care and existential needs of individuals they began to integrate their experience, contemplate their physical decline, treatment limitations, and transitions to end of life care.

Conclusion: The desire to connect and live from a place of authenticity has been identified as an important need to those with a life-threatening illness. Redefines what "a successful outcome" in haematology looks like and challenges all clinicians to consider what support is provided to those transitioning to end of life care.

HP186

Establishing a Cancer Survivorship Surveillance Clinic: Enhancing Care Beyond Treatment

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Aim: The Victorian Cancer Plan 2021-2024[1] identified survivorship care as a key component in improving the well-being and support of patients with cancer. The primary objective of Northern Health (NH) Cancer Survivorship/Surveillance Clinic (CSSC) is to provide comprehensive, multidisciplinary care tailored to the unique needs of cancer survivors. By offering personalised survivorship care plans, CSSC aims to address physical, psychosocial, and long-term health issues that arise post-treatment.

Method: CSSC offers comprehensive support for haematological cancer survivors, including survivorship care plans, screening tools, education, counselling, surveillance for late effects, and psychosocial support. The Patient Activation Measure (PAM) questionnaire assesses patients' readiness for self-management, guiding early interventions. The NH Supportive Care Screening (NCCS) guideline aids in addressing diverse healthcare needs and managing distress.

Results: CSSC has seen 49 new individuals and over 74 encounters between 17/2/2023 – 17/05/2024**.** There was an intentional bias with the start of the service towards recruiting younger patients. Reflecting our catchment, over half of patients were from a CALD (culturally and linguistically diverse) background. Majority of patients rated a PAM score of 3 (44%), whilst it was more even scores of 1 and 2 (15% and 19%).

Patient characteristics	
Median age (range)	28 (21-77)
Gender (male/female)	26/22 (54%/46%)
Australian born / CALD	21/27 (44%/56%)
Months post end of treatment	
0-60 61-120 >120	27 (56%) 16 (33%) 5 (10%)
Disease	
Hodgkin lymphoma Non-Hodgkin lymphoma Leukaemia Transplant Other	13 (27%) 17 (35%) 9 (19%) 4 (8%) 1 (2%)
Patient activation measure (PAM) score	
1 = overwhelmed and unprepared to play an active role in their own health	7 (15%)
2 = lack knowledge and confidence for self-management	9 (19%)
3 = beginning to take action but lack confidence and skill to support behaviours	21 (44%)
4 = adopted many of the behaviours to support their health, but may not be able to maintain them in the face of life stressors	3 (6%)
Referrals	
Exercise Physiology Psychology	31 (65%) 15 (31%)

Conclusion:
The establishment of the CSSC and the use of the PAM questionnaire, coupled with early interventions based on the results, presents a pivotal advancement in cancer care. Implementing early interventions guided by PAM results not only enhances patient engagement but also fosters proactive management of healthcare needs. This approach empowers patients, facilitates timely interventions, and ultimately contributes to enhanced well-being and survivorship outcomes within the haematology community.

Reference: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Distress Management (V.2.2013). © 2017 National Comprehensive Cancer Network, Inc..

ANZSBT Poster Presentations

AP001

Medical management of Jehovah's Witnesses — a collaborative approach

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Medical management of patients who are Jehovah's Witnesses (JWs) can present a challenge, due to their refusal of blood transfusions. The aim of this presentation is to acquaint clinicians with the information needed to collaborate, thereby enabling the best quality medical care without blood transfusions for this patient cohort.

Three keys to successful collaboration employed by clinicians around the world focus on: (1) understanding the position of JWs on medical treatment, (2) implementing evidence-based strategies to avoid blood transfusions (i.e. minimization of blood loss, enhancement of hematopoiesis, tolerance of anemia and autologous blood management) and (3) utilizing the network of Hospital Liaison Committees (HLC) for JWs.

The international HLC network of community-based ministers offers the following services without charge:

- provide peer-reviewed clinical papers and information for managing patients without allogeneic blood transfusion,
- facilitate physician-to-physician consultations,
- assist with patient transfer when necessary,
- make presentations to physicians and other hospital and legal professionals,
- clarify ethical issues for JW patients or clinicians related to medical care, and
- arrange for pastoral care and practical assistance to hospitalized JW patients.

Successful collaboration to implement patient-centred strategies results in positive outcomes. Timely involvement of the HLC can help facilitate successful interpersonal communication and shared decision-making between physicians and bloodless medicine patients[4]. Applying multimodal and multidisciplinary strategies to avoid blood transfusion results in decreased mortality, lower infection, shorter hospital stays and reduction in other complications[5]. Furthermore, the Western Australia Department of Health initiated a comprehensive health-system-wide patient blood management (PBM) program over a six-year study period and estimated the gross savings to be between AU$80 million and AU$100 million[6]. Therefore, hospital administration, clinicians, the patient, and the HLC, can collaborate by maintaining good

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[4] Johnson-Arbor K, Verstraete R. **Bloodless management of the anemic patient in the Emergency Department**. Ann Emerg Med 2022;79(1):48-57. [PMID: 34353645]
[5] Leahy MF, Hofmann A, Towler S, Trentino KM, Burrows SA, et al. **Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: a retrospective observational study in four major adult tertiary-care hospitals**. Transfusion 2017;57(6):1347-58. [PMID: 28150313]
[6] WHO. **The urgent need to implement patient blood management: policy brief**. World Health Organization; 2021. p. 1-24. [ISBN: 978-92-4-003574-4]

communication and displaying mutual respect to employ patient-centred solutions that avoid the use of blood transfusion.

AP002

Comparison of ABO blood group antibody titration between 'automated gel column agglutination' and 'manual gel column agglutination' techniques

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Aim: Accurate measurements of antibody titres (AT) are important. Column Agglutination Technique (CAT) and automation have improved AT testing. This study aimed to compare the precision, repeatability, and accuracy of manual CAT (man-CAT) and through an automated platform (auto-CAT).

Method: The study was conducted at a hospital blood center. IgM and IgG AT of 92 blood samples were performed using auto-CAT and man-CAT. Precision was determined by repeating the titres of five samples five times by both techniques. For evaluation of inter-operator variability, ABO AT of five samples were tested by five independent operators.

The statistical analysis was done using SPSS. The overall analysis of the data was done using the chi-square test with a two-sided Fisher exact test The Pearson correlation coefficient was used for the comparison of auto-CAT and man-CAT. Repeatability was assessed using the Cronbach's Alpha and Kendall's concordance coefficient

Results: Auto-CAT and man-CAT agreement for the overall IgM AT, the exact percentage agreement, percentage agreement within ±1 and ±2 doubling dilutions was 21.43%, 88.10%, and 99.21% respectively, for IgG AT, it was38.89%, 96.83%, and 100% respectively. These results show that auto-CAT and man-CAT have a very high correlation. The reproducibility of titres by auto-CAT was high with intra-class correlation coefficient of auto-CAT for IgM and IgG was 0.976 and 0.980 ($p<0.0001$) respectively, while by man-CAT it was 0.944 and 0.966 ($p<0.0001$) respectively, showing highly reproducibility in both. On studying inter-operator variability, the results of auto-CAT were more reproducible (IgM=86% and IgG=89%) as compared to man-CAT by five independent operators (IgM=70% and IgG=68%).

Conclusion: Auto-CAT is a standardized and reproducible system for the consistent AT testing. Man-CAT is also a comparable AT testing. In resource constraint settings, man-CAT may be a good alternative for the auto-CAT.

AP003

Comparison of the impact of different suspension mediums on ABO antibody titres.

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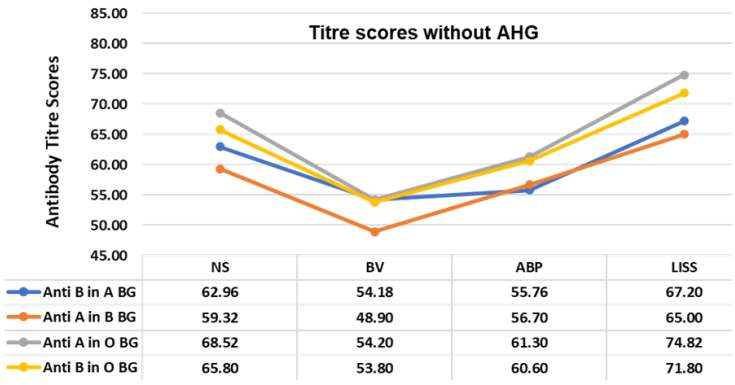
Aim: Titration of ABO antibodies is a critical procedure in blood banking. This study aims to compare the effects of four different diluents: 0.9% Normal Saline (NS), 6% Bovine Serum Albumin (BSA), AB plasma (ABP) and Low Ionic Strength Solution (LISS), which are commonly used as suspending medium for titration of ABO antibodies.

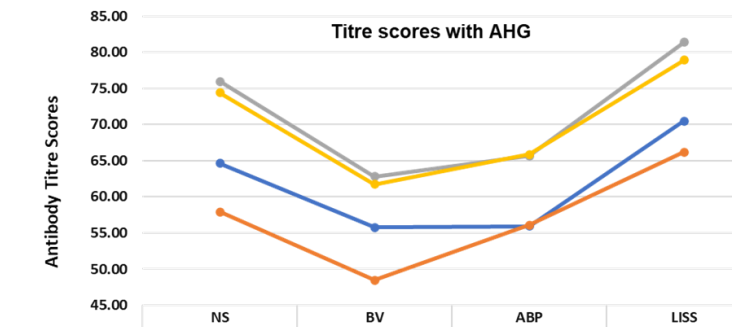
Methods: The study was performed for ABO antibody titration of plasma of 200 healthy male Rh D-positive blood donors at a hospital-based blood centre. Out of 200 donors, 50 were of the A and B blood groups each and 100 were of the O blood group. ABO antibody titrations were performed using each diluent (NS, BSA, ABP, and LISS) for the blood sample by tube method under identical conditions. Titers were grouped into high titre (≥128) and low titre (≤64) for the assessment of agreements of titre with different diluents. The mean titre scores obtained with each diluent were recorded and analysed by SPSS-23 for variation with different diluents.

Results: The study found that using NS as the standard, titres using LISS diluent were enhanced, resulting in agreement of high titres in 99.2% while in BSA and ABP showed high titres only in 42.1% and 57.8% of samples respectively. Further, 55.7% sample with LISS showed high titer values in compared to the NS showing LISS diluent as highly sensitive in detecting antibody titres. Further when AB plasma was used as diluent, it showed no enhancement on addition of AHG compared with other diluents.

Conclusion: LISS appears to be the most sensitive diluent using the tube technique and may overestimate the titre; NS is an optimal diluent for tube technique. These findings emphasize the importance of selecting an appropriate diluent and the need for standardization in ABO antibody titration protocols.



	NS	BV	ABP	LISS
Anti B in A BG	62.96	54.18	55.76	67.20
Anti A in B BG	59.32	48.90	56.70	65.00
Anti A in O BG	68.52	54.20	61.30	74.82
Anti B in O BG	65.80	53.80	60.60	71.80



	NS	BV	ABP	LISS
Anti B in A BG	64.64	55.76	55.90	70.50
Anti A in B BG	57.92	48.44	56.10	66.20
Anti A in O BG	75.98	62.78	65.64	81.40
Anti B in O BG	74.42	61.72	65.84	78.90

Effect of Different Diluents on Titre Scores

AP004

Development of a manufacturing process for allogeneic serum eyedrops

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[1]Australian Red Cross Lifeblood, [2]Australian Red Cross Lifeblood, [3]Australian Red Cross Lifeblood

Aim: Lifeblood has been making and supplying autologous serum eyedrops to meet the needs of a small segment of the Australian clinical community for over twenty years. Many ophthalmic patients are however unable to access serum eyedrops (SED) for severe dry eye conditions due to an ineligibility or incapacity to donate their own blood (i.e., make an autologous donation). Development of an allogeneic serum eyedrop (AlloSED) manufacturing process will improve equity of access to eligible patients throughout Australia.

Method: Development of an AlloSED manufacture process was achieved via collaboration between Lifeblood medical specialists, research scientists and processing specialists to define donor selection criteria, manufacture process parameters and controls, and to develop the overall presentation and packaging of the final product. A survey of international practice was also undertaken to support process development and informed decision making.

Results: Donor selection criteria were developed based on those used internationally. These included:

- Donor assessment against Lifeblood Guidelines for the Selection of Blood Donors
- Negative for all mandatory tests (infectious disease markers)
- Male (nulligravida females only if insufficient male donors)
- Group AB (non-Rh-specific)
- Red cell antibody status negative

A closed system SED manufacture process was developed using a dedicated vial system and a weldable saline product to enable manual serum dilution to 20%. Process time constraints for serum separation and SED manufacture were defined following extensive evaluation. To support patient handling, individually labelled vials are packed into cartons containing a one-month supply. Component specifications for bacterial contamination screening and total protein to monitor dilution accuracy were also developed.

Conclusion: Lifeblood has developed an AlloSED product to meet the needs of Australian patients suffering from severe dry eye conditions, who have failed to respond to conventional therapies. The Therapeutic Goods Administration granted approval for AlloSED in 2023.

AP005

Serum eyedrop demand in the Australian community

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Aim: Lifeblood has been manufacturing and supplying serum eyedrops (SED) for over twenty years to meet the needs of a small segment of the Australian community. They are a highly specialised and high-cost intervention reserved for patients suffering from severe ocular disorders who do not respond to conventional therapies. As such, not all requests for SED can be supported. Initially, only autologous SED (AutoSED) were provided, where a patient donated their own blood for SED preparation. Since August 2020, patient-tailored SED (PT SED) have been offered; prepared from volunteer blood donations and requiring individual patient-based approval from the National Blood Authority. Demand for SED has grown consistently, and since 2020 exceeded Lifeblood's capacity to supply.

Method: To address increasing demand for SED, Lifeblood has collated request and clinical data, reviewed relevant literature, and explored alternative options. Lifeblood also consulted international counterparts to understand their experiences and processes, including eligibility criteria and guidelines for provision of SED. In 2020, Lifeblood adopted UK clinical ophthalmology guidelines and has actively monitored demand and eligibility trends thereafter.

Results: Over the past two decades, Lifeblood has supplied SED to more than 8000 patients. The proportion of AutoSED to PT SED requests is stable at 70% and 30% respectively, as is the ratio of new patients to repeat patients (31% and 69%). The most prevalent clinical indications for supply of SED include:

- Sjogren's and severe dry eye syndrome,
- Neurotrophic cornea,
- Graft Versus Host Disease, and
- Supportive therapy to promote epithelial repair after surgery or trauma.

Conclusion: As demand for SED exceeds Lifeblood's capacity to supply, clinical eligibility criteria play a vital role in assuring that patients presenting with the more severe conditions are prioritised for supply. To address demand and improve equity of access, Lifeblood is actively working towards the introduction of allogeneic SED.

AP006

What blood products are available in prehospital settings? A survey of emergency medical services in Australia and New Zealand

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Aim: To conduct research that improves how we use blood products for patients in prehospital emergency settings, we first determined to understand which products are currently used by services across our region, and when and where they are available.

Method: A cross-sectional study of blood product use by Australian and New Zealand emergency medical service organisations was conducted via online questionnaire. Services providing prehospital, retrieval and/or inter-hospital transfers via ambulance were approached to participate. The online survey included questions about types of blood products routinely available, the logistics of carrying blood in prehospital settings, along with details of the personnel involved, governance, and factors limiting the use of blood. The project was approved by Monash University's Human Research Ethics Committee (#31304).

Results: Thirty-one organisations were identified, and invited to participate. The survey was completed by 17 emergency medical services (55%). Responses were obtained from services operating within each Australian state and territory, and both islands of New Zealand. Blood products were routinely available in 13 (76%) of services surveyed, and their use was typically associated with aeromedical (helicopter or fixed-wing) retrievals. All 13 (100%) carried red cells. A combination of platelets, plasma, cryoprecipitate, fibrinogen concentrate, and/or prothrombin complex concentrates were also available for use in 7/13 services. In 2 services, 6 different types of product were carried. There was variability between services regarding when products were carried, how they were delivered to vehicles, the personnel involved, and governance processes in place.

Conclusion: Blood products were routinely used by three-quarters of the surveyed emergency medical services operating in Australia and New Zealand, and typically associated with aeromedical operations. While red cells were available in all services that carried blood, the availability of other products varied widely. Knowledge of current practice will be used to inform future research trials.

AP007

O negative red blood cell (RBC) utilisation in regional and rural Australia: how do we reduce wastage while supporting national supply shortages?

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[1]Murrumbidgee Local Health District, [2]NSW Health Pathology

Aim: To review utilisation of O negative RBCs in the Murrumbidgee Local Health District (MLHD) to determine whether inventory could be better aligned to patient blood group distribution and transfusion requirements, reducing demand on national supply while limiting wastage.

Method: A retrospective review of O negative (O neg) RBC data was obtained from the Laboratory Information System (LIS) for a 6-month period, including detailed product and patient information. Data was cross-referenced against RBC transfers, age and location at transfusion, determining utilisation based on wastage avoidance. The information was then compared against patient blood group distribution, age, gender and location to determine whether inventory could be altered to support local utilisation, blood group distribution, transfusion requirements and clinical service provision.

Results: Patient Blood Group O neg distribution for the MLHD was 5%, which was slightly lower than the national rate of 6.5%[1]. 92% of the O negative RBCs transfused were crossmatched with the following recipient blood groups receiving the units;

Recipient Blood Group	% of O neg RBCs transfused	% MLHD Patient RBC Group Distribution
O negative	22%	5%
O positive	28%	39%
A negative	13%	5%
A positive	23%	37%
B negative	3%	0.7%
B positive	8%	9%
AB negative	2%	0.8%
AB positive	1%	2%

38 units were issued under an indication of “emergency” with 43% recommended O neg red cells (female ≤ 50 years of age or male ≤ 18years of age).

Conclusion:
Clarification of RBC inventory levels and utilisation will form the basis of updated stock inventory, enabling a reduced O negative RBC level without compromising patient access for compatible RBCs or increased RBC wastage.

AP008

Anti-Jka alloimmunisation in patients with JK*A c.130G>A variant encoding Jk(a+w): a case series resolved by massively parallel sequencing.

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Aim: The Kidd (Jk) blood group system is encoded by the *JK* gene.[1] Major alleles *JK*A* (*JK*01*) and *JK*B* (*JK*02*) encode antithetical antigens Jk^a (c.838G) and Jk^b (c.838A), respectively, with phenotyping generating three common phenotypes: Jk(a+b–), Jk(a+b+), Jk(a–b+). A fourth phenotype, Jk(a–b–) or Jk_{null}, is rare.

Single nucleotide variants (SNV) in *JK* can produce weak or altered Jk^a/Jk^b antigens.[1] The most prevalent is *JK*A* c.130G>A (*JK*01W.01*). RBCs from individuals with *JK*01W.01* can present as Jk(a–) or Jk(a+^{w}) depending on the typing reagent and/or method used. This allele has been identified in Europeans, Africans, and Asians.[2] One case of a chronically transfused Jk(a+) patient carrying *JK*01W.01* formed anti-Jk^a leading to a haemolytic transfusion reaction.[3] The aim of the study was to review the full *JK* genotype for Red Cell Reference Laboratory investigations of four patients with anti-Jk^a.

Methods: Phenotyping and antibody screening were performed. Genomic DNA was extracted from whole blood samples. The *JK* gene was investigated by Massively Parallel Sequencing (MPS). DNA sequences were aligned with the *JK* reference gene (NG_011775.4) for variant detection.

Results: Anti-Jk^a was detected in all four cases. Cases 1, 2, and 3 were recently transfused and no Jk phenotyping had been performed. Case 4 was phenotyped as Jk(a+b+). Red cells from Case 4 reacted with multiple anti-Jk^a typing reagents.

DNA sequencing showed Cases 1 and 2 were *JK*01W.01* homozygote predicting Jk(a+^{w}b–). Case 3 was genotyped as *JK*01W.01/*02* predicting Jk(a+^{w}b+). For Case 4, MPS detected c.130G>A (p.Glu44Lys), c.588A>G (p.Pro196Pro), and c.838G/A. The genotype call was *JK*01W.06/*02* predicting Jk(a+^{w}b+).

Conclusion: To our knowledge, this is the first Australian report of a case series of Jk(a+^{w}) patients, carrying an altered Jk^a antigen encoded by *JK*01W.01* or *JK*01W.06*, who formed anti-Jk^a antibody. MPS helped explain anti-Jk^a alloimmunisation in Jk(a+^{w}) patients.

Reference:

1. Hamilton JR. Kidd blood group system: outwardly simple with hidden complexity. ISBT Science Series 2019;14: 3-8.
2. Guelsin GA, Horn T, Crowley J, Gaspardi AC, Castilho L, Keller MA. JK nt130G>A found on both JK*01 and JK*02 alleles in US and Brazilian Populations. Transfusion 2013;53 (Suppl 2): 163A [Abstract SP275].
3. Ramsey G, Mroz P, Thompson AA, Williams LM, Lindholm PF, Crowley J, *et al.* Anti-Jkb or hemolytic anti-Jka in two JKA/JKB β-thalassemia patients with weak Kidd mutation 130G>A. Transfusion 2012;52 (Suppl 3): 143A [Abstract SP236].

AP009

Views of General Practitioners and haematologist specialists on shared tasks and task-shifting

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Aim: The study was conducted to ascertain tasks according to both General Practitioners (GP) and haematologists that could be shared and thereby shifted to General Practitioners within their scope of practice. This was because of poor access to specialist care by regional and rural communities as well as low socioeconomic demographics.

Method: The interviews and focus group were conducted in the Illawara Region (New South Wales) spanning metropolitan, regional and rural participants. We explored urgent conditions, iron overload/haemochromatosis, iron deficiency, warfarin management, lymphoma, MGUS, pulmonary embolism, DVT, thrombophilia's, B cell chronic lymphocytic leukaemia, myeloma and lymphocytosis. There were 16 participants in total and these interviews were analysed by NVIVO.

Results: There were some haematological conditions that we found could be managed by General Practitioners. Iron deficiency and hemochromatosis being on the top that could be managed by GPs. There were several instances were phone advice given by a haematologist was sufficient.

Conclusion: There were some shared tasks that were identified which were within the practice scope of General Practitioners that they could uptake to increase access to quality specialist healthcare.

AP010

Benefits of the National Blood Authority Research and Development Program

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Section 8 of the *National Blood Authority Act 2003* prescribes a function of the National Blood Authority (NBA) as being *"to carry out national blood arrangements relating to the facilitation and funding of research"*. In September 2015, governments agreed the NBA undertake two rounds of grants to initiate a nationally coordinated effort to address gaps in evidence in the blood sector. The Program was subsequently extended to six rounds. Since 2015, the Program has funded 40 research projects to a value of $6,572,622.

In 2023, the NBA commissioned an evaluation of the Program to inform deliberations about future investment into, and sustainability of, the Program and to demonstrate accountability to the Australian public.

The evaluation considered value for money, research translation to improved clinical practice, early research pipeline, partnerships and collaboration, and contribution to the safe and effective use of blood products. A mixed methods approach was used using desktop scan and document review, stakeholder consultation, grant recipient survey and case studies.

The evaluation findings indicate significant benefits of the program including:

- translation of research to better clinical outcomes
- niche funding supports better collaboration
- research findings produced by NBA funded projects often lead to further funding from other sources
- support of early and mid-career researchers
- data literacy capacity building
- contribution to education and awareness raising.

Findings indicate the Program provides significant value for money by funding small scale research initiatives that would otherwise not be funded through competitive processes for larger funding sources. Investment in the Program has influenced knowledge development and innovation through its impact on processes, guidance and education, clinical practice and decision making. Investment in the Program has also resulted in sustainable job creation through its ability to build capacity and capability and improve the blood sector researcher base and the Program has provided seed funding to researchers as a platform for larger scale research funded through more significant sources such as the NHMRC.

AP011

Co-design of a 3D Virtual tour of a National Blood Donor and processing centre to enhance Haematology Trainee Learning.

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Aim: Haematology trainees are required to have "advanced knowledge of transfusion medicine, including aspects of donor selection, blood product collection, preparation, storage and distribution, and supply." Only a limited number of trainees can attend an onsite tour of blood collection and processing facilities to experience these processes. We aim to produce a 3D virtual tour to support equity of access for trainees. We are using a co-design process to ensure the tour meets their learning needs.

Method: Indicate the locale, sample number, principal test(s) performed, and the types of statistical analysis employed.

Results: We will collect data on the number of virtual tour views, percentage of trainees who have viewed the tour, trainee and supervisor satisfaction with the tour content and delivery of any associated materials, degree to which the tour's learning outcomes were met, if they would recommend to a fellow trainee and if they would make any changes to their clinical practice. We will also collect data on the satisfaction of the co-design process from trainees, supervisors, and other stakeholders.

Conclusion: Our project will identify opportunities and challenges of the use of innovative technology and a co-design process in the delivery of transfusion medicine education. The core 3D images and videos have the potential to be easily updated and adapted to multiple target audiences. A working prototype of the tour will be ready for demonstration by October 2024.

AP012

Integrating remote double independent blood checks in a community transfusion model

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Aim: The organisation delivers a community-based blood transfusion service. The nurse led model of care is for medically stable people with chronic health conditions.

The service implemented a digital solution using MS Teams for double independent blood checks prior to blood transfusion administration. The process involves one nurse in the home at the transfusion setting and a second nurse undertaking the independent check from their office-based location.

An evaluation aimed to assess the safety, efficiency and acceptability of the virtual double independent blood checks in a community-based blood transfusion service.

Method: We conducted a mixed methods evaluation including focus groups with nursing staff, client survey and review of nursing resources utilised. Over 500 blood transfusions were completed since the pilot commenced and the evaluation is supported by an epidemiological analysis clients referred to the service.

Results: The community blood transfusion delivers approximately 40 transfusions per month and most (91%) transfusions are of Red Blood Cells. Clients referred to the service predominately have haematological cancers with resulting anaemia or anaemia due to other underlying diseases. Low rates of both individual and system adverse events in community blood transfusion have been previously published (Sharp et al., 2021).

The initial pilot showed adherence to safe checking procedure and potential to reduce service delivery resourcing. The metropolitan wide roll-out is currently being evaluated. Our presentation will report on the implementation approach for the virtual double independent blood checks including uptake and acceptability. We will report on efficiency and effectiveness outcomes associated with the virtual checking process.

Conclusion: State the effect of the study on future patient management or the understanding of basic processes

The study will provide insight to the service and client profile of a community-based blood transfusion service. It will highlight enablers and barriers to consider prior to implementing hybrid models of care.

Reference: Sharp, R., Turner, L., Altschwager, J., Corsini, N., & Esterman, A. (2021). Adverse events associated with home blood transfusion: A retrospective cohort study. Journal of Clinical Nursing, 30(11–12), 1751–1759. https://doi.org/10.1111/jocn.15734

AP013

Reporting of non-haematopoietic cells in bone marrow aspirates

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Aim: We sought to review the reporting of non-haematopoietic cells in bone marrow (BM) aspirates in an external quality assurance (EQA) program to determine compliance with the RCPA Bone Marrow Structured Reporting Protocol[1].

Methods: The returned results for the differential counts for the bone marrow aspirates for two cases of metastatic carcinoma from an EQA program - issued in 2017 and 2023 - were evaluated. Participant responses for the presence of non-hematopoietic cells were compared to the RCPA bone marrow specimen (aspirate and trephine biopsy) structured reporting protocol. Where participants enumerated the non-haematopoietic cell line in the "Other" reporting category, the medians of the "other" cells were reviewed along with the impact of including the non-haematopoietic cells in the differential count.

Results: The number of metastatic/other cells reported for the 2017 case ranged from 0 -12, and 48 of 98 respondents chose to enumerate the non-haematopoietic cells. In the 2023 case, the median was 56.4. There was also a wide range of reported non-haematopoietic cells resulting in high CV's for the 2023 case

In both cases, participants reported the non-hematopoietic cells under the "Other" cell line, which skewed the data across the differential cell count. In 2017, of the 98 participants reporting the differential count, 51% excluded the non-hematopoietic cells from the differential in accordance with the RCPA structured reporting guideline (CS3.02b). For the 2023 case of metastatic carcinoma, of the 178 participant responses, only 22 enumerated (12%) the differential without including the non-haematopoietic cells

Conclusion:In 2014, the RCPA established a guideline to assist pathologists with a structured reporting of bone marrow biopsies which outlines the reporting of the nucleated cell differential count. The recommendation is not to include non-haematopoietic cells, such as metastatic tumour cells, in the differential. The review of the two cases shows inconsistencies in the reporting of these cells that could lead to skewed differential counts, ultimately affecting patient results.

Reference:

1. Royal College of Pathologists of Australasia (2014). Bone Marrow Specimen (Aspirate and Trephine) Structured Reporting Protocol. https://www.rcpa.edu.au/getattachment/df755a77-c2d5-422b-a4d9-2f2ca4ab0fa9/Protocol-bone-marrow-specimen.aspx

AP014

Hereditary Spherocytosis in a Newborn requiring Transfusion support.

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Hereditary spherocytosis (HS) is a genetic mutation that causes defects in the erythrocyte membrane cytoskeletons. HS is one of more common causes of congenital haemolytic anaemias. Neonates born with HS usually present with moderate anaemia and all the other hallmarks of red cell haemolysis. Prompt diagnose together with an appropriate treatment plan is important for the development and wellbeing of the neonate. This poster presentation will include the clinical development, testing and treatment of a neonate born with HS.

Full blood examination (FBE) and biochemistry results were obtained using XN-2000 Sysmex and Cobas c 702. Pre-transfusion testing performed on Ortho's Column Agglutination Technique (CAT).

A newborn male presented for routine bloods which revealed abnormal FBE parameters together with marked spherocytosis and polychromasia on blood film. The total bilirubin (TBIL) was increased throughout the course of two weeks with the peak of 319 nmol/L at day 6 and day 9 from birth. Haemoglobin (Hb) was within normal range at birth, however it started to decrease from day 5 with noted rise in Mean Corpuscular Haemoglobin Concentration (MCHC). The Hb continued dropping to 75 g/L at day 13. One unit of paediatric packed red blood cells was requested and transfused. Sample was also sent for Eosin-5-Maleimide binding testing (E5M). The result was reduced which is consistent with HS. TBIL was trending towards the normal range (160 umol/L) at day 19 after receiving phototherapy and folic acid treatment. The neonate continued to improve and is scheduled for periodic review.

Early management of newborn anaemia and jaundice is crucial in preventing further adverse events. This case study highlights the importance of early intervention and the correlation of family history and laboratory results which led to the quick recovery of the neonate.

AP015

The influence of haematological profiles on the management and mortality risk of mothers presenting to the obstetric unit of a South African tertiary medical facility

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Aim: We explore how patient age and haematological results affect transfusion and mortality in a large study of South African pregnant mothers. The haematological profiles of the pregnant patients and factors associated with increased transfusion requirements and mortality were described.

Method: Haematological profiles and transfusion history of 12889 pregnant mothers presenting to a tertiary hospital in Cape Town, South Africa, were evaluated over two years. Full blood count or haemoglobin laboratory results were evaluated for the entire population. HIV serology, prothrombin time, activated partial thromboplastin time, D-dimers, fibrinogen, C-reactive protein and ferritin results were evaluated for the 1570 transfused patients. Age, anaemia, leucocytosis and thrombocytopenia were assessed for transfusion likelihood. Iron deficiency and coagulation abnormalities were assessed in transfused patients. Anaemia, leucocytosis, thrombocytopenia, HIV and transfusion were assessed for mortality likelihood.

Results: Mothers <19-years-old had the highest prevalence of anaemia (31.5%) and proportion of transfusions (19%). The transfusion likelihood was increased in mothers with anaemia (OR = 6.41; 95% CI 5.46 – 7.71), leucocytosis (OR = 2.35; 95% CI 2.00 – 2.76) or thrombocytopenia (OR = 2.71; 95% CI 2.21 – 3.33). Mothers with prolonged prothrombin times received twice as many blood products as their normal counterparts ($p = 0.03$) and those with iron deficiency anaemia, five times more blood products ($p < 0.001$). Increased likelihood for mortality was seen in patients with anaemia (OR = 4.15, 95% CI 2.03 – 8.49), leucocytosis (OR = 2.68; 95% CI 1.19 – 6.04) and those receiving blood transfusion (OR = 3.6, 95% CI = 1.75 – 7.47).

Conclusion: Adolescence, anaemia, leucocytosis and thrombocytopenia expose mothers to a high risk for transfusion and/or mortality. These risk factors should promptly trigger management and referral of patients. Presenting haematological profiles are strong predictors of maternal outcome and transfusion risk.

AP016

Neonatal RBC transfusion in Australia: how components are used

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Aim: In neonatal intensive care units (NICUs), red blood cell (RBC) transfusions may be administered to manage anaemia of prematurity. However, concerns have emerged regarding the associations between RBC transfusion exposure and adverse neonatal outcomes.

In Australia, neonates requiring RBC transfusions commonly receive components produced by dividing standard RBC components into 4 aliquots to minimise product wastage and reduce donor exposure. Yet, these RBC components may not be optimal due to the differences between adult and neonatal RBCs.
Recent research has focused on finding alternative RBC products for transfusion in neonates, such as umbilical cord or stem cell derived products. However, determining how current and novel RBC products could be optimally provided has not been addressed.
We aim to assess how RBC components are currently administered in Australia's neonatal population, with the intention of developing optimised new products to improve transfusion safety while limiting wastage.

Method: A 5 year (2019-2023) retrospective observational review has commenced linking transfusion data between Australian Red Cross Lifeblood (Lifeblood) and Australian NICUs (Table 1). Variation of the number of components issued will be compared through time and space.

RBC component data	Volume of unit
	ABO(RhD) group
	Date of collection (donation)
	Irradiation and washed status
	Donor number – to be used to assess donor exposure
Neonate data	Gestational age and weight at birth
	Age at time of transfusion
	Volume transfused (inc. mL/kg)
	Primary indication for transfusion
	ABO(RhD) group
Neonatal unit data	Annual admissions

Results: Preliminary Lifeblood data identified a decline in distribution of paediatric RBC components over the last 5 years, most prominently since 2021.

Data from three participating Australian neonatal intensive care units will be linked with data from Lifeblood.

Conclusion: Findings may be used to design new strategies to optimise RBC components supplied by Lifeblood and to provide a better product for transfusion to neonates.

AP017

Assessing the impact of the rare Jk null variant beyond transfusion matching

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Aim: We have previously reported that the absence of urea transporter B in Jk null has global effects on the red blood cell (RBC) membrane proteome, identifying the exclusive presence of plasma proteins including haptoglobin, hemopexin and α2-macroglobulin by quantitative proteomics.

These proteins function to bind free heme with significant reduction seen in the plasma of patients with haemolysis and their presence on Jk null RBCs suggests protective compensatory mechanisms may be at play. This study assesses the potential inflammatory milieu of the Jk null phenotype.

Method: Plasma was collected and RBC ghosts prepared (5x washes, phosphate buffer) from EDTA blood samples from Jk null donors. Levels of haptoglobin, hemopexin and α2-macroglobulin in plasma and on lysed RBC membranes were assessed by ELISA (Abcam). Inflammatory cytokines, IL-1β, IL-6, TNF-α and IL-12 were quantified in plasma samples using cytometric bead analysis (BD). Samples were interrogated using BD FACSLyric and data were analysed using FCAP array (Softflow). Results were compared to normal Jk positive donors using unpaired t-tests (GraphPad Prism 9). $P<0.05$ was considered statistically significant.

Results: Apparently decreased mean levels of plasma proteins, haptoglobin (P=0.563), hemopexin (P=0.143), and α2-macroglobulin (P=0.712) were seen in the plasma of Jk null donors and apparently increased mean levels of haptoglobin (P=0.244) and α2-macroglobulin (P=0.608) were observed on Jk null RBCs. None of the results were statistically significant compared to normal Jk positive RBCs.

Levels of inflammatory cytokines in the plasma of Jk null donors had an overall higher mean than normal Jk positive donors but did not show statistical significance.

Conclusion: Healthy Jk null donors were sampled in this study and sample size was small (n=10) due to the rarity of this blood group, which may have influenced the results.
Further investigation on the significance of the presence of plasma proteins on Jk null RBCs as shown by previous proteomics results is needed.

AP018

Quality Improvement in Blood Transfusion Informed Consent Processes - Integrating the Consumer Perspective

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Aim: Informed consent for blood transfusions ensures patients are provided adequate information by their healthcare provider in a language they can comprehend and format consistent with National Standards. This quality activity illustrates how well consumers feel informed about transfusion risks, benefits, and alternate treatment options within Gold Coast University Hospitals' cancer and blood disorders unit.

Method: A survey, including eight questions, was used to attain feedback on consumer experience, and understanding of treatment.

Result: 50 consumers completed the survey. Respondents were from diverse demographic groups and varying disease profiles. All had received red blood cell and/or platelet transfusions in the inpatient or outpatient setting.

The results suggest overall satisfaction with the consent process with 98% of consumers reporting the doctor explained the reasons why a transfusion was required. 83% of consumers knew the blood product being transfused and 23% provided specific blood group details. While 20% of respondents stated that they were not aware of transfusion risks, only 2% had concerns. 28% of respondents did not recall receiving written information.

In accordance with consent guidelines blood consent is valid for twelve months if given for the same clinical indication (QH, 2024). This may have impacted results due to a delay between consent and patient recollection.

Conclusion: The results identified that consumers understood their transfusion requirements. Further work is required to ensure all elements of blood consent processes are performed. Respondents did not recall receiving written information, upon further investigation some areas used an abbreviated version of the required documentation, and not all consumers were aware of transfusion risks. To ensure consistency the ARC Lifeblood Informed Consent guidelines were circulated to ensure standardised processes and maintain consumer satisfaction.

AP019

Working together to understand Red Blood Cell Demand in Australia

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[1]National Blood Authority

Aim:

The National Blood Authority (NBA) closely monitors inventory, supply and demand pressures for blood and blood products. Demand for RBC decreased by 23.1% from 2012-13 to 2019-20 with the successful introduction of several national and local initiatives including:

- introduction of BloodNet – an order and inventory system
- publication of the patient blood management guidelines
- patient blood management implementation activities such as single unit transfusion, interoperative cell salvage and anaemia management
- implementation of the National Wastage Reduction Strategy (and subsequent Blood Product Management Improvement Strategy)
- implementation of the National Safety and Quality Health Service Blood Management Standard

Method and Results:

Following the COVID-19 pandemic, however, the demand for RBC has increased by 12.6% since 2022-21. All jurisdictions and the NBA are working closely to identify the reasons for this increase and to determine whether it is sustainable. Early indications are that the demand may be due to an increased number of emergency transfusions, extended oncology treatments, the impacts of the ageing population, and a catch up of surgical procedures halted during the pandemic. Management of the increase in demand is complicated by inventory and supply challenges exacerbated with changes in donor behaviour, local natural events (floods/bushfires) and donor illness.

Short and long-term initiatives have been implemented to assist in determining and managing the increase in RBC demand and to improve inventory management. These initiatives include:

- data definition of current and historical RBC transfusion data and data linkage opportunities
- managing inventory holdings including ABO RhD group distribution, days' cover, emergency stocks
- managing stock transfer arrangements and logistics
- ensuring consistent messaging and improved reporting and dashboards

Conclusion:

A collaborative partnership between the NBA, jurisdictional governments and the Australian health sector is key to understanding the recent increase in RBC demand, improving inventory management and achieving viable and ongoing results to assist with supply planning.

AP020

Rotational thromboelastometry in lupus anticoagulant hypoprothrombinemia

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Introduction: Lupus anticoagulant hypoprothrombinemia syndrome (LA-HPS) is a rare clinical syndrome that involves the association of acquired factor II deficiency and lupus anticoagulant that may cause haemorrhagic complications. We describe a case of LA-HPS in a previous healthy man, with data from rotational thromboelastometry (ROTEM).

Case: A 71-year-old male presented with 3 days of epistaxis and haematuria. Past medical history was unremarkable and examination revealed no bruising or petechia. Activated partial thrombin time (aPTT) was 165s (25-36s), prothrombin time (PT) 52s (10-15s) and fibrinogen 5.3g/L (1.5-4.0g/L). Mixing studies demonstrated partial correction (PT 15s, aPTT 76s). The working diagnosis was an acquired coagulation factor.

He was initially managed with fresh frozen plasma and cryoprecipitate, prednisolone 2mg/kg and oral cyclophosphamide, with mild improvement in measured coagulopathy and epistaxis. Over the next 24 hours, he developed a headache and radiological imaging revealed bilateral subdural haemorrhages which progressed despite activated recombinant factor VIIa (rFVIIa). He died in the following 6 hours.

Factor II assay was measured to be 13% and a lupus anticoagulant was found with an APTT sensitive to resistant ratio of 1.6. ROTEM prior to rFVIIa showed marked prolongation of clotting times (CT) in all assays, most marked in tissue factor-initiated curves (EXTEM, FIBTEM and APTEM). Despite normal fibrinogen and platelet count, EXTEM amplitudes were markedly reduced (A5 5mm (32-52)). FIBTEM showed minimal clot formation. INTEM A5 was mildly reduced 28mm (33-52) and MCF was normal at 63mm (51-69). Fibrinolysis was not detected. rFVIIa corrected clot amplitudes but only partially corrected CTs.

Conclusion: This is the first report of viscoelastic testing in LA-HPS. While CT was prolonged with extrinsic and intrinsic pathway activators, clot formation was more markedly impaired with extrinsic pathway activation. rFVIIa showed incomplete correction with persisting delayed clot formation. Use of prothrombin complex concentrates should be considered.

AP021

Review of monocyte-like immortal cell lines as alternative cell sources for use in the monocyte monolayer assay.

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Aim: The monocyte monolayer assay (MMA) is an important tool in predicting haemolytic reactions in patients who have developed anti-Red Blood Cell (RBC) antibodies. The in vitro, functional MMA uses monocytes from freshly isolated peripheral blood mononuclear cells to determine if the patient's alloantibody would destroy transfused RBC if antigen negative blood is not available. Freshly collected monocytes can be difficult to obtain, store and maintain for the assay. The requirement for freshly collected monocytes has been prohibitive for the assay being developed in some countries. We assessed whether monocyte-like cells would be a suitable for use in the MMA based on functionality, accessibility, longevity in culture and storage.

Method: A literature review was performed to compare the phenotypic and phagocytic characteristics of classical monocytes (as used in the standard MMA), with monocyte-like immortal cells THP-1, U937, Mono-Mac-6 and Mono-Mac-1.

Results: THP-1 cells were similar to classical monocytes in terms of Fc gamma receptors (FcγR) as well as cytokine and chemokine expression; however, differentiation of THP-1 with PMA or LPS was required to achieve a similar functionality. U937 cells did not express the same FcγR as classical monocytes and a reduced cytokine repertoire was reported. Mono-Mac-1 cells expressed FcγRI and demonstrated phagocytosis with LPS stimulation, but no specific reference in capacity for erythrophagocytosis was found. Mono-Mac 6 cells expressed FcγRI, FcγRII, many of the same cytokines and chemokines as classical monocytes and showed strong phagocytosis of opsonized erythrocytes.

Conclusion: Based on phenotypic and phagocytic characteristics, unstimulated Mono-Mac-6 or primed THP-1 cells appear the most suitable for use in the MMA. Future studies of the capacity for Mono-Mac-6 and THP-1 cells to differentiate clinically significant antibodies from non-clinically significant antibodies would be needed to determine if these immortal cell lines could be used in an MMA to predict haemolytic transfusion reactions.

AP022

The Australian Blood Donor Study and Biobank for Donor Health and Transfusion Safety Research

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Background: Research on blood donor health attributes could address issues associated with blood donation and blood product quality and provide insight into long-term health and well-being of donors as well as transfusion safety. We established a cohort of donors who consented to data acquisition through surveys and linked health data sources, and blood collection for genomic and biochemical analysis. We aimed to assess the feasibility of sample collection and processing using existing Australian Red Cross Lifeblood (Lifeblood) operations and to demonstrate the utility of this biobank for donation and transfusion safety research.

Methods: Recruitment of whole blood and apheresis donors into the Australian Blood Donor Study (ABDS) commenced with a small pilot in November 2022, then ongoing collection of blood samples throughout Australia during 2023/24. Eligible donors were recruited two weeks prior to their scheduled donations. Data from donors collected through demographic, health, lifestyle and behavioural surveys were managed in a REDCap database. Blood samples were transported to the ABDS Biobank in Sydney using existing Lifeblood logistics. Deidentified serum, plasma and buffy coat samples were extracted and stored at -80°C for future analysis and DNA extraction.

Results: The average participant age was 50 years; 55% were female and 97.1% gave permission for external data linkage. By mid-May 2024, 7376 donors had been recruited, of which 72% provided blood samples. From 5292 donor samples entered in the biobank, 97% included buffy coat samples for genomic studies, and 75% included serum for biochemistry analysis. Recruitment into the study and DNA extraction for approved genomic studies of red cell storage and donor iron metabolism is ongoing.

Conclusions: These findings confirm that recruitment of donors into an expanded longitudinal cohort study and biobank is feasible within Lifeblood operations. Our biobank samples and data are available for further health and transfusion safety research.

AP023

Preservation of functionality, immunophenotype and recovery of HIV RNA from PBMC's cryopreserved for 27 years.

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Background: Repositories of cryopreserved peripheral blood mononuclear cells (PBMC) are costly to maintain, but their suitability for immunovirological studies after decades of storage is uncertain. Cryopreserved resources in Lifeblood laboratories include cell lines and PBMC from study participants and matched transplant donor/recipient pairs, back to 1987. To determine functional integrity of legacy collections compared to recently cryopreserved PBMC, we investigated cell surface phenotypes, in-vitro function, and vial reservoirs in PBMC from HIV+ and healthy controls after 27 and 24 years, respectively.

Methods: Thawed PBMC were tested for viability, and 18-colour flow cytometry for major lymphocyte, monocyte and dendritic cell subsets. T cell subset analysis was also compared with the original immunophenotyping results from the same fresh blood sample drawn for PBMC extraction. CD4 T cell function in thawed PBMC was assessed by polyclonal activation (anti-CD3/CD28/CD2) and response to influenza antigen, by measuring CD25/CD134(OX40) upregulation (day 2 cultures) and proliferative CD25+ CD4 blasts (day 7 cultures). Intracellular HIV RNA was extracted from proliferating CD4+ blast cells. Short amplicons were quantified using pi-code assays of the Double-R and pol regions, and full-length sequencing was performed on long 4kb amplicons.

Results: Major PBMC sub-populations were well conserved. Proportions of naïve, memory and effector subsets of T cells in cryopreserved PBMC correlated with archived results from fresh blood, except for a decrease in activated (CD38+HLA-DR+) CD4 and CD8 T cells from HIV+ PBMC samples. Polyclonal and antigen-specific T cell OX40 and proliferation responses were readily detected in cryopreserved PBMC from both HIV+ patients and healthy control donors. Reactivation of HIV RNA production correlated with plasma viral loads at time of collection. Full-length sequences from 5/12 donors were ≥80% wild-type, consistent with replication competence.

Conclusion: This unique study provides strong rationale and validity of retaining well-maintained biorepositories to support immunovirological research even decades after collection.

AP024

A snapshot of our potential future blood donor population - neonatal blood group distribution from an Australian paediatric tertiary centre.

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Aim: To ascertain the distribution of ABO and RhD blood group prevalence amongst neonates undergoing routine blood group analysis.

Method: A retrospective review of neonatal blood groups at a paediatric tertiary hospital in Australia between 1st January 2015 – 29th May 2024. Cases were identified from the laboratory information system record. Data was extracted for patients < 4 months of age at the time of blood collection using the XMB code. Duplicate MRNs and 'unknown' results were removed prior to analysis. Data extraction included: date of birth, age, sex, ABO and RhD blood group and the presence of any antibodies.

Results: A total of 2,837 neonates were identified with an ABO and RhD blood group. ABO and RhD prevalence are presented in the table below. The most common blood groups were O (43.1%) and A (36.5%). The majority of neonates were RhD positive (88%), with 11.5% RhD negative. Maternal antibodies were identified in 50 patients, 47 of which were remnant passive anti-D.

ABO GROUP	RhD+	RhD-
O	38%	5.1%
A	32%	4.5%
B	13%	1.3%
AB	4.5%	0.6%

Conclusion: There appears to be a changing prevalence of ABO and RhD distribution in Australia, which may reflect the changing demographics of the Australian population due to factors such as increased migration. Our study suggests that the proportion of RhD negative individuals may be decreasing, compared with a recent study by Hirani, Weinert and Irving (2022) that reported RhD negative rates of 17.2% in individuals 0 – 9 years. We also note increasing prevalence of individuals of blood groups B and AB. Our study provides a snapshot of the prospective blood donor pool within Australia.

AP025

Assessing the impact of climate change on blood safety and sufficiency: A Scoping Review

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Introduction and Aim: Climate change poses significant threats to human health, potentially impacting the safety and sufficiency of blood and blood products. While existing literature has explored the link between climate change, emerging infectious diseases, and blood supply (1,2), a comprehensive understanding of the holistic effects of climate change on blood safety, sufficiency, and supply and demand, remains elusive. To address this gap, we conducted a scoping review examining the impacts of climate change on blood and blood product safety and sufficiency.

Method: Articles published between January 1st 1975 and April 1st 2024, were identified from PubMed, Scopus, and Web of Science. Two concepts were utilised: “Climate Change” and “Blood Supply” (table 1). Only full-text peer-reviewed original research articles, in English and with a focus on the aim were included.

Results: Out of 2,483 articles initially identified, subsequent removal of duplicates and screening left 1,206 articles. These articles were assessed for eligibility, leaving 2 papers. The first focused on dengue virus outbreaks in Australia (3), while the second on West Nile virus (WNV) outbreaks in Europe (4). Both studies projected increased viral spread under climate change scenarios. Semenza et al (2016) estimated disease prevalence in blood donor populations (4), while Bambrick et al (2009) demonstrated significant declines in blood donation, reaching up to a 100% in some affected regions (3).

Conclusion: Our review highlights that existing research is focused on the influence of climate change on transfusion-transmissible pathogens such as dengue and WNV. Further investigation is imperative to grasp the broader implications of climate change for blood safety and sufficiency.

Table 1: Concept search terms used for scoping review to identify articles relevant to climate change and the respective impact on blood product safety and sufficiency.

Concept 1 – Climate Change	Concept 2 – Blood Supply
“Global warm*” OR “Clima* chang*” OR “Temperature* chang*” OR “Clima* cris*” OR “Clima* emergenc*” OR “Global heat*” OR “Greenhouse effect*” OR “Clima* variab*” OR “Sea* level* ris*” OR “Anthropogenic” OR “Worldwide warm*” OR “World-wide warm*” OR “Internation* warm*” OR “Terraformer warm*” OR “Global heat*” OR “Internation* heat” OR “World-wide heat*”	“Blood safet*” OR “Blood securit*” OR “Blood sufficienc*” OR “Transfusion transm*” OR “Blood suppl*” OR “Blood cent*” OR “Blood bank*” OR “Blood operator*” OR “Blood servic*” OR “Blood transfusion*” OR “Blood don*” OR “Blood qualit*” OR “Dono* deferral*” OR “Adverse Event*” OR “Blood distribut*” OR “Blood logistic*” OR

OR “Worldwide heat*” OR “Greenhouse” OR “Sea* level* increas*” OR “Earth* warm*” OR “Earth* clima* warm*” OR “Clima* warm*” OR “Earth* heat*” OR “Chang* Clima*” OR “Global clima* chang*”	“Transfusion safet*” OR “Transfusion-transm*”

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AP026

A comparison study of antibody screening cells manufactured by Immulab and Bio-Rad

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Background: Sullivan Nicolaides Pathology (SNP) is one of Australia's largest and most respected diagnostic testing laboratories.
Since 2013, all SNP blood banks have utilised Immulab Abtectcell 0.8% screening cells to detect red cell antibodies. Weak reactions in screening cells as the result of clinically insignificant interference are seen sporadically and differ among batches of cells.
The aim of this comparative study was to evaluate antibody screening cells manufactured by Bio-Rad as a suitable alternative screen if required.

Method: All testing was conducted between April – May 2024 on the Bio-Rad IH500. Samples were selected to represent a range of antibody strengths and specificities. Each cohort also contained at least 30 samples with negative antibody screens. 3 consecutive cohorts (n=58, n=67, and n=58) were tested with Immulab Abtectcell Abtectcell 0.8% screening cells and Bio-Rad ID-DiaCell 0.8% screening cells in parallel.

Results: Immulab and Bio-Rad showed no less than a 90% sensitivity and specificity for each cohort of samples. 5 false positives were observed, all with unlikely clinical significance after follow up investigation using tube technique, 0.8% Immulab ID panels and 0.8% Bio-Rad enzyme enhanced panels. Immulab Abtectcell gave 3 false negative results (anti-M and cold agglutinins) and Bio-Rad ID-Diacell gave 4 false negatives (anti-Jk(b), anti-P1, prophylactic anti-D, and a cold agglutinin). None of these antibodies were positive by IAT tube technique using both Immulab and Bio-Rad 3% screening cells.

Conclusion: Unexplained weak reactivity in screening cells not attributed to clinically significant antibodies causes increased serological work and support to regional laboratories. Preliminary data from September 2023 to February 2024 showed most anti-HLA interference observed in patient samples with routine methods was removed when using Bio-Rad ID-Diacell 0.8% screening cells.

This study was conducted to determine if this reduction in interference had any implications for the detection of clinically significant antibodies.

The results of this study concluded Bio-Rad ID-Diacell 0.8% screening cells are comparative to Immulab Abtectcell 0.8% screening cells for the detection of clinically significant antibodies at a strength able to be detected by IAT tube technique.

AP027

Retrospective Review of Allo-immunisation Events in Pregnant Rh(D) Negative Women with Large Volume Feto-Maternal Haemorrhage Testing Performed through Pathology Queensland, Between 2011 and 2020.

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Aim: Detection and quantification of feto-maternal haemorrhage (FMH) guides dosage of RhD immunoglobulin (RhD Ig) for RhD negative women[1,2,3]. Current guidelines suggest confirmation of the Kleihauer-Betke (KB) test by flow cytometry especially in cases with a FMH of two millimetres or more. In our laboratory from the year 2000 until 2011, anti-D flow cytometry was reported concurrently with anti-F flow cytometry[2]. This was ceased in 2011 and anti-F flow cytometry reported solely (in conjunction with KB test result).

This audit seeks to evaluate the outcome of RhD negative women with a large volume FMH (>6ml) since this change in laboratory practice.

Method: A retrospective review was conducted of all RhD negative women, with a RhD positive infant, who had undergone FMH quantification through Pathology Queensland between 2011 and 2020 with both KB test and anti-F labelled flow cytometry. The historical charts were also reviewed to look for evidence of subsequent allo-immunisation in women with a large volume FMH, and the results of FMH quantification (using both methods) in these individuals were compared.

Results: Of the 102 patients included, 6 patients were found to have developed anti-D allo-antibodies. In these patients, there was a discrepancy between the FMH volume reported based on the KB test versus anti-F flow cytometry.

Conclusion: There was a substantial number of sensitisation events in this cohort and there was a discrepancy between methods used in our laboratory to quantify large volume FMH[4]. The discrepancy in FMH quantification between methods might have impacted the RhD Ig dosing, however given the retrospective nature of this study, it is hard to attribute causality. Further studies are necessary to validate these findings and explore their long-term clinical impacts in a broader patient cohort.

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AP028

The development, Implementation and Operationalisation of a state-wide regional Electronic Blood Refrigerator monitoring system.

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Aim: Monitoring of blood refrigerator temperatures and alarms is critical for the safety and quality of stored blood. Regional South Australia (SA) hospitals with on-site laboratories all have the Intech electronic monitoring system in place whereas ones without laboratories rely on paper-based temperature chart systems. The aim of the Intech Project was to connect all SA regional blood refrigerators with their partnered transfusion laboratory using the Intech system.

Method: The project was sponsored by SA Health's Regional Support Service, SA Pathology and the BloodMove Program, each providing either equipment purchase support and/or staff for installation. Using a staged approach, the Calibration and Testing Laboratory of SA Pathology (NATA certified for AS3864.1 and AS3864.2) installed the Intech equipment, complementing the existing hospital alarm system. Upon installation, temperature or power outage fridge alarms were acted on locally by onsite staff whereas temperature monitoring was performed electronically with the connected off-site partnered laboratory.

Results: The success of the Intech Project relied on sponsor collaboration and commitment. The process of staged trialling was successful i.e., n=1, n=7 with full rollout at n=26 sites. Challenges encountered included geographical area, site unpreparedness (i.e., backup power and network connections), staff unawareness/training and available resources. Ongoing operational issues were observed, the most common being intranet/internet network outages, preventing continuous temperature monitoring by the partnering laboratory. These outages mainly lasted for a few seconds, but longer periods could be up to a few hours. These were dealt with by system adjustments and development of robust backup processes.

Conclusion: Success of large complex projects involving many stakeholders requires commitment and collaboration. Such projects proposing unique and complex challenges and arrangements may encounter unexpected issues thereby necessitating project agility. All SA regional hospital blood refrigerators now have their temperature monitoring with their partnered laboratory, as such, ALL blood refrigerators in the SA public system now have their temperature monitored electronically with a laboratory.

AP029

Testing Blood Supply Management Through a Mass Casualty Simulation

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Aims: Effective planning, management, and coordination of the response to blood supply failures and/or demand surges is vital for optimum patient outcomes. An exercise was developed to test and evaluate state and local emergency blood management plans, including escalation and communication pathways, blood inventory management and stock movement, and to identify where improvements can be made.

Methods: A simulated mass shooting incident at a major sporting event was developed that resulted in casualties with gunshot wounds and other injuries. The exercise was undertaken with experienced personnel from the transfusion laboratory, haematologists, emergency staff, ambulance service, blood supplier, and the state incident management team. On completion, a post-exercise survey was sent out to participants. The survey included questions about appropriate communication pathways, strategies to optimise the use of blood and blood products, where blood management plans worked well and the areas for improvement and further discussion.

Results: The exercise took place over four hours. Within less than 90 minutes the majority of laboratory blood product inventory was depleted, and blood conservation strategies had to be implemented. The survey showed more than 60% of the respondents agreed their Local Health Networks had appropriate communication and escalation pathways with the relevant stakeholders. Strategies used during the exercise to optimise the use of available blood product included reducing product quantities issued in massive transfusion packs, stock rotation between laboratories, cancellation of non-urgent surgeries, and ceasing urgent and non-urgent transfusions. Areas for improvement and further consideration include clinical prioritisation, strategies for blood product ordering and distribution, removal of check grouping, splitting platelets and use of a real time dashboard for viewing stocks around the state.

Conclusions: A state-wide exercise, developed specifically to test emergency blood management plans proved an effective method and provided invaluable insights that are being evaluated to improve plans and to consider other strategies to manage any future unexpected, sudden demand on blood supply.

AP030

Building an Allogeneic Cell Therapy supply chain in Australia

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Aim: Allogeneic cell therapies present two important advantages over autologous cell-derived therapies. Healthy donor cells have a superior cell fitness and functionality compared to a patient's own cells which may be exhausted and depleted in number. Additionally, allogeneic donors allow the creation of banked off-the-shelf cellular products, therefore patient access is immediate compared with a wait of several weeks between collection and treatment for autologous therapies.

Method: In 2023 a market assessment was conducted by Australian Red Cross Lifeblood (Lifeblood) with the following scope:

- Explore whether there is a local market for further research grade, and/or new clinical grade starting materials for cell and gene therapies (CAGT).
- Identify what specific products and/or services Lifeblood could/should provide for enabling CAGT.

Over 30 interviews were conducted with CAGT experts from across Australia.

Results: According to sector experts and supported by AusBiotech's report: *Catalysing Regenerative Medicine in Australia*, *Strategic Roadmap (2021),* access to high quality, low-cost, clinical grade starting materials was a defined gap for CAGT development in Australia. While this includes viral vectors to support CAR transfusion of cells, the most pressing need were also enriched populations of peripheral blood mononuclear cells blood cells (PBMC).

There was general sentiment that Australian organisations would prefer to source enriched populations of PBMC either from buffy coats or Leukopaks produced by Lifeblood. One participant noted that "Lifeblood should position itself as the national provider of clinical grade starting materials".

Conclusion: Research and Development at Lifeblood will lead a project to lay the scientific foundations for future clinical grade allogeneic cell provision in Australia.

We will be working together with cellular therapy researchers who are developing future clinical trial applications by providing the first step in the chain of immunotherapy development.

Lifeblood will explore partnership-building with key players across the sector (nationally and internationally), engage with governments and assess funding pathways to support clinical grade product development.

AP031

Therapy and Outcomes for anticipated NAIT Pregnancies in the Australian Neonatal Alloimmune Thrombocytopenia (NAIT) Registry

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Background: International variation exists in the antenatal treatment of NAIT in at-risk pregnancies. Australian government criteria for IVIg access specify dosing at 1-2g/kg with dose capping at maternal weight of 100kg; however in some international jurisdictions, a lower dose (or no IVIg) is considered for lower-risk pregnancies (defined as no prior neonate with intracranial haemorrhage).

Aim: To describe standard of care therapy in women with NAIT anticipated or identified prior to delivery and outcomes in the Australian NAIT registry.

Method: All cases registered from 2009 to 2024 were included, defined as: pregnant women treated antenatally for NAIT, regardless of laboratory results, with antenatal therapy data and newborns from these cases.

Results: Of the 178 pregnancies in the Australian NAIT Registry, 59 cases were anticipated prior to pregnancy (9/59 were high-risk and 50/59 were standard-risk) and 16 were identified during pregnancy prior to delivery. Antenatal therapy is listed in Table 1. High-risk cases were more likely to receive IVIg and steroids and to commence IVIg earlier in pregnancy. There was no difference in the IVIg dose administered. No mothers received corticosteroids alone.

Table 1 Antenatal therapy

Factor	Anticipated high-risk	Anticipated standard-risk	Not anticipated, identified during pregnancy	p-value
N	9	36	11	
IVIg dosing				
0.5 g/kg	0/8 (0%)	2/31 (7%)	0/5 (0%)	
1 g/kg	8/8 (100%)	28/31 (90%)	5/5 (100%)	
2 g/kg	0/8 (0%)	1/31 (3%)	0/5 (0%)	
Therapy Type				0.025
IVIg only	3/9 (34%)	27/34 (79%)	4/7 (57%)	
IVIg & corticosteroids	6/9 (67%)	7/34 (21%)	3/7 (43%)	
Time from IVIg start date to delivery, median (IQR) days	162 (148, 192), N = 9	136 (111, 158), N = 34	108 (77, 138), N = 6	0.026
Time from corticosteroid start date to delivery, median (IQR) days	135 (79, 226), N = 6	28 (26, 82), N = 7	54 (2, 105), N = 2	0.11

High-risk pregnancies resulted in 9 live births; standard-risk pregnancies resulted in 36 live births, of which 2 neonates had bleeding; Cases identified during pregnancy resulted in 2 fetal deaths in utero and 8 live births.

Conclusion: IVIg therapy was recorded for 78% of anticipated NAIT pregnancies and 44% cases identified during pregnancy, with the most common dose being 1g/kg; 30% of women received both IVIg and steroids. High-risk cases were more likely to receive IVIg earlier in pregnancy, plus steroids; there was no difference in doses of IVIg. Defining current standard care in Australia is important for the design of future interventional studies of novel agents for NAIT.

AP032

Outcomes of Massive Transfusion recipients administered ABO-incompatible Fresh Frozen Plasma

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Aim: To compare characteristics of patients who received ABO-compatible or ABO-incompatible FFP during a massive transfusion (MT) episode due to any cause of critical bleeding, and assess the impact of incompatible FFP transfusion on in-hospital mortality.

Methods: Using the Australian and New Zealand Massive Transfusion Registry (ANZ-MTR), data were extracted for patients aged ≥18y who received an MT (defined as ≥5 red cell units in 4h) between April 2011 and October 2018. Incompatible FFP was defined as transfusion of ≥1 unit of FFP with a bidirectional or minor ABO-mismatch in the first 24h from MT initiation. Categorical outcomes were compared using Fisher's exact test or Chi-square. Continuous outcomes were compared using the Wilcoxon rank sum test. A mixed model logistic regression analysis, clustered on hospitals, assessed the correlation of provision of incompatible FFP with in-hospital mortality.

Results: 7340 patients from 28 participating hospitals were included. 77 (1%) patients received incompatible FFP (26 trauma, 51 non-trauma). A median of 7 units of FFP was received by those who had incompatible FFP, compared to 5 units in those who only received compatible FFP, p=0.005. A total of 226 units of incompatible FFP were provided. Provision of incompatible FFP was not independently associated with in-hospital mortality in MT (HR of 1.40 [95% CI 0.84-2.26, p=0.2]). Variables independently associated with in-hospital mortality included increasing volume of FFP given in the first 24h, age and Charlson comorbidity index score, and lower pre-transfusion fibrinogen and peri-transfusion pH values.

Conclusion: Transfusion of incompatible FFP in MT in our cohort was not independently associated with higher in-hospital mortality, although the number of patients who received incompatible FFP was small. To our knowledge, this is the first study to evaluate provision of incompatible FFP to patients in MT in non-trauma settings.

Table 1: Definition of minor-mismatched and bidirectional incompatible FFP

Patient blood group	Blood group of FFP received
B, AB	A
A, AB	B
A, B, AB	O

AP034

Quantifying the impact of an Emergent Pathogen on the Economic value of Pathogen reduction technology for Platelets

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Aim: Pathogen reduction technology (PRT) is an intervention designed to proactively reduce the amount of known and unknown pathogens in donated blood whilst maintaining the therapeutic value of the components. The aim of this study was to quantify the impact of an emergent pathogen on economic evaluation of PRT for platelets.

Method: We built a Markov cohort model assessing the economic value of PRT versus bacterial screening for platelets in the UK. Input data were obtained from the existing PRT literature, national sources, or by conservative assumption. The primary objective of the study was to perform an economic evaluation of PRT for platelets focused on quantifying the value of mitigating the risk of transfusion-transmitted infections caused by an emergent pathogen. Deterministic sensitivity analysis explored the impact of alternative time-to-emergence and incremental intervention cost scenarios.

Results: The cost-effectiveness of PRT is highly contingent on an unknown pathogen emerging and on the incremental intervention cost. PRT will be more cost effective the sooner the unknown pathogen emerges and the smaller the incremental intervention cost. In the base-case scenario, the deterministic incremental cost-effectiveness ratio was £281K/quality-adjusted life-year (QALY) gained if the pathogen emerged immediately and rose to £3.5M/QALY gained if the pathogen emerged after 25 years. Probabilistic sensitivity analysis incorporated the inherent uncertainty in predicting the morbidity and mortality profile of an unknown pathogen.

Conclusion: At current prices, PRT is unlikely to be cost effective when judged against thresholds for medicines and treatments. Given significant additional willingness-to-pay for blood safety, PRT is only likely to be cost-effective if either a previously unknown pathogen that causes chronic infection with significant morbidity and mortality emerges very soon after implementation, or the cost of PRT is significantly reduced.

AP035

Comparative Analysis of Post Transfusion Increment in Platelet Counts in Patients receiving Single Donor Platelets by Apheresis versus Random Donor Platelets

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Aim: Compare and analyse post transfusion increment in platelet counts in patients receiving SDPs vs RDPs by calculation of the absolute count increment, corrected count increment (CCI) & percentage platelet recovery (PPR) after SDP & RDP transfusion to indicate Quality analysis of Blood Centre components and their association with various disease conditions.

Method and type of study: Analytical cross-sectional study

Study Locale: Department of IHBT & Pathology, AIMSR Punjab India

Study Duration: 1.5 years (Sequential Sampling)

Sample number: 76 transfusions of each component

Principal tests performed: 3 outcome measures

1. Absolute count increment in platelet count

2. Corrected count increment in platelets (platelet $m^2/\mu l$)

3. Percentage of platelet recovery

Statistical analysis: The outcome measures were expressed as **mean and S.D.**
Statistical analysis was done using **paired and unpaired t-test, and chi square test.**

Results: Amongst 76 transfusions per SDPs and RDPs where 4-6 RDPs per transfusion were given as compared to 1 SDP, no significant difference was observed in increment parameters between both, indicating **Null hypothesis**.

No case of platelet refractoriness and transfusion reaction was reported indicating **good platelet yield and adequate storage** at Blood centre.

Conclusion: I conclude that major drawback of RDPs is not related to increment but 5-6 folds higher risk of bacterial contamination and 2 folds higher risk of TTIs as compared to SDPs. Not increment but affirming safety may justify higher production cost of SDPs in India.
As the difference between increment parameters of both products is insignificant; the decisiveness on choosing the suitable component culminates at various other factors like **cost effectiveness, availability of apheresis donors and risk of bacterial contamination/TTIs especially in developing countries like India.**

AP036

Scrutiny and significance of unknown and eluted peaks in HPLC analysis for Hemoglobin variants- A case series

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Aim: To study different haemoglobin peaks on high performance liquid chromatography in order to make a diagnosis in view of prenatal screening or HPLC screening for other medical signs like anemia.

Method:

Locale- Dept of IHBT, AIMSR Bathinda

Sample number- 06 cases

Principal tests performed- HPLC, CBC

Methodology- Cation exchange High Performance Liquid Chromatography.

Results: HPLC Screening led to diagnosing different anomalies related to haemoglobin like **Beta thalassemia major, HbD Punjab, HbE and HbQ india** leading to enhanced genetic counselling. But a proper guide to analyse different unknown peaks, eluted peaks, different levels of HbF & HbA2, different retention times is very important to NOT miss prevalence of any variable haemoglobin.

Conclusion: HPLC is an **affordable** method of screening amongst Indian population in which most **residents do not go for expensive DNA analysis** for prenatal screening. Although it is not a diagnostic test, it shortens the circumference of patients to be counselled and sent to higher centres for DNA testing.

It promotes **carrier screenin**g which involves identification of heterozygous individuals. Heterozygous persons should not marry another heterozygote for the same gene due to the risk of having affected children.

In **genetic counselling**, couples at risk are explained various options available such as **prenatal diagnosis** of affected fetus and counselling for selective termination of pregnancy and alternative methods for having a child such as artificial insemination, **adoption**, etc.
We have been frequently diagnosing different Haemoglobin variants in our population which has led to increased awareness about the importance of prenatal screening in Malwa belt of Punjab which is also a part of **Thalassemia belt** in India, but the patients are not very economically rich to afford expensive testing.

AP037

CD38 Expression is Not Varied on Donor Red Blood cells

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Aim: CD38 is a glycoprotein expressed at low levels on red blood cells[1]. Daratumumab is an anti-CD38 monoclonal antibody used in treatment of multiple myeloma known to interfere with serologic blood bank testing without causing clinically significant red cell haemolysis[2]. This study aimed to evaluate the potential variability in CD38 expression on donor red blood cells (RBCs). The study was prompted by an unexpected case of incompatible crossmatch testing (2/4 on indirect antiglobulin testing (IAT)) in a patient on daratumumab. The patient's sample had only a weakly positive antibody screen (1/4) and autocontrol. This prompted investigation of the donor unit in question, with high CD38 expression on that particular donor's red cell identified through antibody titration. The goal was thus to determine if there was significant variation in CD38 expression, which could impact appropriate red cell selection for transfusion in such patients.

Method: The study was conducted at the Australian Red Cross Lifeblood, involving 50 donor RBC samples tested in triplicate against 9 different serum samples from patients on daratumumab. Both group O and A donor red cells were used. Antibody titration at 1/10, 1/20, 1/40, 1/80, 1/160, 1/320, 1/640, 1/1280, 1/2560 and 1/5120 was performed and scores totalled to assess CD38 expression levels on donor RBCs. Statistical analysis included calculating the mean CD38 expression levels, evaluating variation using ANOVA, and calculating confidence intervals (CIs).

Results: There was no significant variation in CD38 expression among the 50 donor RBC samples tested. The mean CD38 expression across all samples was 47.3 (95% Confidence Interval 44.2 to 50.4; p 0.432).

Conclusion: The study's findings indicate that there is no significant variability in CD38 expression on donor red blood cells. The lack of significant variation in CD38 expression supports the reliability of current transfusion protocols and suggests that additional measures to account for CD38 variability are not necessary.

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AP038

A review of the RCPAQAP Transfusion Compatibility EQA program

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Aim: To evaluate the accuracy of antibody screening and identification among laboratory participants enrolled in the Transfusion Compatibility EQA provided by the Royal College of Pathologists of Australasia Quality Assurance Programs (RCPAQAP), specifically focusing on detecting and differentiating antibodies in whole blood samples.

Method: 499 laboratory participants submitting results for the 2024 January survey were assessed for their antibody screening and identification ability. The expected result was a positive antibody screen with anti-D detected. Participants utilised various techniques, including the manual tube method, to determine the presence of anti-D and other potential antibodies. The results were analysed to determine the accuracy of the screening and identification processes.

Results: Of 499 participants, 498 (99.8%) correctly reported a positive antibody screen, while 1 (0.2%) incorrectly reported a negative screen using the manual tube technique. Of the 439 participants who performed antibody identification, 365 (83.1%) correctly identified anti-D, 15 (3.4%) detected anti-D but recommended further testing to exclude additional antibodies, and 59 (13.4%) reported the presence of both anti-D and anti-C.

Conclusion: Most participants successfully identified anti-D in plasma samples, demonstrating high accuracy in antibody screening. However, a small percentage misreported results or required further testing to confirm the presence of other antibodies. The study highlights the importance of accurate antibody specificity assignment, particularly in distinguishing between anti-C+D and anti-G, to ensure appropriate RhD-Ig prophylaxis and management. Laboratories should consider the limitations in available testing resources and employ supplementary methods, such as enzyme-treated panel cells, to enhance the accuracy of antibody identification.

AP039

Transfusion Laboratory Essentials - Building transfusion knowledge for new Laboratory Scientists

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Aim: A needs analysis conducted by a national blood service identified a gap in transfusion education resources for new and returning scientists. Transfusion scientists must have sound knowledge of laboratory practice to provide a safe transfusion service. Stakeholder engagement supported the concept of an e-learning course of microcredentials. The free online course is designed to complement existing training programs with interactive modules, utilising contemporary instructional design and adult learning techniques. Although designed for new and returning transfusion scientists, the course can also be undertaken by other health professionals to gain a better understanding of the transfusion laboratory.

Method: A project team was established to develop this course including laboratory and clinical transfusion subject matter experts, instructional designers, graphic designers, and communication experts, with a transfusion medicine specialist overseeing the course.
Each module covers an essential laboratory element of the transfusion process with clear learning outcomes. Learning checks and downloadable resources will be incorporated into modules as job aids and to help reinforce key learnings. Each module will conclude with assessment questions and a downloadable certificate.

Modules in progress include: 'Blood group systems', 'ABO and Rh discrepancies', and 'Antibody investigations,' with future modules covering topics such as crossmatching, blood products and adverse transfusion reactions.

Results: The first three modules available now are: 'The Australian Transfusion Community', 'Pretransfusion testing', and 'Pretransfusion labelling requirements'.

Evaluations at the end of each module have helped us gain insight into how these modules are being received and identify what is working and what needs improving. The first three modules have been positively received, with 369 participants currently enrolled (as of 27/5/24). More statistics and feedback are being analysed.

Conclusion: This course will give new transfusion scientists the knowledge and confidence to undertake their role in a transfusion laboratory and help contribute to safer transfusions and better patient outcomes.

AP040

Highlighting the Discrepancy Rate between Lewis Phenotyping and Secretor Genotyping.

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Aim: Serological Lewis grouping is used to predict secretor status[1]. This study aimed to highlight the discrepancy rate between the predicted secretor status and the true genotype – as determined by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) analysis in healthy individuals, as well as illustrating the ease of applying molecular methods in secretor status determination.

Method: 113 participants were recruited from Dunedin, New Zealand. Participants varied in age, sex, and self-reported ethnicity. EDTA samples from each participant underwent Lewis grouping by tube agglutination and PCR-RFLP analysis to determine FUT2 (secretor) genotype. The PCR-RFLP method followed an optimised version of the Svensson, et al genotyping protocol[2]. Results were analysed to determine the discrepancy rate.

Results: Lewis grouping results predicted the sample to contain 81 (72%) secretors, 20 (18%) non-secretors, and 5 (4%) partial secretors. 7 (6%) of samples were not able to have their FUT2 activity predicted due to being Lewis negative.

PCR-RFLP analysis determined that the sample contained 88 (78%) secretors, 18 (16%) non-secretors, and 7 (6%) partial secretors. 9 allelic combination variations were observed in our multi-ethnic cohort.

4 samples (4%) had a discrepancy between the Lewis predicted secretor status and the FUT2 genotype. All discrepancies involved the partial secretor phenotype/genotype. Overall, 11 (10%) samples could not have FUT2 genotype accurately predicted by Lewis phenotyping.

Conclusion: The discrepancy rate between Lewis phenotyping predicted secretor status and PCR-RFLP FUT2 genotyping highlights the unreliability of the serological method. Lewis grouping is not sufficient to predict the partial secretor FUT2 genotype. To accurately determine the secretor status of an individual it is preferable to perform a PCR-RFLP analysis. The method undertaken in this project was robust and could be used for resolution of anomalous Lewis phenotypes, and as a research tool in disease association studies involving carbohydrate blood groups.

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AP041

Establishment of a service providing HLA compatible Red cells for Transfusion

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Aim: In response to clinician demand, we examined the feasibility of providing HLA compatible red cells for HLA typed recipients as a patient-tailored product, in the setting of kidney disease and transplantation.

Method: 1. A blood donor pool was generated using an existing panel of donors typed at HLA Class 1 for single donor platelet transfusions, with additional typing of these donors at Class 2 loci (DRB1 +/- DQA1 and DQB1), as well as Class 1 and class 2 typing of additional donors.

2. A process for receiving and assessing requests, searching the blood donor pool using an HLA-Matchmaker based matching algorithm incorporating Class 1 and Class 2 compatibility, selecting suitable donors and irradiating and supplying the product, was developed.

3. Three prospective clinical trials (HAbIT1, HAbIT2 and HAbIT3) were established with the aim of clarifying the incidence of HLA sensitisation after transfusion and ascertaining the efficacy of the product. The product was provided in the context of two of these trials (HAbIT1 and HAbIT3).

Results: A total of 84 patients were transfused with a total of 150 selected units as part of the trials. Failure to supply was rare (3 patients). 418 units were supplied but not required- all were returned to general stock. 23 patients received other cellular blood products (red cells and/or platelets) in addition to the HLA selected red cells supplied.

No de novo Class 1 HLA antibodies directed towards patient-blood donor mismatches (blood donor specific antibodies, bDSA) were detected. A de novo Class 2 bDSA was detected in 1 of 27 (5.6%) patient who received HLA selected units only, of uncertain significance.

Background rate of de novo HLA sensitisation (measured 4-8 weeks post-transfusion in comparison to a pre-transfusion sample) is estimated as 6-18% (Class 1) and 0-5% (Class 2) from the observational part of the study (HAbIT2).

Conclusion: Red cell transfusions from HLA compatible donors can be supplied as part of a blood transfusion service and may be able to prevent sensitisation to potential organ donor mismatches.

AP042

Twin to Twin transfusion and Twin Anaemia Polycythaemia sequence

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Aim: In monochorionic diamniotic (MCDA) gestations the twins share a placenta within which there are multiple vascular anastomoses, which run on the surface of the chorionic plate, and allow the blood to flow between the twins in foetal life or during delivery. Although the blood flow is balanced in most cases, in up to 15%1 of cases, net blood flow is toward one of the twins. When this occurs before birth, this is known as Twin-to-Twin Transfusion (TTTS) or Twin Anaemia Polycythaemia Sequence (TAPS), depending on the size of the vascular anastomoses and associated clinical symptoms. TTTS is caused by imbalanced blood flow through relatively large placental anastomoses from donor to recipient. TAPS on the other hand is caused by unbalanced slow transfusion of red blood cells through a few small placental ateriovenous anastomoses. When bleeding between the twins occurs during delivery, it is known as peri partum or acute TTTS. Both conditions can lead to large inter twin haemoglobin differences resulting in anaemia of donor twin and polycythaemia in the recipient twin. In this case presentation of TAPS, we reviewed clinical and laboratory features of Twin 1 (donor twin) and Twin 2 (recipient twin)

Method: Haematology results were obtained using Sysmex Haematology XN10 analysers and blood film features on both twins were reviewed morphologically. Pre-transfusion testing was performed on Bio-Rad IH500 analyser.

Results: Twin 1 (donor twin) showed a haemoglobin of 66g/L, reticulocyte count of 22.9% and Twin 2 (recipient twin) showed a haemoglobin of 247 g/L and reticulocyte count of 4.1%.

Conclusion: From antenatal ultrasound and postnatal laboratory results a diagnosis of TAPS was established.

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AP043

Community priorities for Future Transfusion Medicine Research in Australia: Outcomes of a community consultation and modified-Delphi consensus study

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Aim: To identify transfusion research priorities from the Australian community, including research that could make a difference in care delivery to transfusion recipients.

Method: We conducted a cross-sectional community survey using open-ended questions to identify transfusion research priorities. A content analysis was undertaken, whereby 1) open codes were developed and applied to each suggestion to group like suggestions together, 2) ideas that had substantial existing evidence were removed, 3) axial coding developed overarching research priority statements, and 4) the priority statements were classified into domains. Double coding, researcher discussion and consensus provided rigour. Prioritisation of research statements used a modified Delphi method via a panel of experts (including healthcare professionals, researchers, and consumers). Participants rated statements using a 5-point Likert scale. Statements that achieved consensus (≥75% of respondents rated 'important' or 'very important') were then ranked to identify the top 10. The project was approved by Monash University's Human Research Ethics Committee (#39301)

Results: The survey received responses from 101 participants, including 87 respondents who identified as recipients, carers, or blood donors. Participants provided 232 transfusion research priorities, which were grouped into 54 research priority statements across 11 domains. 23 statements reached consensus to proceed to the final ranking stage. The top-ranked statement was, to: Expand clinical trial networks to ensure a sustained focus on transfusion research, harmonise research activities, generate new knowledge, mentor younger researchers and provide trial opportunities for patients. Other priorities in the top 5 included a national antibody register, improving understanding of blood use and clinical need, establishing a national haemovigilance database, and improving information and data-sharing between laboratories and health services.

Conclusion: The community consultation engaged participants with lived experience alongside those with transfusion expertise to identify 10 priority statements, helping to progress the development of national research priorities.

AP044

Levels of agreement between various serological and molecular tests for HIV screening in blood donors.

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Aims– To reduce the spread of HIV transmission through blood transfusions many serological and molecular tests are available. The level of agreement among all these test results has hardly been accessed.

Materials and method – This was a prospective epidemiological study done for a period of 18 months from November 2021 to May 2023. Out of 5428 samples tested during the study period, 59 came positive for fourth-generation ELISA. All these reactive samples were tested by other platforms such as 3rd gen ELISA, Enzyme Linked Fluorescent Assay (ELFA), PCR, and Rapid card tests. An equal number of negative samples (i.e. 59) were also tested by all platforms.

Result – Out of all 59 samples which were positive in 4th generation ELISA only 17 came positive in 3rd generation ELISA. Out of which 13 only came to be positive in PCR. Similarly, 14 samples came to be positive in the ELFA test and Rapid test. In our study, we found the agreement to be 0.18 which is a fair level of agreement between 3rd and 4th generation ELISA.

Conclusion – Although 4th generation HIV ELISA has 100% sensitivity, false positives are more in comparison to 3rd-generation ELISA. This study reflects the burden of HIV in the local population and this result can beconsidered as a preliminary step in quantifying the risk of transfusion-transmitted HIV and implementation of different tests in blood donors.

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AP045

Total protein testing for quality control monitoring of blood components.

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Aim: To introduce protein testing using an automated testing platform for:

1. Serum eyedrops, to measure the protein concentration in the precursor serum and the diluted serum eyedrop (SED) samples, it aims to monitor the accuracy and consistency of the manual SED dilution step during the manufacturing process.
2. Pooled platelets, to measure the protein concentration in the final component, it aims to monitor and assure that target plasma content is consistently achieved, and the manufacture process is stable.

Method: The two sample matrices were assessed for their appropriateness for use with the commercial test assay, Abbott Total Protein assay (Total Protein, 7D73) on the Abbott Architect c8000 platform. They were evaluated and validated using Lifeblood test method validation procedures. Quality monitoring was implemented in August 2023 after verification for use with the Abbott Total Protein 2 (TPRO2, 04T81) assay on the current Lifeblood biochemistry testing analyser, the Abbott Alinity c platform. 1% or 4 components (whichever is greater) per month are tested and results reported in the quality control report monthly.

Results: Quality monitoring has demonstrated that SED dilution is accurate and reproducible. Specification limits were established as 11 to 17g/L, with an average total protein concentration of 13 ± 1 g/L (n= 402). Pooled platelet component quality monitoring has shown the average percentage of plasma in the components is consistent nationally across all manufacturing sites at 28 ± 2 % (n=708).

Conclusion: Total protein measurement was introduced onto the Abbott Alinity c platform for the purpose of monitoring serum eyedrop dilution accuracy and component integrity, and plasma content in pooled platelets. Testing verifies the integrity of manufacture processes for both SED and pooled platelet components.

AP046

A comPLEX situation: Therapeutic Plasma exchange in a Patient with Two Ventricular assist Devices

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Introduction: Ventricular assist devices (VADs) are increasingly being used as a bridge to cardiac transplant in children and adults. HLA-sensitisation (usually secondary to blood products required during VAD implantation) may preclude eligibility for transplant due to risk of hyperacute rejection. The addition of therapeutic plasma exchange (TPE) is an option for desensitisation protocols (Category II, Grade 1C)[7], though is technically difficult[8] and may be associated with significant complications (including bleeding and stroke).[9,10]

Case Report: Here we present the case of a 17-year-old boy with two different left and right ventricular assistance devices (VAD) for ischaemic cardiomyopathy, who was treated with TPE alongside intravenous immunoglobulin in an attempt to reduce circulating anti-HLA antibodies and enable listing for cardiac transplantation. The patient was highly sensitized, and previous pharmacologic-based desensitisation had been unsuccessful and associated with complications.

Discussion: We discuss the unique challenges of TPE in individuals with VAD, including management and monitoring of anticoagulation (with conversion to bivalirudin peri-procedure), concerns around maintenance of required flow across multiple circuits (including pulsatile flow in his BerlinHeart VAD), choice of replacement fluid and management of electrolytes. Staff from multiple services including apheresis, cardiology, intensive care and haematology planned and worked together to successfully perform multiple procedures across several weeks without complication.

As VAD use becoming more common in Australia, this case highlights the need for a multidisciplinary approach to a rare and complex procedure.

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AP047

A Comparative Study on Enzyme-Linked Immunoassay and Rapid Screening Methods in Blood Donors in Resource Constraint Settings

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Aim: To compare the effectiveness of ELISA and Rapid test methods for screening blood donors in resource-constrained settings.

Method: This study was conducted at AIIMS Bhopal's Department of Transfusion Medicine and Blood Bank over 18 months, from October 2018 to March 2019. A total of 492 blood samples from voluntary donation camps and replacement donations were randomly selected. Donors were screened following National Blood Transfusion Council (NBTC) guidelines through detailed history and physical examination. Blood samples were collected in labeled vacutainers during donation and screened for HBV, HIV, and HCV using ELISA. These samples were then retested using Rapid tests for HIV, HBsAg, and HCV. Reactive donations were discarded. Statistical analysis was performed using Microsoft Excel, with data expressed in frequencies and percentages.

Results: Among the 492 donors, 464 (94.3%) were male, and 28 (5.7%) were female. Voluntary donors constituted 136 (27.6%), and replacement donors were 356 (72.4%). First-time donors were 207 (42.1%), and repeat donors were 285 (57.9%). Most donors were aged 18-30 years. ELISA identified 7 reactive samples: 1 for HIV, 5 for HBsAg, and 1 for HCV. Notably, 1 HCV sample reactive by ELISA was non-reactive by Rapid test. All other results matched between ELISA and Rapid tests.

Conclusion: Screening for transfusion-transmissible infections (TTIs) is vital for safe transfusions. Rapid tests showed a false negative for HCV, likely due to their lower sensitivity and inability to detect certain genotypes and window period infections. It is essential to evaluate the sensitivity of rapid tests to ensure they can detect geographical virus subtypes. External factors like storage conditions and staff training also impact assay performance. Enhancing public awareness, vigilance, technical expertise, and educational programs can significantly reduce the incidence of TTIs.

AP048

Seroprevalence of hepatitis B core antibody in Australian blood donors

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Title: Seroprevalence of hepatitis B core antibody in Australian blood donors

Aim: Hepatitis B virus (HBV) infects the liver and is known to be transfusion-transmissible (TT). Whilst donor testing has decreased TT-HBV, occult hepatitis B infection (OBI) remains a risk. OBI is typically characterized by loss of HBsAg, but detectable antibodies to hepatitis B core antigen (anti-HBc). The risk of TT from OBI donors is decreased when anti-HBc screening is implemented. In Australian Red Cross Lifeblood, a risk estimate of <1 in 1,000,000 per component transfused (1) has been regarded as acceptable. For a contemporary risk-based assessment on the risk of TT-OBI, it is important to have a current measurement of the prevalence of anti-HBc in Australian donors.

Method: A national serosurvey of 10,000 Australian blood donors is being undertaken (5,000 first time and 5,000 repeat donors) with initial testing on the Abbott Alinity I analyser for anti-HBc, with initial reactives submitted for external confirmatory testing using the DiaSorin Liaison anti-HBc CLIA. We present initial data of 2921 donors, from Brisbane and Perth processing sites, from July 2023 to April 2024. Proportions were compared using chi-squared test, with $p< 0.05$ considered significant.

Results: Preliminary results from 2921 donors indicate 47 were anti-HBc initial reactive, with 43 confirmed reactive (1.47% CI=1.04-1.91%). The rate for confirmed anti-HBc was similar in first-time donors (21/1488, 1.41% CI=0.81-2.01%) and repeat donors (22/1433, 1.54% CI=0.90-2.17%) ($p = 0.81$).

Conclusion: For 1.47% of donors tested to date anti-HBc was confirmed, which is slightly lower than a prior limited serosurvey. When complete, this study will provide a current measure of the prevalence of anti-HBc in the Australian donor population. The findings will be used to model the impact of various testing strategies in Australia, options include maintaining current practice, testing of first time donors or universal anti-HBc testing.

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AP049

Treponema Pallidum Lineage prevalences in Blood from Donors Seropositive for Syphilis

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Aim: Detection of *Treponema pallidum* in donor samples has been reported previously (1). Further molecular typing was applied to determine subtypes present and compare with frequencies reported nationally and internationally.

Method: *T.pallidum* DNA detected using quantitative real time PCR, targeting conserved regions of *pol-A* and *16S rRNA* (7 *pol-A* and 4 *16S rRNA*) locally has been previously reported. All four *16S* positive PCR samples were characterised using a multi locus sequence typing (MLST) scheme (2)

Results: MLST subtyping of the 4 samples positive by *16S* indicated three SS14 subtype 2 and one Nichols subtype 20 clonal complexes.

Conclusion: Positive samples belonged to the SS14 and Nichols clonal complexes, consistent with reports of *T. pallidum* lineage prevalences both globally and locally (3). As previously reported our risk management and modern processing protocols ensure the risk of syphilis transfusion transmission in Australia is negligible.

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AP050

Non-invasive Prenatal testing using massively Parallel Sequencing: A single test system for Fetal Blood Group Genotyping.

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Aim: Maternal alloimmunization against red blood cell (RBC) antigens and human platelet antigens (HPA) can cause haemolytic disease of the fetus and newborn (HDFN) or Fetal and neonatal alloimmune thrombocytopenia (FNAIT).[1,2] Non-invasive prenatal testing (NIPT) using massively parallel sequencing (MPS) has been utilised to predict the fetal antigen status, assisting in the management of at-risk pregnancies. NIPT MPS technology tests multiple targets in a single run.[3] This study aimed to assess the sensitivity, specificity, and utility of MPS in predicting fetal phenotype.

Method: A custom MPS probe-panel targeting 43 single nucleotide variants (SNV), associated with red blood cell (RBC) antigens/human platelet antigens (HPA), and six exonic regions in the RH and MNS systems was designed. Alloimmunised pregnant women were enrolled with informed consent.

Variant calling and allele frequency was undertaken using bioinformatics software. MPS predictions were compared with various reference methods (NIPT droplet digital PCR (ddPCR), cord blood genotype and neonatal phenotype) where available.

Results: From 91 blood samples, there were 113 variant predictions (49 antigen-negative, 56 antigen-positive); eight were inconclusive. Reference method results were available for 60 MPS predictions (34 negative and 26 positive) showing 96.66% concordance. The specificity and sensitivity were calculated at 100% and 92.86%, respectively.

For one case, blood samples collected from two gestational time points were received for *RHCE*c* investigation. At 15-weeks, MPS predicted c+ while ddPCR was inconclusive, whereas, at 20-weeks, both MPS and ddPCR predicted c+. A further two cases showed discordance where ddPCR predicted C+ and E+ while MPS predicted C– and E–.

Conclusion: Ongoing comparison of results between MPS NIPT and reference methods is crucial in this study. This allows evaluation of specificity and sensitivity, and identification of method and panel enhancement opportunities early in the design and validation phase.

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AP051

Understanding trends in Immunoglobulin use in South Australia

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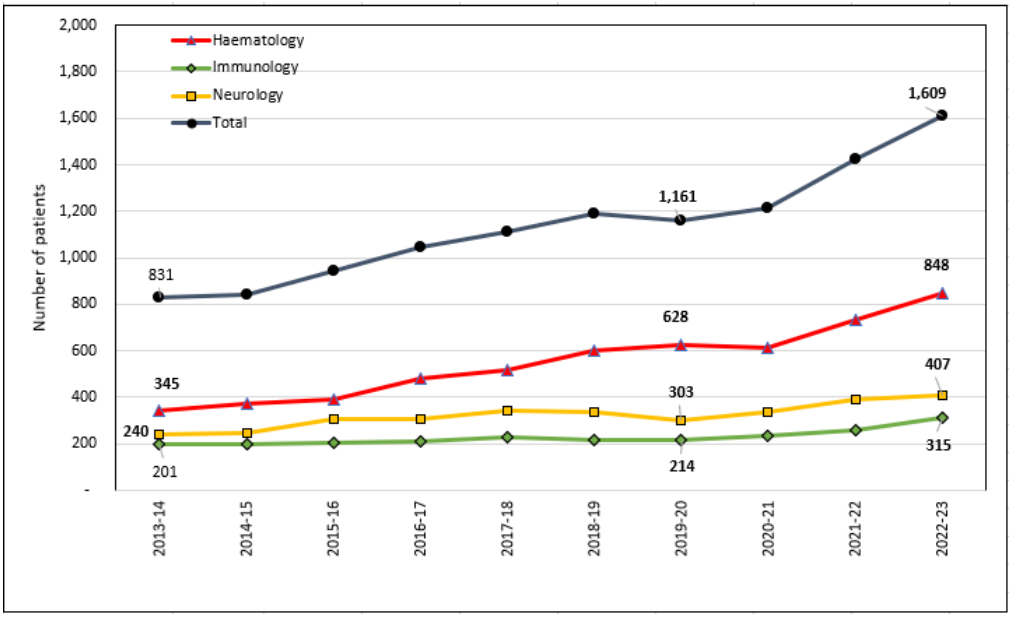
Aim: Immunoglobulin (Ig) is critical replacement therapy for immunodeficiencies and immunomodulatory treatment for autoimmune and inflammatory diseases. Despite strict criteria for use, demand for Ig has increased in South Australia (SA). The aim of the study is to examine the trends of immunoglobulin use in SA.

Method: Deidentified aggregated data provided by National Blood Authority was utilised. The number of SA patients receiving Ig and the total grams of Ig by haematology, immunology, and neurology patients between 2013-14 and 2022-23 financial year were considered.

Results: The top 10 most common specific conditions using Ig in SA are Chronic inflammatory demyelinating neuropathy (CIDP), Multiple Myeloma, Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukaemia, Multifocal motor neuropathy, Common Variable Immune Deficiency, Necrotising autoimmune myopathy, Myasthenia Gravis, Dermatomyositis and Immune thrombocytopenia. During the study period, the overall usage of Ig increased by 11.9% per year. The highest increase was seen in haematological conditions (18.5%) per year followed by neurological conditions (9.0%) and immunological conditions (5.8%) per year. Unique patient numbers increased by an average of 9.4% per year over the study period. This was reflected in annual increase of 14.6% in patients with haematological conditions compared with 9.4% increase in neurological and 7% increase in immunology patients (fig1). In 2022-23, acquired hypogammaglobulinemia secondary to haematological malignancies used 78% of the total haematology Ig and 32% of the total Ig.

Conclusion: This study provides an overview of Ig increase in South Australia especially in haematological conditions. An extension to this study is in progress to understand the Ig dosing, treatment frequencies and Ig levels prior to Ig therapy in patients with acquired hypogammaglobulinemia secondary to haematological malignancies.



AP052

Understanding the Causative Factors of Wrong Blood in Tube Incidents through a Reflection Tool.

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Aim: Wrong blood in tube (WBIT) errors, where the blood in the tube is not that of the patient identified on the label, may lead to catastrophic outcomes, such as death from ABO-incompatible red cell transfusion. A South Australian (SA) state-wide reflection tool was developed in 2019 for staff involved in a WBIT incident. The intention of the reflection tool is to allow staff an opportunity to reflect on the incident and how/why it happened, with the aim to assist with a change in practice where possible. The reflection tool forms part of the incident reporting through SA Health's incident reporting system. The aim of this study was to identify and examine contributing factors to SA WBIT incidents and to support improvement processes across the state.

Method: All WBIT incidents from 2019 to 2023 that included a reflection tool were included. All incidents were added to the REDCap database. The tool includes background information about WBIT events, instruction for consistent reporting methodology, incident details, contributing factors, suggestions for improvement and previous education regarding specimen collection.

Results: An initial 12 forms were assessed. Patient identification protocols were followed correctly in 17%, partially in 33% and not at all in 42%. The labelling process was not correctly followed in 45.3%. The tubes were not labelled at the bed side in 54.5% incidents. The main reason provided was the printing of labels outside of patient's room. The IT system (62.5%), pressure (50%), distraction (38%) and staffing levels (25%) were the most common contributing factors listed. Respondents noted that education/information in relation to specimen collection and labelling was received via eLearning, University and transfusion-service and colleagues.

Conclusion: Protocol departures from patient identification and specimen labelling processes contribute to WBIT errors. This highlights the deficiency of the IT systems as the main contributing factors.

AP053

Massive Transfusion Protocol Activations in prehospital settings

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Aim: Blood product support for SA Ambulance Service MedSTAR Emergency Medical Retrieval service has been in place since its commencement in 2009. The process evolved from daily rotation of three pre-prepared shippers each with two units of emergency O Neg red cells (RC) to a compliant monitored blood fridge being established at the retrieval operations base storing 8 units of O Neg RC being rotated fortnightly since 2015. In late 2018, a massive transfusion protocol (MTP) pack was introduced for blood product resuscitation of critical bleeding patients consisting of RC, plasma (FFP) and platelets. The MTP is carried in a bespoke lightweight, cleanable shipper suitable for the aeromedical environment. The aim of the study was to examine the blood and blood product use through MTP to manage patients during MedSTAR missions.

Method: Data on blood and blood product transfused including patient details collected during MedSTAR retrieval missions between January 2019 and March 2024 was analysed.

Results: Massive Transfusion Protocol was activated 69 times for retrieval missions during the study period. The main indications for ordering MTP pack were gastrointestinal bleeding (40.6%), trauma (15.9%) and surgery (21.7%). Since majority of the retrieval missions were interhospital transfer, 63 (91.3%) of the patients received red cells or and at least one other blood product in the treating hospital. MTP was used in 40 patients with blood product/s in the MTP pack mainly used partially. Fresh frozen plasma and platelets were used in 23 (57.5%) patients. Combining treating hospital and prehospital, the median total red cells transfused was 4 (2-6), median FFP of 2(2.0 -2.2), median platelets of 1 (1-2) and cryoprecipitate of 2(1-4) units. Of the available data, overall, in-hospital mortality was 18.8% (6/32) and within missions where MTP was used, it was 22.7% (5/22).

Conclusion: Contrary to typical activation for trauma patients in a tertiary hospital setting, the MTP was primarily activated for bleeding from other causes. Early identification of the need for a MTP is essential to support the resuscitation of critically bleeding patients and provide retrieval services teams the capability to manage transfusion in this cohort much earlier in the patients critical bleed event. .

AP054

Anti-CD36 – a new contender in HDFN or another nuisance antibody?

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Introduction: CD36 is widely considered a platelet antigen but has recently been recognised as a new blood group system by the ISBT. The antibody is now known to interfere in red cell antibody screening, showing weak non-specific reactions that may have previously been unresolvable. Anti-CD36 is implicated in FNAIT with limited evidence showing that it may also be implicated in HDFN. We describe the investigation of an antenatal patient of African descent with panagglutination detected during routine red cell antibody screening.

Method: Serology was performed using column agglutination technique (Grifols and Bio-Rad LISS-Coombs) and tube technique by PEG-IAT (Immucor). Genotyping was performed by HEA BeadChip (Immucor) and Next Generation Sequencing (NGS; Illumina).

Results: Reactivity was seen with all panel cells tested, untreated and papain treated, with a ≤2+ grading (0-4+ scale) by column agglutination. Reactivity was weaker by tube technique with only microscopic reactions seen. CD36- reagent red cells were not available and exclusion of underlying antibodies could not performed. NGS detected homozygosity for the nucleotide substitution (c.975T>G) which leads to a premature stop codon (p.[Tyr325Ter]) in the CD36 blood group protein.

Discussion: CD36 is now known to be expressed during erythroid differentiation and maturation, with low levels on reticulocytes and mature red blood cells. The highest level is seen in early erythroblasts, drawing similarities to other blood groups implicated in HDFN such as KEL. As such, antibodies directed against CD36 may lead to suppressed erythropoiesis during pregnancy.

The CD36 null phenotype is uncommon with the highest prevalence seen in African and Asian populations. There have been reported cases of severe FNAIT including fetal anaemia that have required treatment with intrauterine transfusion of red cells and platelets, however a recent report of 76 obstetric patients of African descent with anti-CD36 found no cases of severe fetal/neonatal thrombocytopenia.

The outcome for this pregnancy is not yet known.

AP055

Characterisation of THP-1 Cell activation to assess the suitability of these Cells as an alternative Cell source for the Monocyte Monolayer Assay (MMA)

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Background and Aim: The monocyte monolayer assay (MMA) is a functional in vitro assay used to predict whether antigen-positive RBCs are safe to transfuse to an alloimmunised patient. Monocyte-mediated RBC clearance is an active process involving receptor binding, cell activation, cytoskeletal rearrangement and cytokine production. MMA requires fresh monocytes, traditionally obtained by isolating peripheral blood mononuclear cells (PBMCs) from whole blood. This is a barrier to implementing MMA in some countries. THP-1 cells, a monocytic-like cell line, may be an alternative to monocytes. Therefore, we characterised the mechanisms of THP-1 activation in a modified MMA.

Method: THP-1 cells replaced monocytes in a modified MMA. THP-1 cells were left untreated (negative control), incubated with lipopolysaccharide (LPS; positive control), saline-treated RBC (RBC negative control) or anti-D-sensitised RBCs (RBC positive control) for 1 or 4 hours (h; 37^{o}C, 5% CO_2, n=6). Changes in expression of THP-1 cellular markers of cell activation, co-stimulation and adherence were assessed via flow cytometry (CD9, CD38, CD40, CD80, CD83, CD86, and HLA-DR). Statistical significance was determined using a two-tailed T-test ($P<0.05$).

Results: Compared to untreated THP-1 cells, exposure to LPS resulted in a mean decrease in THP-1 expression of CD38 (1h) and an increase in expression of CD9 (4h) and CD83 (1h and 4h). Compared to saline-treated RBC, exposure to anti-D sensitised RBC resulted in no significant change in THP-1 cell surface markers after 1h, but a reduction in mean CD38 and HLA-DR expression and an increase in CD40 expression after 4h.

Conclusions: Our preliminary findings indicated that exposure to anti-D sensitised RBC significantly modulated THP-1 cell activation in a modified MMA. Additional research is required to further characterise the response of THP-1 cells to RBC sensitised with other clinically significant anti-RBC antibodies and to assess if THP-1 could replace monocytes in a modified MMA.

AP056

Evaluation of Clinical Grade Human Serum Albumin for Therapeutic laboratory grown red cells

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Aim: Growing red cells in the laboratory requires highly defined, specialised media and growth factors. Human serum albumin (HSA) is an essential supplement that promotes cell growth and reduces cell damage by lowering reactive oxygen and nitrogen species.[1] Production of HSA differ, and a stabilising additive used in clinical preparations affects growth of mesenchymal stem cells in vitro.[2] Thus, this study aimed to evaluate clinical grade HSA (cgHSA) as a regulated and cost-effective alternative to research grade HSA (rgHSA) for therapeutic red cell manufacture.

Method: CD34+ stem cells were isolated from buffy coats by positive selection (Stemcell Technologies) and cultured to red cells in 20% rgHSA (control), 5%, 20% and 50% of cgHSA (n=3). Cell expansion, viability, morphology, and enucleation rates were evaluated on day 7, 10, 14, 17 and 21. Expression of erythroid cell surface markers (including glycoprotein A (GPA) and α4 integrin) were compared using flow cytometry.

Results: Compared to rgHSA, cells grown in 5% and 20% of cgHSA had a 1.5 and 2-fold higher total expansion rate, respectively. High cell viabilities of >89% were seen in all conditions. GPA was similarly expressed in cells grown in all conditions. Cells grown in rgHSA had highest enucleation rate of 69% on day 21. In contrast, enucleation rates decreased with higher concentration of cgHSA in culture. Erythroblast numbers and α4 integrin expression indicating cell immaturity were higher in 50% cgHSA at later stages of culture as compared to other conditions.

Conclusion: Due to their comparative expansion and enucleation rates, 5% of cgHSA appears to be a suitable alternative to 20% rgHSA. This provides a regulatory approved supplement and reduces the cost of red cell manufacture. Further work is planned to optimise cgHSA concentrations throughout culture to achieve maximum expansion rate versus enucleation rates to maximise red cell yields.

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AP057

Review of rural Victorian health services emergency use O RhD negative red blood cell (emergency RBC) holdings

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Background: One-hundred and eighteen Victorian sites (metropolitan, regional & rural) hold ≥2 emergency use O RhD negative RBC (emergency RBC). Most aren't used for emergencies, and transfused to non-group O negative patients to prevent expiry. There is no state-wide governance process to evaluate emergency RBC holdings.

O negative RBC demand has increased compared to other blood groups and O negative donors are frequently asked to donate to address the supply/demand mismatch.

Aims: To understand how emergency RBCs are managed in rural Victoria, including:
- clinical case mix supported
- geographical access to supplying laboratory and other services holding emergency RBCs
- how often emergency RBCs are used, and for what indication (emergency or non-emergency)
- stock management
- clinical governance - alignment with standards & guidelines.

Method: Surveys were sent to 37 rural health services holding emergency RBC (31 public, 6 private).

Results:
- 35 responses (95%), report 103 emergency RBCs held (average 2.9, range 2-6)
- 86 transfusion episodes were reported using ≥1 emergency RBC in previous 2 years (74 (86%) used appropriately)
- Unclear correlation between stock held, clinical case mix & distance from other emergency RBCs
- 33 (94%) report policies to manage bleeding patients
- 26 (74%) have a policy to collect preoperative pretransfusion specimens
- 21 (60%) receive laboratory reports related to emergency RBC governance, mostly wastage (52%)
- All sites (100%) report emergency RBCs available when needed.

Conclusion: Emergency RBCs are needed to provide safe care for patients, particularly where there is no on-site laboratory. A state-wide governance process could enhance transparency of emergency RBC holdings.
Health services are recommended to:
- Regularly review emergency RBC stock in relation to case mix, frequency and appropriateness of use and time to access emergency RBCs with their blood management committee and laboratory
- Review policies to align with standards & guidelines.

AP060

Investigating a novel technology for the cryopreservation of platelets

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Aim: Cryopreserved platelets have reduced platelet recovery and function following thawing and efforts to improve their quality are warranted. Vitrafy™ is a vertically integrated cryopreservation platform used to preserve numerous biological materials. The aim of this study was to compare platelets frozen using Vitrafy's technology with standard cryopreservation methods.

Method: Apheresis platelets (n=8) were prepared for cryopreservation with 6% DMSO and were concentrated by centrifugation in 2mL tubes. Platelets were frozen using either a liquid nitrogen free controlled rate freezing system (Vitrafy) or by placing directly into a -80°C freezer (control). Vitrafy platelets were thawed using the Vitrafy controlled rate thawing system and control platelets were thawed in a standard laboratory water bath. Platelets were resuspended in freshly thawed plasma and assessed by flow cytometry and thromboelastography (TEG).

Results: Platelet recovery was significantly higher in Vitrafy platelets. Surface expression of GPIIb, GPIIIa, and GPIbα was high and not different between groups. A lower proportion of Vitrafy platelets expressed GPVI and CD62P, while a higher proportion externalised phosphatidylserine compared to control platelets. The release of microparticles was higher from Vitrafy platelets. While the time to clot formation (R-time) was comparable between groups, Vitrafy platelets formed weaker clots (maximum amplitude).

	Vitrafy	Control
Recovery (%)	95±11	77±15*
GPVI (% positive)	22±5	28±9*
CD62P (% positive)	28±5	33±6*
Annexin V (% positive)	70±7	60±12*
Microparticles (x10^9/L)	183±31	155±37*
TEG R-time (minutes)	4.9±0.2	5.1±0.2
TEG Maximum amplitude (mm)	54±5	60±4*

Mean±SD; * indicates $p<0.05$ using a paired t-test

Conclusion: Overall, minor differences were observed between Vitrafy and control platelets. These data confirm the capability of Vitrafy's system to cryopreserve platelets. Further investigations and scale-up are warranted to determine if Vitrafy's technology and specific heat transfer rates produce similar results or if any enhancements to cryopreserved platelets are possible.

AP061

MDSLink: a multi-site Australian myelodysplastic syndromes registry - results update

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Aim: MDSLink aims to describe demographic, clinical and diagnostic features of patients with MDS and their treatment and clinical outcomes to enable quality improvement projects, optimise clinical practice and assess variation in care.

Method: Data on patients with newly diagnosed MDS are collected using a REDCap database and an opt-off model of consent to optimise participation. We analysed baseline data from 247 patients from four pilot sites.

Results: Data from Austin (n=57), Cabrini (n=111), Royal Adelaide (n=49) and Monash Medical Centre (n=30) were analysed. Median age was 75.3 years (67.5-81.4 years), and 63.8% cases were male.

Patients were categorised as *de novo* MDS (81.4%), therapy-related myeloid neoplasm (6.4%) and MDS/MPN (12.3%). Using WHO 2017 classification, MDS with excess blasts (MDS-EB; 40.8%) was most prevalent subcategory with MDS with multilineage dysplasia (MDS-MLD; 35.6%), MDS with ringed sideroblasts (MDS-RS; 11.5%), MDS with single lineage dysplasia (MDS-SLD; 6.3%) and others including isolated del(5q) and unclassifiable making up 5.7%.

Cytogenetic results were available for 196 patients, 60,2% normal karyotype 35.7% abnormal. Cases were classified as IPSS-R Very low (17.8%), Low (32.4%) and Intermediate (21.6%) risk. While 26.3% cases were classified as High (15.0%) and Very high risk (11.3%). Somatic mutations were available in only 29.6% patients, precluding IPSS-M analysis.

44.0% patients were red cell transfusion dependent at diagnosis, however no patients were recorded as receiving iron chelation, while 4.8% received growth factors. Most frequent disease modifying therapies were azacytidine (25.2%) chemotherapy (8.8%) and clinical trial (9.5%).

Conclusion: The successful piloting of MDSLink across four Australian sites has established the feasibility of collecting MDS patient data. MDSLink will enable further research including current projects exploring survival, health-related quality of life and describing transfusion reactions and alloimmunisation in this cohort. This multisite cohort will enable future comparison of newer classification and prognostic scoring systems.

AP062

Review of EQA performance in a Fetomaternal Haemorrhage Estimation program over 4 years.

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Aim: Detecting and accurately quantifying the volume of fetal haemorrhage is important for the welfare of RhD negative women and their newborn by guiding on the appropriate dose of RhD prophylaxis following a sensitising event. The ANZSBT updated their Guidelines for Laboratory Estimation of Fetomaternal Haemorrhage in 2021[1]. We sought to determine if the updated guidelines had any impact on the performance of participating laboratories in a Fetomaternal Haemorrhage (FMH) program provided by an Australian EQA over a 4-year period.

Method: The EQA program consists of 4 surveys of 2 samples per survey. Analytical Performance Specifications (APS) based on professional clinical opinion were used to assess the quality of returned results for Kleihauer percentage and volume (mL) and Flow cytometry method percentage and volume (mL) calculations. Analysis was performed by correlating target medians by year to the number of outliers that fall outside the upper and lower limits of the specifications that should normally prompt participant review and follow up.

Results: Between 2021 and 2024, the number of outliers remained consistent year-on-year with no significant difference ($p>0.05$) while the correlation between the target median and number of outliers also demonstrated no statistical significance ($p>0.05$). It was also noted that an average of 89% of participating laboratories were able to achieve results within the APS for both Kleihauer and Flow methods, also indicating they are performing appropriately. Subsequently, the number of RhD Immunoglobulin vials (625IU) participants elected to prescribe were appropriately correlating to their fetal bleed volume estimations.

Conclusion: The overall performance in the FMH program was stable over the 4 years. Further updates to the program are under review to better reflect the current ANZSBT FMH guidelines and related clinical context.

Reference:

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AP063

Building Australia's national transfusion data infrastructure: the National Transfusion Dataset (NTD) project

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Aim: To establish an integrated national Australian dataset on blood product use, from donation to transfusion to clinical outcome.

Method: Building on existing partnerships and working arrangements of the Australian and New Zealand Massive Transfusion Registry, the NTD will capture data on all blood products transfused in patients ≥18 years at participating hospitals, ambulance and retrieval services. Data items include demographics, ICD codes for diagnoses and procedures; laboratory results and transfusion information.

Natural language processing using the AI CogStack platform is being tested to supplement structured hospital datasets with unstructured EMR data, including transfusion reactions, cell salvage and TEG/ROTEM use. The core dataset will be linked with clinical outcomes data housed in participating registries, including critical care and blood disease registries. Looking ahead, the NTD will link with Lifeblood donor and product data to form a 'vein-to-vein' picture of transfusion practice and outcomes.

Results: Datasets covering 2017-2023 have been incorporated from 4 hospitals and health services and 2 ambulance services, comprising nearly 50,000 transfusion episodes. Pilot linkages have been completed with the intensive care ANZICS Adult Patient Database, the Aplastic Anaemia and other Bone Marrow Failure Syndromes Registry, Lymphoma and Related Diseases Registry, and Myeloma and Related Diseases Registry. Approvals have been received from a further 28 sites with data requests underway.

The NTD is being used to study hospital blood product use and provide feedback to clinicians and benchmarking reports as the NTD grows. Similar work is underway to produce reports for participating ambulance and retrieval services. Projects exploring blood product use and patient outcomes are underway in collaboration with Lifeblood and the ANZCTS Cardiac Surgery Registry.

Conclusion: The NTD will deliver a more complete picture of transfusion practice, provide evidence on blood use to support policy decisions and improve blood utilisation, and support improving outcomes for Australian patients.

AP064

What an even bigger headache, paediatric experience with Privigen® AU.

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Background: In May 2023, Privigen® AU (CSL Behring) was introduced as the domestically supplied Intravenous Immunoglobulin (IVIg) product in Australia, with limited safety data for children. The Product information notes no difference in adverse events in children compared with adults in terms of frequency, nature, or severity. Based on our experience with increased reactions following the introduction of Intragam® 10, tailored IVIg infusion protocols were implemented to minimise potential side effects in children.

Aim: To evaluate the safety profile of Privigen® AU in children and compare rates of adverse events with Intragam® 10.

Method: A retrospective, comparative study at a tertiary paediatric hospital reviewing acute and delayed adverse events, following implementation of Intragam® 10 in May-June 2017 and Privigen® AU (May-August 2023). All neonates and children who received Privigen® AU were identified through the Blood bank laboratory information system records. The Electronic Medical was reviewed to obtain information related to indication, prescribing data, dose, infusion rate, and incidence of acute or delayed adverse events.

Results:

	Intragam® 10	**Privigen® AU**
	May-June 2017	May-August 2023
Patients	123	108
Total infusions	201	212
Age (median)	9.6 years	8.0 years
Age range	1 day - 19.8 years	1 day – 18 years
IVIg dose (mean)	0.8g/kg	0.9g/kg
IVIg dose range	0.2 – 2.1g/kg	0.2 – 2.2g/kg
Acute adverse events	76/212 (35%)	57/201 (28%)
Delayed adverse events		48/201 (24%)
Aseptic meningitis	1/212 (0.5%)	2/201 (1%)*

* 4 other patients with symptoms of possible aseptic meningitis

Conclusion: Introduction of Privigen® AU has seen a significant increase in rate-related acute infusion side effects and delayed adverse events, both locally, but also nationally through adverse drug reaction reporting through the Therapeutic Goods Administration. Rates of aseptic meningitis are higher than previously reported. There is a lack of a nationally consistent means to collect data, report or monitor adverse events to IVIg.

AP065

Does the use of Non-steroidal Anti-inflammatory (NSAID) medication by Blood Donors contribute to Allergic Transfusion reactions?

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Introduction and Aim: Adverse reactions are well documented with NSAID/aspirin use, with hypersensitivity to aspirin reported in 5.7% of the population in Finland (1) and 12.5% of serious drug reactions in children due to NSAIDs (2). Mild allergic adverse transfusion reactions (ATRs) occur in 1-3% of transfusions and anaphylaxis at 1:20,000-50,000 (3, 4). Most allergic ATRs do not have an identifiable cause. As the use of NSAIDs/aspirin is common we aimed to assess any association between donors taking NSAID/aspirin before donation and allergic reactions in transfusion recipients.

Method: Data from Lifeblood ATR and donor databases were examined for 2015-2021. The ATR database captures ATR reports based on voluntary reporting from hospitals. The National Blood Management System records recent use of NSAIDs by blood donors, within the previous 2 days for NSAIDs and 5 days for Aspirin.

Results: Of 3628 ATRs, 266 were classified as allergic reactions; 241 ATRs contained sufficient component information for analysis. Of 353 implicated blood components, donor information was available for 214 - of these, 7 donors (3.3%) had records of recent use of NSAID/aspirin implicated in 6 ATRs. In 2023, recent NSAID aspirin use was reported at 4.4% of donor attendances.

Implicated components in allergic ATRs were whole blood derived (WBD) fresh frozen plasma (n=88; 24.9%), apheresis derived (APD) fresh frozen plasma (n=26; 7.4%), WBD cryo-depleted plasma (n= 3; 0.8%), WBD cryoprecipitate (n=8; 2.3%), APD cryoprecipitate (n=2; 0.6%), paediatric fresh frozen plasma (1, 0.3%), red cells (78, 22.1%), WBD platelets (89, 25.2%) and APD platelets (58, 16.4%). Components associated with donors taking NSAID/Aspirin were red cells (n=3), cryoprecipitate (n=2) and fresh frozen plasma (n=2).

Conclusion: These findings are limited by the small number of ATRs and donors, and the non-mandatory reporting of ATRs, though suggest that NSAID/aspirin use by donors is not a major contributor to allergic transfusion reactions.

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AP066

Inclusion of RiaSTAP in a regional trauma centre's massive haemorrhage protocol

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Aim: Trauma induced coagulopathy is a predictor of mortality in severely injured patients. Optimal management is not fully delineated, but early fibrinogen replacement may be beneficial. Fibrinogen replacement is available from cryoprecipitate or fibrinogen concentrate (RiaSTAP). In our regional Queensland setting, administration of fibrinogen concentrate is more rapid than cryoprecipitate and massive haemorrhage protocols (MHPs) frequently are deactivated before administration of blood products due to early activation. Our hospital, a regional trauma centre, changed our MHP to include RiaSTAP after transfusion of group O red cells, with the goal of availability of early fibrinogen replacement for severely injured patients. The aim of this study was to 1) determine the usage of RiaSTAP when MHP was activated 2) determine patients mortality rate with usage of RiaSTAP 3) assess benefits of RiaSTAP replacement over the alternative of cryoprecipitate, in terms of wastage and cost in the setting of early deactivations.

Method: A single centre retrospective audit was conducted of MHPs for a period of 9 months following the addition of RiaSTAP 3g after transfusion of 4 Group O red cells. Administration of RiaSTAP was left to clinician discretion and any unused quantity was returned to the Transfusion Medicine Department.. The de-identified patient details, location dispensed, transfused date and quantity of RiaSTAP used were collected. We will present an updated analysis (i.e., period of 12-18 months) at Blood 2024.

Results: In total, there were 42 MHP activation in above period. Only 50% on these MHPs received RiaSTAP. Mortality rate in this group was 48%. The equivalent dose of 3g RiaSTAP to 3g fibrinogen content of cryoprecipitate was $1000 more expensive, however it was noted this product was frequently returned and reissued for alternative patients. This was not deemed possible with cryoprecipitate given the short 6hr expiry once thawed.

Conclusion: Introducing RiaSTAP due to its extended stability and easy handling has reduced blood product wastage if fibrinogen was to be administered in its alternative, cryoprecipitate. Overall cost of RiaSTAP vs. cryoprecipitate will be compared in a longer time period and presented at Blood 2024.

AP068

A five-year review of Therapeutic Plasma exchange at Townsville University Hospital: Indications, coagulopathy and blood product usage

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Aim: Therapeutic plasma exchange (TPE) removes a patient's plasma along with pathogenic antibodies or other molecules, followed by volume replacement with albumin or donor plasma. Whist well-tolerated overall, TPE poses risks including depletion coagulopathy, citrate toxicity and transfusion reactions. The primary aim was to investigate procedure congruence with guidelines in addition to the impact on coagulation parameters, blood product usage and complications.

Method: A clinical audit was undertaken focusing on TPE procedures performed at Townsville

University Hospital between January 2017 and December 2021. Adult patients receiving at least one full exchange for an acute indication were included in the data set. Descriptive statistics were primarily used in addition to Mann-Whitney-U testing to compare means of pre-procedure clottable fibrinogen levels between different exchange frequencies. The significance of citrate toxicity rates and post-procedure cryoprecipitate use relative to replacement fluid type were each analysed using Chi-square testing.

Results: A total of 433 TPE procedures over 88 different acute episodes were performed. Procedures followed American Society for Apheresis guidelines regarding exchange frequency and replacement product use in 75% of cases. Post-procedure values for clottable fibrinogen were shown to decreased by an average of 49.5%. For patients being exchanged against albumin there was a significant difference is pre-procedure clottable fibrinogen between the daily (median=1.76g/L) and the less frequently exchanged group (median=2.17g/L); U=597, p=.008. Transfusion reactions and citrate toxicity were more common in exchanges against plasma products.

Conclusion: The majority of exchanges being performed are congruent with guidelines. Hypofibrinogenaemia is more likely following daily exchanges against albumin when compared to less frequent procedures. Less frequent exchanges where clinically appropriate will reduce plasma product usage. Higher rates of citrate toxicity and transfusion reactions need to be considered when using plasma. Bleeding events complicating TPE are rare.

AP069

Establishing a massive haemorrhage protocol in rural Australia - because one size does not fit all

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Aim: To develop a practical, evidence-based protocol that considered limited, variable resourcing across the regional and rural health district, while promoting improved outcomes.

Body: Establishing an evidence-based approach to the implementation of guidelines which considers available resources, remains challenging in the setting of regional and rural Australia. In 2023 the National Blood Authority (NBA) updated the *National Patient Blood Management Guideline for Adults with Critical Bleeding*[1], which included key recommendations and practice points for improved outcomes for patients presenting with critical bleeding.

In this rural health service, there is significant variation in resources related to accessibility of interventional radiology and surgery, blood product availability, and pathology services for specimen processing and product dispensing. The challenge being, development of a MHP that optimises local resourcing and service provision across all 31 hospital facilities, while incorporating recommended evidence-based practice. The key objectives included: improving service access to manage critical bleeding effectively; optimising patient outcomes through targeted therapy and reducing coagulopathy related complications; and preventing avoidable wastage of blood products. Inventory challenges are compounded by the need to balance product readiness and avoidable wastage and preventing the oversupply of emergency release blood products such as AB plasma and O negative red cells.

All MHPs over a 12 month period were reviewed to understand barriers and challenges in the management of patients with critical bleeding. Extensive consultation improved understanding of local resourcing requirements to enhance the MHP. Key outcomes included: initiating an internal triage and transport network service and; separating transfusion treatment packs into a “Controlled Critical Haemorrhage Pack” or a “Massive Haemorrhage Pack”.

Conclusion: Rural facilities can safely optimise patient outcomes and provide evidence-based care for patients with critical bleeding. This requires targeted consultation and consideration of local challenges.

AP070

Are we going backward: increase in overnight transfusion post pandemic

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Aim: Non-essential overnight transfusion interrupts the recipient's sleep and also that of neighbouring patients. Transfusing overnight can also expose the patient to avoidable risk factors such as inadequate observation and monitoring, related to the reduced lighting and lower staffing levels. NZBS conducted an audit of overnight transfusion in 2011 and recommendations were implemented in strengthening blood policy to avoid overnight transfusion and maximise the opportunity to transfuse during the day.

Three years on since the Covid 19 pandemic was declared, Auckland Blood Bank has noticed a higher number of blood requests arriving in the evening. Feedback from ward nursing teams at Auckland City Hospital is that blood transfusion is being prescribed later in the day.

To see the percentage of the red cell units administered overnight between the hours of 8pm and 8am post pandemic compared with pre pandemic levels and with NZBS' 2011 multi-site audit.

Method: The transfusion nurse specialist undertook a retrospective audit of red cell issues at Auckland Blood Bank, New Zealand's busiest blood bank, during the audit months in 2019 and in 2023. The total number of red cell transfusions of the audit period was provided by NZBS' data analyst.

Results: Overnight transfusion post pandemic has indeed increased (13.9% vs 17.8%, $p = 0.021$). During March and April in 2019, total 1,731 units were transfused with 260 units overnight. The number of units transfused overnight during the same months in 2023 was 294 out of 1636 units. However, both audit periods had more than doubled or nearly tripled compared to the NZBS' multisite audit in 2011 where the overnight transfusion in Auckland City Hospital was 6% ($p < 0.00001$ when compared with 2019 and 2023).

Conclusion: This audit has shown a significant increase in the amount of overnight transfusion compared to the 2011 audit. Although the recommendations in 2011 have been implemented, it does not appear hospital adheres to the policy increasing safety risk in patients.

AP071

Self-managed red cell transfusions: poor specificity causes risks in chronic transfusion

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Aim: To pilot, using a mixed methods design, patient requested red cell transfusions.

Method: Patients requiring chronic red cell transfusions, other than for haemoglobinopathies, were recruited at a single centre. Following informed consent, patients were transfused a single unit of red cells daily until they felt they felt symptoms were managed. The haemoglobin level was used to guide further transfusion dosing, which were initiated by patients based on symptoms. Patients were blinded to their haemoglobin results. Patient outcomes were measured by FACT-An scores, six minute walk tests and a daily diary.

Results: Of a planned 15 patients, 3 were recruited before study cessation. One patient continued to request red cells during their second transfusion episode, due to persisting dyspnoea. Medical review revealed congestive cardiac failure and the patient had symptomatic improvement with diuresis despite a fall in haemoglobin. Another was successfully managed with self-directed transfusions for several months, however received transfusions with normal or near-normal haemoglobin levels due to fatigue, palpitations and shortness of breath unrelated to anaemia. The patient reverted to scheduled transfusions. The third patient requested transfusions while being treated for sepsis with a haemoglobin of 127g/L. Six minute walk tests did not always improve following transfusion, in this limited sample.

Conclusion: All three patients requested transfusions for symptoms unrelated to anaemia, potentially leading to harm from transfusion associated circulatory overload in one case, and ineffective therapy in others. Self-managing transfusion was deemed potentially harmful due to poor specificity of the symptoms of anaemia in a population with multiple comorbidities. Further research should identify patient factors that may assist in selection or physiological measures of the impact of anaemia.

AP072

Distribution of ABO Predicted Phenotypes among Voluntary Blood Donors by Next Generation Sequencing - Insights from Kenya

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Aim: The ABO system is a major determinant for successful blood transfusion and organ transplantation. Serology is the gold standard for ABO blood group determination, however, it has a limitation particularly in the identification of the weak subtypes in the ABO system which carries a threat of haemolytic transfusion reaction to transfusion recipients. Hence, the need for genetic analysis of ABO antigens evaluation in cases where serologic testing may fail to accurately determine the presence of these weak phenotypes. The study aimed to investigate the ABO genotypes in a Kenyan blood donor population to enhance safety in transfusion and transplantation practices[1].

Method: Blood samples were collected from 191 blood donors at the Kenya National Blood Transfusion Service. Red cells were phenotyped for ABO. Genomic DNA was extracted from whole blood and sent to Australian Red Cross Lifeblood, Brisbane for next generation sequencing using a custom capture panel. Determination of genotypes and phenotypes was via use of VCF files, wANNOVAR and RBCeq webservers plus ISBT tables[3, 4, 6,]

Results: Of the 191 samples, eleven phenotype combinations were predicted: O (50.3%), A_1 (16.2%), B (10.5), A_1 or B (6.8%), A_1 or A_2 (5.8%), A_2 (4.7%), A_1 or A_X/A_{weak} (1.6%), B or B_3 (1.6%), A_1B (1%), A_2B (1%) and B_{weak} (0.5%). A genetic variant was identified at nucleotide c.655C>T, resulting in an amino acid change, p.His219Tyr, in the protein.

Conclusion: Sequencing detected alleles associated with weak antigen expression that were missed by serology (A_1, A_2, A_{weak}, B_3 and B_{weak})[2]. Comparing the outcome between phenotyping and genotyping, it is evident that serology method was limited in the identification of the weak types including those of A and B[5]. This data forms the evidence to advocate for a genotyping reference laboratory and a red cell panel that is African specific.

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AP073

Estimation of Blood utilization in common Elective surgeries: A key to formulate Maximum Surgical Blood Ordering Schedule

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Aim: This study aimed to estimate blood utilization and design a blood ordering schedule as a guide to normal transfusion needs for common elective surgeries in a tertiary care hospital in northern India.

Method: Observational-cross sectional study was undertaken for 12 months. 53 elective surgeries across 8 different specialties were analysed including Urology, Cardiothoracic, Gastroenterology, Paediatrics, Oncology, Orthopaedics, Obstetrics and Gynaecology, and Otorhinolaryngology. Blood utilization indices – Crossmatch to Transfusion (CT) Ratio, Transfusion Probability (TP), Transfusion Index (TI), Blood Utilization%, Non-Utilization Probability, and Blood Ordering Quotient (BOQ) were calculated against standard blood usage to formulate the Maximum Surgical Blood Ordering Schedule (MSBOS).

Results: For 882 patients, 1160 PRBC units were requested and cross-matched. 574 units were transfused. Non-utilization of 586 units (51%) suggested indiscriminate ordering of blood. The non-utilization of units cross-matched ranged from 27% to 100% in different surgical specialties. Overall TP was 48.64%, varying from 13.37% in Urological Surgeries to 88.89% in Cardiothoracic Surgeries. The CT ratio ranged from 1.37 to 7.31 and TI from 0 to 2.03 in different procedures. While overall CT ratio, TP, and TI were acceptable, ineffective blood usage was observed in 22 of the 53 surgeries.

Conclusion: Developing countries face challenges in ensuring adequate blood supply due to a lack of voluntary donors, inadequate storage facilities, and improper ordering practices. Given the limited availability of blood and the associated risks with transfusions, it is essential to use blood judiciously. Based on research findings, revisiting blood ordering patterns can reduce over-ordering. Hence, implementing MSBOS would enhance blood utilization efficiency during elective surgeries.

AP074

Blood Product Transportation from Blood Bank via Pneumatic Tube System to Operating theatres -validation and set-up.

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Aim: At Australia's first heart hospital, the Victorian Heart Hospital, we aimed to validate blood product delivery via the Pneumatic Tube System (PTS) to operating theatres (OT) to facilitate timely delivery.

Method: Pre-programmed Radio Frequency Identification (RFID) canisters were used to transport fresh blood products between blood bank (BB) and OT. These canisters are programmed to travel only between these two locations and prioritised over canisters along other routes.

Up to 4 (250mls each) saline bags were transported to and from BB and OT to validate transport time, test the maximum weight/space capacity of canisters and ensure arrival at the correct site. This established that the canisters were able to hold up to 1kg in weight and arrive at the correct destination. Blood products were then transported which included:

a. Red cells – 14 units
b. thawed fresh frozen plasma (FFP)– 8 units
c. thawed cryoprecipitate units- 20 units
d. Platelets – 4 units

We used a surface infrared thermometer (FLUKE566) to measure the pre-launch and post–arrival temperatures of products, to ensure acceptable temperature range during transport.

Results: We established that up to a maximum of 4 red cell units, 4 FFP units, 2 platelets and 10 cryoprecipitate units, can be transported in a single canister, without affecting the validity of the product (integrity and temperature) and arriving at the correct site within 5 minutes). The tracking and timestamping requirements resulted in extra paperwork and increased preparation time for products compared to manual transportation. Further, the maximum number of units per canister limits the speed of product delivery.

Conclusion: We successfully validated the PTS system for transport of blood products from Blood Bank to Operating theatres, first establishing transport time and weight capacity of the canisters and then ensuring blood products remained in acceptable temperature and had timely delivery.

AP075

Saving out CELL'ves.

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Introduction: Cell salvage is a safe and effective established mode of conserving a patient's own blood during surgical procedures.

Aim: To review the use of Cell-salvage and the cost savings at a tertiary paediatric hospital and determine whether receiving cell salvaged blood intra-operatively reduced the need for post operative Red Blood Cell (RBC) transfusions.

Method: Data was collected from cell salvage report data and the digital medical record to determine patients who received cell salvaged blood between January 2022 and December 2023 including surgical specialty and procedure type, as well as the laboratory Information System (LIS) for blood product usage. This data was reviewed to determine volume of intraoperative autologous transfusions received and costings of blood product savings, as well as to determine any post-operative allogeneic blood transfusions received. The National Blood Authority "what blood products are supplied" document was used to determine cost savings.

Results: Between January 2022 and December 2023, 112 patients received intra-operative autologous blood via intra-operative cell salvage with a total of 25,628mL transfused.

Based on a standard RBC bag (~250mL) costing $375.03, approximately 103 standard RBC units were saved, with a cost saving of $38,628 during the audit period.

Three main specialties utilised Cell Salvage methods with Spinal being the biggest user (49%), followed by Cardiac (38%) and Orthopaedic (13%).

Nine (9) patients received allogeneic RBC transfusion post-operatively, 78% (n=7) of these were complex cardiac patients, with the remaining 22% (n=2) patients being spinal patients. Sixty seven percent (67%) of patients received one unit (range 1-2), with 67% of recipients receiving the RBC on day one post operatively (range 1-6).

Conclusion: This retrospective review showed that the use of cell salvage was effective in both cost saving to the hospital as well in reducing post-operative allogeneic transfusion to patients.

AP076

Implementing a Patient Blood Management (PBM) pre-operative anaemia protocol during the COVID-19 pandemic at a multi-site tertiary health service: did it work?

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Aim: PBM guidelines recommend optimising preoperative anaemia (PA) & preoperative iron deficiency (PID) prior to major elective surgery. In May 2021, during the COVID-19 pandemic, we implemented a PA/PID screening and management protocol in Victoria's largest public-health network (encompassing four hospitals). We aimed to evaluate the effectiveness of protocol implementation, including practice changes and patient outcomes (RBC transfusion rates, length of stay [LOS]), comparing "pre-implementation" vs "post-implementation" periods.

Method: Retrospective audit of all patients>18years admitted for major elective surgery from 1st August 2019–28th February 2023. Anaemia defined as: Hb<120g/L (females), Hb<130g/L (males). ID defined as ferritin<30ug/L; or ferritin 30-100ug/L if CRP>5mg/L.

Results: 1277 patients (54% male, median age 67y) were admitted, totalling 1412 surgical admissions (Table 1); 767(54.3%) pre- and 645(45.7%) post-implementation. PA prevalence overall was 28.5% (403/1277), of whom 22%(88/403) had confirmed iron deficiency anaemia. PA and PID prevalence increased post-implementation (Table 2). ***Practice changes (Table 3):*** Post-implementation, preoperative ferritin testing increased (51.0%*vs*22.7%,p<0.001), as did preoperative iron infusions (10.4%*vs*6.9%,p=0.02). Iron infusions were given 27 days (median) preoperatively (IQR 7-82). ***Outcomes:*** LOS was longer in patients with PID (7*vs*6 days, p<0.001) and PA (9*vs*5 days, p<0.001). For patients with PA, there was no difference in LOS pre-*vs* post-implementation (9*vs*10 days, p=0.2). Postoperative RBC transfusion occurred in 16.7% of admissions, with no difference post-implementation(15.5%*vs*17.8%,p=0.2). Patients with PA treated with IV iron tended to have lower transfusion rates vs untreated, though not statistically-significant (24.2%*vs*33.3%,p=0.097).

Table 1: Admitting elective surgery specialties

Specialty*	***N (%)***
Orthopaedics	715 (50.6%)
Colorectal	372 (26.4%)
Upper gastrointestinal	171 (12.1%)
General surgery	30 (2.2%)
Gastroenterology	28 (2.0%)
Gynaecology	17 (1.2%)
Other	79 (5.6%)

**Only includes elective surgeries at risk of major blood loss (postop Hb drop ≥30g/L)*

Table 2: Prevalence of preoperative anaemia, ID and iron deficiency anaemia (IDA)

Prevalence* of	***Total (N=1412 admissions)***	***Pre-implementation (N=767)***	***Post-implementation (N=645)***	***p-value***
PA (n,%)	403 (28.5%)	177 (23.1%)	226 (35%)	**<0.001**
Preop iron def anaemia (n,%)	88 (6.2%)	27 (3.5%)	61 (9.5%)	**<0.001**
PID (n,%)	156 (11.1%)	42 (5.5%)	114 (17.7%)	**<0.001**

**Based on 1229 patients with preop Hb & 502 patients with ferritin available in medical records*

Table 3: Changes in practice pre vs post-implementation

Preoperative practices	***Total (N=1412)***	***Pre-implementation (N=767)***	***Post-implementation (N=645)***	***p-value***
Ferritin testing (n,%)	503 (35.6%)	174 (22.7%)	329 (51.0%)	**<0.001**
Hb testing (n,%)	1229 (87.0%)	661 (86.2%)	568 (88.1%)	0.3
Iron infusion (n,%)	120 (8.5%)	53 (6.9%)	67 (10.4%)	**0.02**

Conclusion: Preoperative iron testing and iron infusions increased, as expected, following protocol implementation. PA was common (28%) and associated with increased LOS. We implemented the protocol successfully during the pandemic. The trend towards lower transfusion rates in patients with PA treated with IV iron is encouraging. We identified areas for further PBM work including improving preoperative Hb/ferritin testing rates and evaluating the role of peri/postoperative iron infusions.

AP077

Are you Kidd-ing me? Managing Rare Donors and Inventory for increasing numbers of patients with an anti-Jk3

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Aim: The aim of this study is to review our current pool of Jk(a-b-) donors and compare this to the number of potential recipients (patients) identified with an anti-JK3 across Australia from 2023-2024.

Method: A retrospective review of all patients identified through the Lifeblood Red Cell Reference Laboratory (RCRL), with the Jk(a-b-) phenotype and an associated anti-JK3 was performed. Data extracted included patient gender, ABO and Rh phenotype. Serological investigations were carried out using standard RCRL procedures. Confirming the specificity of the antigen was achieved via phenotyping in combination with the 2M Urea lysis test.

Results: We identified 15 Jk(a-b-) potential recipients, of whom five were male and ten were female. Nine were group O, and the remaining six group A. Nine individuals were noted to have an anti-Jk3 in isolation, whereas the other six had multiple alloantibodies, the most common of which was anti-Jk^a. We provide details regarding the number of potential donors, a ratio of potential donor to recipients with respect to ABO and Rh phenotype, and review the impact of individuals who are concurrently both potential donors and recipients.

Conclusion: The Jk(a-b-) phenotype is rare, with sensitisation leading to a possible anti-JK3. Supporting patients with an anti-JK3 can be challenging, a problem that is increasingly complex when there are a number of patients with an anti-JK3 reliant on a small donor pool. This donor pool is impacted by ABO and other phenotype requirements for donations, illness and pregnancy, and the need to replenish their own red cell stores between donations. Opportunities to increase the recruitment of Jk(a-b-) donors is discussed, and the ethical considerations relating to the allocation of donations where multiple recipients require transfusion support simultaneously.

AP078

Implementation of Smart Fridge Technology to improve patient safety

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[1]Alfred Health

Aim: To mitigate the risk of removing incorrect blood from a remote blood fridge. This safety improvement initiative was prompted by a serious incident where a patient was administered blood products that were cross-matched and labelled for a different patient.

Method: The transfusion team proposed the implementation of a smart fridge that uses barcode scanning technology to only release blood products for the named patient. The optimal smart fridge solution was identified and funding secured. Multiple teams collaborated to build, test and plan the rollout. Laboratory staff worked with Information Technology to ensure system functionality and conduct testing and integration within the laboratory system. Training sessions were organized for both clinical and laboratory staff. Staff were provided with barcodes for name badges to facilitate ease of access to the smart fridge. Implementation occurred with live onsite support from the Transfusion Team and the vendor during the initial week. Ongoing monitoring is conducted.

Results: In the six months' post implementation 91 units of red cells have been remotely dispensed. No instances of incorrect blood product transfusions or near-miss episodes have been recorded. Staff feedback from end users indicates satisfaction with its user-friendly interface. Blood product traceability and storage has also been enhanced as the blood bank now has access to real-time product movement and temperature deviation alerts. Despite encountering some unforeseen technical challenges during the initial phases of implementation, prompt resolutions have been achieved.

Conclusion: The implementation of smart fridge technology has increased patient safety and positively impacted the storage and tracking of blood products. This experience has the potential for broader adoption in other areas of the Health Service.

AP079

Optimization of Anaemia in Pregnant women with Bleeding disorders: A single tertiary-centre experience

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Background: Women with bleeding disorders face significant haemostatic challenges during pregnancy and childbirth, with increased risk of post-partum haemorrhage[1] (PPH). All pregnant women should be assessed for iron deficiency and anaemia at 28 weeks with optimization prior to labour [2].

Aim: Document treatment of iron deficiency in pregnant patients with bleeding disorders. Methods: Single-centre audit of pregnant women with bleeding disorders who delivered at a tertiary hospital, March 2023- March 2024. Haemoglobin, ferritin, and interventions were documented at 28 weeks gestation, re-assessment, and term. Iron deficiency was defined as ferritin<30[2] and anaemia haemoglobin<110g/L[2]. Optimization and PPH outcomes were measured.

Results: 38 post-partum women with bleeding disorders were identified, including thrombocytopenia 68%, Von Willebrand 24%, factor deficiencies 8%. Only 89% had FBP and ferritin testing at 28 weeks gestation. Of these, 62% had ferritin<30 (19% anaemic), with 81% appropriately managed as per guidelines. On response assessment 4 weeks later, 19% had been optimized with adequate iron replacement (ferritin >30). Concerningly, 67% remained iron deficient, without a change in therapy. 14% did not have response assessment. Additionally, by 36 weeks gestation, 31% of those not previously requiring intervention became iron deficient, with only 25% treated. At term 16% had PPH, with 33% having ferritin <30. Only 50% of those with PPH had post-partum FBP, none had ferritin re-checked, none were transfused.

Conclusion: Optimisation of iron deficiency and anaemia is standard of care in pregnancy. In patients with increased bleeding risk, this is an opportunity for intervention. In these at-risk groups, testing must comply with obstetric guidelines, and both retesting to assess response to therapy and to ensure those not requiring intervention remain iron replete is essential. PPH can confer morbidity and mortality, therefore optimization of iron deficiency and anaemia is a critical intervention to reduce this risk.

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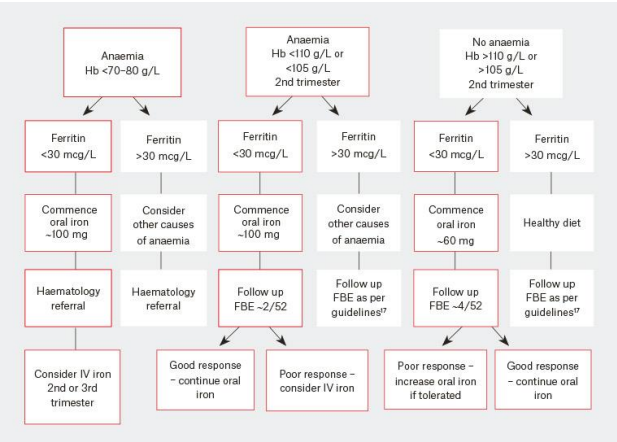

AP081

Prevalence and follow-up of post-operative anaemia in South Australian cardiac surgery patients

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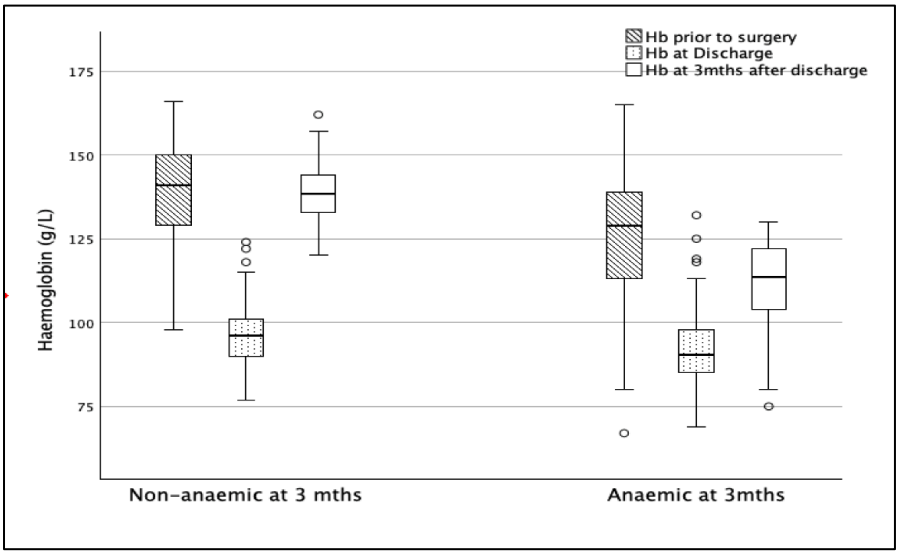
Aim: There are limited data reporting the impacts of post-operative anaemia, particularly in cardiac surgery patients. This study examines the prevalence of anaemia after surgery in patients undergoing cardiac surgery, and to assess the effects of patient blood management (PBM) interventions on post-discharge anaemia.

Method: The current study is a subset of a retrospective study of cardiac surgery patients at Flinders Medical Centre between January 2017 and June 2019. PBM guidelines were followed perioperatively. Discharge haemoglobin (Hb) level, and levels at 3 and 6 months post-discharge were collected where available. Anaemia was defined using World Health Organisation sex-specific cut-off values (Hb <130g/L for men, <120g/L for non-pregnant women).

Results: Of 567 eligible patients, 98% (554) were anaemic on discharge. 172 (30.3%) patients had an available Hb result at 3 months post-discharge, of which, 98 patients (56.9%) were found to be persistently anaemic. Although anaemic and non-anaemic patients shared similar demographics, anaemic patients at 3 months had higher rates of preoperative anaemia (45.9% vs 20.3%, p <0.001), perioperative transfusion (49.0% vs 29.7%, p=0.01), and renal disease (20.4% vs 9.5%, p=0.05). Logistic regression analysis, adjusted for age, gender, diabetes, renal disease, perioperative transfusion, and preoperative anaemia found that preoperative anaemia was significantly associated with anaemia at 3 months.

Conclusion: Whilst preoperative Hb optimisation remains an important modifiable risk factor for reducing postoperative anaemia, this is not always possible due to limited time between assessment and surgery. The identification and management of postoperative anaemia offers a valuable opportunity to optimise Hb in cardiac surgery patients who are exposed to significant perioperative blood loss. Therefore, clinical pathways for the management of postoperative anaemia are required. Further studies are needed to assess the impact of patient blood management, the causes of anaemia, and their impact on patient outcomes.



AP082

Platelet transfusion in a regional centre: Evaluating cost effectiveness of increasing pooled platelet availability at Lismore Base Hospital

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Aim: To analyse the cost effectiveness of increasing pooled platelet availability at Lismore Base Hospital.

Method: A retrospective audit of all episodes of platelet transfusions (including pooled or apheresis) for patients from December 2022 to November 2023 was undertaken. A total of 218 platelet transfusions were analysed. Demographic information, other clinical information, urgency of transfusion, whether transfusion was in line with guidelines, and whether the local Haematology service was consulted prior to transfusion was noted. Number and cost of platelet discards as well as cost of delivery of urgent platelets will be assessed for the final conclusion.

Results: The periods compared were December 2022 to May 2023 and from June 2023 to November 2023. The number of transfusions per month remained relatively constant, with 19.2 transfusions compared to 20.3 transfusions per month. Most transfusions were for patients admitted under Haematology (n=153, 70.2%). The majority of transfusions were to prevent bleed in the context of thrombocytopenia (n=157, 72.0%) and trauma was an indication in only 3 of these cases (1.4%). Urgent transfusions (required within 24 hours) went from 11/96 to 9/122, and transfusions required immediately increased from 0/96 to 5/122. 18/218 (8.2%) transfusions were not in line with the National Blood Authority transfusion guidelines (National Blood Authority, 2012).

Conclusion: While the number of urgent transfusions did not seem to increase after availability of pooled platelets onsite, the total cost effectiveness of increasing availability of pooled platelets onsite will depend on the net cost saving of urgent couriered platelets against likely increased platelet discards.

National Blood Authority. (2012). Patient Blood Management Guidelines. Retrieved from https://blood.gov.au/pbm-guidelines

THANZ Poster Presentations

TP001

Finding Individualised Treatment in Obese Needing Enoxaparin (FIT ONE): A multicentre study of therapeutic enoxaparin and the role of anti-factor Xa monitoring

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Aim: State concisely why the study was conducted.

Enoxaparin is dosed according to actual body weight in treatment of arterial and venous thrombosis. Due to its hydrophilic nature, it distributes according to lean body mass which may be problematic when dosing obese patients as this may increase the risk of bleeding events in this population due to their higher ratios of adipose tissue. Obese patients are often excluded from or underrepresented in pharmacokinetic and clinical trials, thus evidence supporting dosing recommendations in this population is limited.

The aim of this study was to evaluate current therapeutic enoxaparin dosing strategies, including Antifactor Xa (AFXa) level monitoring, in obese patients and to identify factors that contribute to treatment failure and excess anticoagulation.

Method: Indicate the locale, sample number, principal test(s) performed, and the types of statistical analysis employed.

A retrospective cohort study was conducted reviewing patients administered therapeutic enoxaparin between May 2020 and April 2021. Data were collected on patient characteristics, enoxaparin therapy, AFXa monitoring, and outcomes. Regression models were constructed to assess variables of interest to estimate any association with AFXa levels.

Results: Confirm or refute the hypothesis, supported by statistics if appropriate

In total, 762 patients were included in the analysis. The mean initial weight-based dose was 0.95 mg/kg twice daily (SD: ±0.12, IQR: 0.92- 1.01) and 1.04 mg/kg once daily (SD: ±0.26, IQR: 0.93-1.12) and 14.4% of patients had AFXa monitoring. Treatment failure was experienced by 2.2%, and 5% experienced bleeding. The multivariable model found that an increase of 0.1 mg/kg in the weight-based dose increased AFXa levels by 0.107 IU/mL (95% CI=0.034- 0.181, P=0.005). Obesity was not included due to lack of significance.

Conclusion: State the effect of the study on future patient management or the understanding of basic processes

At a mean therapeutic enoxaparin dose of 0.95 mg/kg twice daily and 1.04 mg/kg once daily no excess in treatment failure or bleeding events were observed in obese patients compared to the product information. Obesity was not an independent variable that affected the achievement of target AFXa levels.

"This research was supported by an Australian Government Research Training Program (RTP). The company had no role in analysing the data or preparing the abstract."

TP002

Review of Viscoelastic EQA programs performance post introduction of qualitative interpretations

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Review of Viscoelastic EQA programs performance post introduction of qualitative interpretations

Aim: In 2016 an External Quality Assurance (EQA) program was introduced in Australia for Thromboelastometry and Thromboelastography. A compulsory interpretative assessment of the results was added to the two programs in 2022 to partially reflect how the results may be used in clinical practice. We sought to evaluate the performance of participants in the 2 years since.

Method: The returned interpretation data from 2022 to 2023 for the ROTEM and TEG surveys were analysed to identify potential relationships or discrepancies in reporting. Two surveys were distributed to participants each year, with each comprising two samples. Of the 8 survey samples sent over this period, there were 4 normal samples, 2 low fibrinogen, and 2 with Heparin contamination. The interpretative comment options of 'Heparin Contamination', 'Low Fibrinogen', 'Low Platelets' or 'Normal' were added to the result entry screen. The number of participants reporting concordant, minor discordant and discordant results were compared for inter-survey variation and inter-program disparity with the same expected targets.

Results: The total program enrolments increased from 130 participants in 2022 to153 in 2023. Over the two years, 80-95% of participants reported concordant responses for the Heparin contamination samples, and 81-86% of participants reported concordant responses for the Low fibrinogen samples. For the normal samples, a concordant assessment was given to both 'normal' and 'low platelets' interpretation responses which gave a concordant rate of 76-84% for the 'normal' target samples.

Conclusion: Participants were self-assessing their reports until the compulsory interpretation component of the survey was added. This meant there was no flagging of results on the reports that were performing poorly. After the introduction of the interpretation measurand and educational support, there have been improvements in the reported interpretations and consequently, an increase in the concordant responses. Acknowledging the limitations to these current programs, mainly due to sample matrix, further work is underway to potentially improve the samples to reflect patient material more closely.

TP003

Pharmacological Thromboprophylaxis use in Elderly Medically admitted patients

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Aim: To review the prescription of pharmacological venous thromboembolism (VTE) prophylaxis to elderly medically admitted patients and adherence to institutional guidelines according to VTE risk.

Method: Retrospective cross-sectional study at a quaternary referral centre that included all medical inpatients 60 years and older in hospital on 6 December 2023. Patients were identified via an electronic dashboard report stored on Cerner ® PowerChart. Follow-up was 30 days post-hospital discharge. Data was collected to determine demographics, prescription of pharmacological VTE prophylaxis, adherence to local thromboprophylaxis guidelines (presence of contra/indications, appropriate dosing) and incidence of clinical outcomes. Statistical analysis was conducted descriptively.

Results: Of the 142 patients that were included in the study, 79 (55.6%) were male and the median length-of-stay was 11 days (IQR 6,26). Overall, 99 (69.7%) patients were prescribed enoxaparin for thromboprophylaxis for a median 10 days (IQR 6,23). There were six (6.1%) patients prescribed reduced dose enoxaparin (20mg daily) incorrectly according to weight and renal function. Of those prescribed thromboprophylaxis, 12 (12.1%) were mobile without any specific risk factors for VTE, except age over 60 years. Of the 27 (19.0%) patients with clear contraindications to VTE prophylaxis, 24 (88.9%) were appropriately not prescribed enoxaparin. Undocumented non-prescription of thromboprophylaxis to those with VTE risk factors was present in 6 (4.2%) patients. There were seven clinical events experienced; five (3.5%) minor bleeds (four received thromboprophylaxis) and two (1.4%) VTE (both received thromboprophylaxis).

Conclusion: The majority of medically admitted elderly patients are prescribed pharmacological VTE prophylaxis at our institution and the incidence of VTE and bleeding events are reassuringly low. Without comprehensive consideration of individual related risk factors, particularly mobility, over-prescription of pharmacological thromboprophylaxis is occurring. Clinicians should consider performing formal ambulation assessments when determining need for thromboprophylaxis in this cohort, at baseline and throughout the period of hospitalisation.

TP004

Interim analysis of joint outcomes in patients with severe hemophilia A receiving efanesoctocog alfa during the phase 3 XTEND-ed long-term extension study

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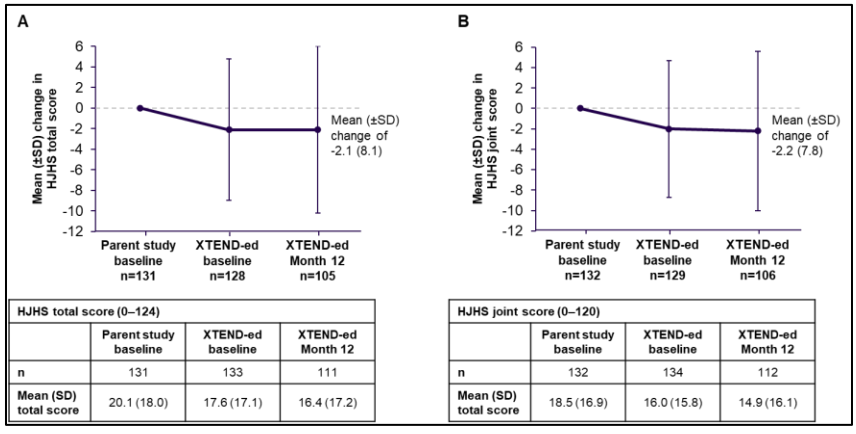
Aims: To assess long-term joint health with efanesoctocog alfa prophylaxis in adults/adolescents with hemophilia A from XTEND-1 (NCT04161495) who continued to the extension study, XTEND-ed (NCT04644575).

Methods: XTEND-ed is an open-label, multicenter study of previously treated patients with severe hemophilia A. Participants provided informed consent; the study was approved by applicable review boards. Changes from parent study (XTEND-1) baseline to Month 12 in XTEND-ed in Hemophilia Joint Health Scores (HJHS) and target joint resolution for participants aged ≥12 years who received once-weekly efanesoctocog alfa (50 IU/kg) prophylaxis for 52 weeks (Arm A) are presented descriptively (data cutoff June 8, 2023). Individual joints (left/right elbows, knees, and ankles) were scored according to 8 HJHS domains; gait was also assessed. Total HJHS score encompasses joint and gait score. Target joints were evaluated based on International Society on Thrombosis and Haemostasis criteria.

Results: Arm A of XTEND-ed enrolled 146 participants from XTEND-1 (additional mean [standard deviation, SD] treatment duration 82.5 [14.3] weeks). By Month 12 in XTEND-ed, joint health had improved or been maintained in evaluable participants compared with XTEND-1 baseline, as measured by HJHS total score, total joint score (**Figure**) and subdomain scores. The HJHS domain with the greatest mean (SD) change from baseline to Month 12 was flexion loss -0.6 (2.7). At XTEND-1 baseline, there were 140 target joints among 45 participants; at 1 year, all target joints (n=132) had resolved in participants exposed for ≥12 months (n=43).

Conclusion: Interim results from XTEND-ed indicate that once-weekly prophylaxis with efanesoctocog alfa is associated with improvement or maintenance of joint health in adults and adolescents.

Figure: Change in HJHS scores for A) total score and B) total joint score from parent study, baseline at end of parent study, and Month 12 in XTEND-ed in participants aged ≥12 years



HJHS total score (0–124)	Parent study baseline	XTEND-ed baseline	XTEND-ed Month 12
n	131	133	111
Mean (SD) total score	20.1 (18.0)	17.6 (17.1)	16.4 (17.2)

HJHS joint score (0–120)	Parent study baseline	XTEND-ed baseline	XTEND-ed Month 12
n	132	134	112
Mean (SD) total score	18.5 (16.9)	16.0 (15.8)	14.9 (16.1)

HJHS, Hemophilia Joint Health Score; LOCF, last observation carried forward; SD, standard deviation. Higher HJHS scores denote worse joint health. An HJHS total score can be calculated if all 48 individual item scores (8 domains × 6 joints, total joint score) and the gait score were present. HJHS assessments within 2 weeks after a joint or muscle bleed are excluded. Joint scores post joint surgeries are replaced using the LOCF method. [a]Data cutoff date June 8, 2023.

TP005

Long-term outcomes with efanesoctocog alfa prophylaxis for previously treated children with severe hemophilia A, an interim analysis of the phase 3 XTEND-ed study

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Aim: Efanesoctocog alfa (formerly BIVV001) is a first-in-class high-sustained factor VIII (FVIII) replacement therapy designed to overcome the von Willebrand factor–imposed half-life ceiling. Once-weekly efanesoctocog alfa 50 IU/kg was well tolerated and provided highly effective bleed protection and factor activity within normal to near-normal levels (>40%) for 3 days, and of ~10% at Day 7, in children with severe hemophilia A in the XTEND-Kids study. Here, we evaluated long-term data on safety and efficacy of efanesoctocog alfa in previously treated children with severe hemophilia A in the XTEND-ed study (NCT04644575; first interim analysis).

Method: XTEND-ed is a multicenter, open-label study that enrolled participants from previous Phase 3 studies, including children <12 years of age who received weekly efanesoctocog alfa prophylaxis for ≤52 weeks in XTEND-Kids, and continue weekly 50 IU/kg prophylaxis in XTEND-ed. The primary endpoint is the occurrence of FVIII inhibitors. Secondary endpoints include annualized bleed rates (ABRs), efficacy for bleed treatment, and safety. Participants provided informed consent and XTEND-ed was approved by applicable ethics committees. Data cut: June 8, 2023.

Results: Seventy-one of 74 males (96%) rolled over from XTEND-Kids to XTEND-ed. The mean (standard deviation [SD]) efficacy period was 35.8 (14.1) weeks. No FVIII inhibitors were detected. The overall mean (SD) ABR was 0.70 (1.27), thus maintaining the low mean ABR observed in the parent study (0.88). Most bleeds (86%; 30/35) resolved with a single dose of efanesoctocog alfa 50 IU/kg, with 96% (23/24) of hemostatic responses rated as excellent or good. Overall, 43 (61%) participants experienced ≥1 treatment-emergent adverse event (TEAE) and 2 (3%) experienced ≥1 serious TEAE.

Conclusion: Long-term results in children with severe hemophilia A in XTEND-ed show that once-weekly efanesoctocog alfa continues to be well tolerated, with no FVIII inhibitors reported, and provides highly effective bleed protection.

TP006

Severe haemophilia B in a neonate requiring spina bifida repair

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Introduction: Spina bifida is a congenital neural tube defect requiring surgical intervention shortly after birth[11]. Its occurrence in conjunction with haemophilia B is exceptionally rare and poses unique challenges due to risk of bleeding complications. We report a unique case of haemophilia B in a neonate requiring urgent spina bifida repair.

Case: Male neonate born by lower caesarean section at 37+5 weeks with a known pre-natal lumbar myelomeningocele diagnosed on antenatal ultrasound screening.

Post-natal results:

- Coagulation screening - APTT 111 secs
- Clotting factor assays – factor VIII 1.26 (126%), factor IX 0.027 (<1%)
- Cranial ultrasound – no parenchymal or ventricular haemorrhage

Management and postoperative course:

- Given 500 IU Alprolix™ (Extended Half Life Recombinant Factor IX) as IV bolus 1 hour pre-operatively.
- Commenced Alprolix infusion after bolus at 10 IU/hr intraoperatively.
- Successful lumbar myelomeningocele repair without bleeding sequalae.
- Post-operative Factor IX (FIX) levels were maintained with continuous FIX infusion before transitioning to 2 weekly Alprolix prophylaxis on discharge.
- Genetic testing: Hemizygous F9: c.-35G>A mutation detected by sanger sequencing. Consistent with mild to moderate disease (Haemophilia B Leyden).
- Unsupported FIX level of 8% at 4 months of age
- Management altered based on genetic testing with early cessation of Alprolix prophylaxis and institution of on demand therapy with no bleeding complications.

Discussion: Haemophilia B is a congenital X-linked recessive bleeding disorder caused by mutations in the F9 gene[i]. Haemophilia B Leyden a rare variant, characterised by a gradual rise in FIX levels from puberty to low normal levels by early adulthood[ii]. Contemporary research suggests that this increase in FIX may commence earlier in early childhood[iii] with the pre-eminent role of growth hormone confirmed in murine models[iv]. This case outlines a successful perioperative management approach for a neonate with severe Haemophilia B. Underscoring the value of early genetic testing. This facilitated a safe, early transition to a less invasive management strategy.

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TP007

Performance of factor VIII extended half-life product measurement – a global external quality assurance program study

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Aim: To gain an overview of the variation in results when measuring five different factor VIII (FVIII) extended half-life (EHL) products in spiked plasma using numerous reagents, instrumentation, and analytical principles via external quality assurance (EQA) programs.

Method: In 2023, three EQA providers (RCPAQAP, UKNEQAS and ECAT) conducted a global study to investigate the performance of laboratories measuring FVIII in samples spiked with FVIII extended half-life products. The lyophilised plasma samples were spiked with Afstyla, Esperoct, Jivi, Kovaltry and Novoeight at ~6 IU/dL and ~60 IU/dL to represent pre and post FVIII treatment levels. 275 laboratories from Australasia (RCPAQAP n= 25), Europe (ECAT, n=150) and the UK (NEQAS, n=100) performed FVIII assays utilising their routine methods and provided detailed information via an online questionnaire including assay methodology, instrumentation, reagent/kit and calibration material.

Results: For laboratories utilising one stage clotting assays (OSA) (n=203) the medians are as follows for the ~6IU/dL and ~60IU/dL samples: Afstyla 4.9IU/dL; 33.8IU/dL, Esperoct 5.0IU/dL; 43.0IU/dL, Jivi 7.8IU/dL; 64.0IU/dL, Kovaltry 7.0IU/dL; 57.1IU/dL, and Novoeight 7.3IU/dL; 63.5IU/dL.

For laboratories utilising chromogenic assays (CA) (n=156) the medians are as follows for the ~6IU/dL and ~60IU/dL samples: Afstyla 6.4IU/dL; 62.1IU/dL, Esperoct 5.5IU/dL; 48.8IU/dL, Jivi 5.0IU/dL; 55.3IU/dL, Kovaltry 6.0IU/dL; 59.0IU/dL, and Novoeight 7.0IU/dL; 72.1IU/dL.

Results submitted by participants demonstrate that FVIII assays do not provide consistent results of EHL products with both an under- and over-estimation of the expected recovery based on sample concentration.

Conclusion: This collaborative EQA study provides data on the assay variability that may be encountered when measuring FVIII EHL products. Product specific calibration curves could be considered to reduce this variability when testing with OSA or CA alone. Accurate FVIII results in patients who use these EHL products lowers their risk of bleeding and thrombotic complications.

TP008

Dilemma of management of factor XIII (FXIII) inhibitor in inherited FXIII deficiency.

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Aim: To highlight the challenges in the management of a FXIII inhibitor in a patient with inherited FXIII deficiency.

Background: Inherited factor XIII (FXIII) deficiency is an exceedingly rare clotting factor deficiency with an estimated incidence of 1 in 2-5 million people in the general population(1). It is due to mutation of either *F13A1* gene located on chromosome 6p24.2-p23 or *F13B* gene located on chromosome 1q31-q32.11. Inheritance is autosomal recessive. FXIII cross-links fibrinogen to stabilize the clot and is important in angiogenesis and wound healing(2). The severity of bleeding correlates relatively well with plasma level of FXIII. Common bleeding symptoms in FXIII are prolonged bleeding from umbilical stump, epistaxis, mucosal bleeding, ecchymoses, haematomas, hemarthrosis and recurrent miscarriage. Thirty percent of affected individuals can have spontaneous intracranial bleeding(1).

A literature review identified limited information on the management of patients with inherited FXIII deficiency who developed an inhibitor to FXIII concentrate(3).

Clinical case: We present a case of a paediatric patient who was diagnosed with FXIII deficiency following a spontaneous intracranial haemorrhage complicated by post-op bleeding and poor wound healing. He was commenced on prophylactic FXIII concentrate at 40U/kg once every three weeks. Due to rapid clearance of FXIII concentrates, a FXIII inhibitor was suspected less than one year after commencing prophylaxis resulting in frequent prophylactic doses. The presence of a FXIII inhibitor was confirmed by Bethesda assay. The patient received one course of Rituximab over four weeks that led to a temporary improvement in FXIII clearance. He is now on weekly prophylactic dosing.

Conclusion: Alloantibody production in response to FXIII concentrate in inherited FXIII deficiency is a challenging complication. There is little evidence to guide management of FXIII inhibitor and a lack of by-passing agents. The long-term management of this case will pose significant challenges.

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TP009

Factor VII inhibitor in a patient with inherited factor VII deficiency

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Aim: To describe the management of a patient with factor VII deficiency who developed FVII inhibitor.

Background: Inherited factor VII (FVII) deficiency is a rare clotting factor deficiency, with an estimated incidence of 1 per 500,000 individuals(1). It is due to mutation of the *F7* gene on chromosome 13q37 and inheritance is autosomal recessive. The clinical bleeding phenotype correlates poorly with plasma FVII level, though bleeding is unlikely in patients with FVII level >10%(2). Bleeding symptoms in FVII are variable, and includes mucosal bleeds, bruising, joint bleeds and intracranial haemorrhage.

Although FVII deficiency is the most common of all the rare factor deficiencies, there is little literature available addressing the development of inhibitor to FVII and how this can be managed. A similar case in the United Kingdom (UK) was identified.

Clinical Case: We present a case of a paediatric patient who was diagnosed with inherited FVII deficiency, following presentation with recurrent prolonged epistaxis, easy bruising and recurrent unexplained ankle swelling. Her initial coagulation studies showed a prothrombin time (PT) of >120secs and plasma FVII level of <1%. She was commenced on prophylaxis with thrice weekly recombinant activated FVII (rFVIIa). She was subsequently discovered to have developed an inhibitor (alloantibody) to FVII, forty-seven days following commencement of prophylaxis.

The FVII inhibitor level was initially monitored and rFVIIa prophylaxis was increased to twice daily to control bleeds. Due to rising inhibitor titre and frequent bleeding symptoms, she was then commenced on rituximab and had a total of four doses over four weeks. The prophylactic rFVIIa has been continued.

Conclusion: The management of FVII inhibitors in patients with inherited FVII deficiency is not well established due to the rarity of this condition. Immunosuppression with rituximab in this case reduced both the inhibitor titre and the clinical bleeding symptoms in the short term.

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TP010

Assessment of Plasmin generation in Patients with Diabetes Mellitus

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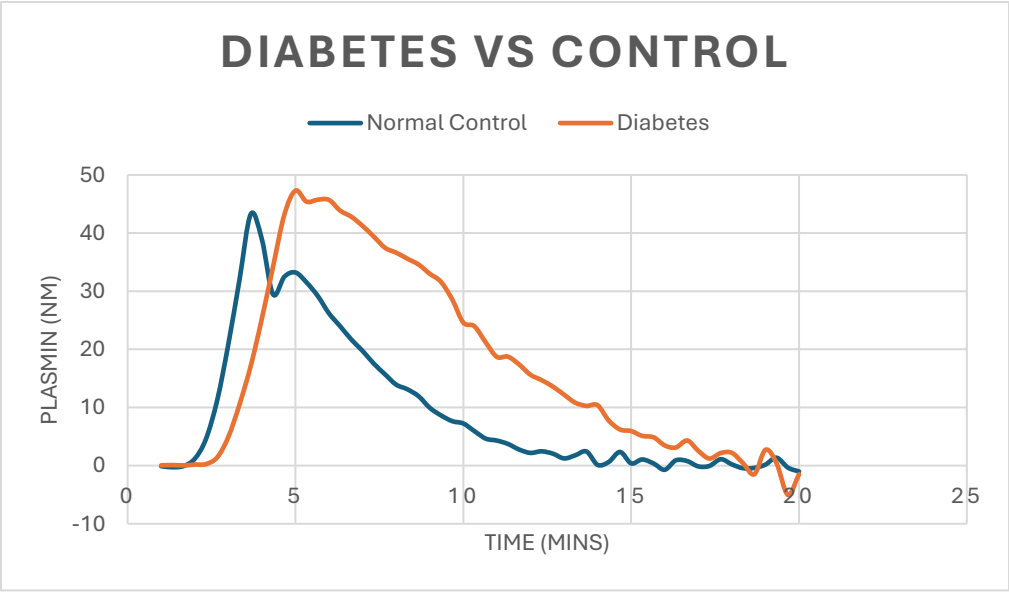
Aim: Hypofibrinolysis is a key abnormality in diabetes and contributes to increased risk of atherothrombosis in this patient cohort. However, the optimal assay to test the efficiency of fibrinolysis is yet to be established. In diabetes, the glycosylation of plasminogen can impair its conversion to plasmin, a critical enzyme for clot dissolution. This study aims to assess the dynamic process of plasmin generation in patients with diabetes mellitus.

Method: Diabetes patients were recruited from Endocrinology Outpatients at Northern Health. Patients on anticoagulation or with active malignancy were excluded. Plasmin generation was tested in platelet-poor citrated plasma using a calibrated, automated method based on established principles used to measure thrombin generation. The results were compared with healthy controls.

Results: Plasmin generation testing was performed on samples of 104 diabetes patients and 105 healthy controls. Diabetes patients demonstrate a longer lag time to plasmin generation (2.6 vs 2.3 min, p<0.001) and time-to-peak (5.0 vs 4.6 min, p<0.001) indicating a hypofibrinolytic state. Paradoxically, patients with diabetes have higher endogenous plasmin potential (EPP, 297 vs 259 nM/min, p<0.001) and plasmin peak (46.0 vs 43.4 nM, p=0.008), as well as a lower endogenous thrombin potential (ETP) to EPP ratio (ETP:EPP) (4.3 vs 5.3, p<0.001). Diabetes patients with more cardiovascular risk factors appear to have higher EPP levels, while there was no correlation between EPP and HbA1c levels. Figure 1 shows an example of plasmin generation assay trace of a diabetes patient compared to control.

Conclusion: Our interim analysis has shown delayed plasmin generation in diabetes patients, which may be a contributing factor to hypofibrinolysis, and an association with increased cardiovascular risk factors. Further analysis to investigate association with clinical outcomes and incorporate plasmin generation into our multimodal biomarker risk stratification model for prediction of atherothrombosis in diabetes patient is being performed.

Figure 1 shows an example of plasmin generation curve of a patient with diabetes (orange) compared to a healthy control (blue)



TP011

A Ten year Retrospective Evaluation of the Management of Iliofemoral Deep Vein Thrombosis in Australia

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Aim: To characterize the real-world management of IFDVT in an Australian population.

Method: Retrospective evaluation of IFDVT managed at Northern Health, Victoria, Australia from January 2011 to December 2020. The analysis included demographics, risk factors, management, and outcomes, with median follow-up 26 months. Malignancy provoked VTE were excluded and results were compared to non-iliofemoral lower limb DVT.

Results: A total of 276 IFDVT episodes (median age 66 years; 55.4% female (n=145)) were diagnosed. 47.8% (n=132) were provoked events, most commonly due to immobility/injury (n=73, 26.4%). 30.8% (n=85) had a prior VTE. 26.8% (n=74) of patients had concomitant pulmonary embolism, while 7.2% (n=20) had bilateral DVTs. Seven cases were associated with May-Thurner syndrome, all were treated with catheter-directed thrombolysis, and five received iliofemoral stenting.

IFDVT patients more often received warfarin treatment (51.4% vs 42.9%, p=0.008) and longer duration (8 vs 6 months, p<0.001) or indefinite anticoagulation (29.0% vs 16.0%, p<0.001) compared to other DVTs. VTE recurrence (2.7/100PY) (HR 0.84 95% CI: 0.56-1.25) and major bleeding (2.7/100PY) (HR 1.68, 95%CI: 0.88-3.23) were not significantly different between both groups. However, the 30-day all-cause mortality (5.1% vs 1.2%, p<0.001) including death due to thrombosis (1.4% vs 0.4%, p=0.023) were more common with IFDVT. 35 patients (12.4%) reported PTS, including four patients with May-Thurner syndrome.

Conclusion: While the VTE recurrence and major bleeding were comparable between patients with IFDVT and non-IFDVTs, mortality was higher in the former. This suggests a high-risk cohort that warrants careful assessment.

TP012

Measuring Apixaban & Rivaroxaban in the presence of Heparin/LMWH using a Heparin Neutralisation procedure.

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Aim: When patients taking direct Xa inhibitors apixaban or rivaroxaban are switched to UFH or LMWH the clearance of the DOAC sometimes needs to be measured. DOAC levels can be spuriously elevated where UFH/LMWH is not accounted for. This study aimed to validate a plasma heparin neutralisation procedure that allows accurate measurement of apixaban and rivaroxaban during the bridging period.

Method: Samples from healthy volunteers, as well as excess plasma from patients treated with apixaban/rivaroxaban/UFH/LMWH were double spun and frozen at -40ºC before testing. ACLTOP750 analyser was used with Instrument Laboratory reagents for apixaban, rivaroxaban, LMWH and UFH assays. Normal donor plasma and plasma from patients taking DOACs were tested for apixaban and rivaroxaban in three sequential stages: (a) baseline; (b) post-spiking with UFH and LMWH; (c) post treatment of the UFH/LMWH-spiked plasma with Hepzyme® (Siemens). Plasma from patients receiving DOACs were tested only for the specific DOAC they were receiving. All spiking was done at two levels of UFH and two levels of LMWH (0.5/1.0 IU/mL for both). Hepzyme treatment involves adding 1mL citrated plasma to a vial of lyophilized material and incubating 30m at room temperature before testing.

Results: Fifty-one patients on DOAC and three normals were tested. DOAC levels assayed at ~80-160ng/mL in UFH/LMWH-spiked normals, which was reversed by Hepzyme to levels below the assay's detection limit. All patient sub-groups showed significant over-estimation of apixaban and rivaroxaban levels post-spike at both concentrations of UFH/LMWH (20%-60% increase over baseline), with all P-values ≤0.0006. Post Hepzyme treatment, mean apixaban or rivaroxaban levels returned to within ≤11ng/mL of their baseline, indicating effective neutralisation of UFH/LMWH (see table).

Conclusion: Accurate measurement of apixaban and rivaroxaban is possible using Hepzyme to remove UFH or LMWH when it is concurrently present in test plasma. This may have benefits in an urgent pre-surgical setting.

Doac and spike level in IU/mL **N=3 to 9**	**Mean Baseline DOAC ng/mL** **(a)**	**Mean post-spike DOAC ng/mL** **(b)**	**Mean post-Hepzyme DOAC ng/mL** **(c)**	**P-values Baseline vs Post Spike** **(a) v (b)**	**P-values Baseline vs Post -Hepzyme** **(a) v (c)**	**Mean change in DOAC ng/mL** **(a) - (c)**
Apix 0.5 LMWH	195	258	198	<0.0001	0.238	-3
Apix 1.0 LMWH	198	287	206	0.0006	0.126	-8
Apix 0.5 UFH	180	251	178	<0.0001	0.049	2
Apix 1.0 UFH	177	284	186	<0.0001	0.094	-9
Riv 0.5 LMWH	246	300	243	<0.0001	0.474	3
Riv 1.0 LMWH	254	333	265	<0.0001	0.058	-11
Riv 0.5 UFH	250	307	251	0.0001	0.717	-1
Riv 1.0 UFH	256	379	255	0.0001	0.879	1

TP013

Proteomic profiling of Cryoprecipitate, fresh frozen plasma, and their Derived extracellular vesicles: Insights into complement and coagulation associated proteins.

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Aim: To investigate the proteomic profiles of cryoprecipitate, fresh frozen plasma (FFP), and their derived extracellular vesicles (EVs) using mass spectrometry.

Method: Clinically transfusable blood components (cryoprecipitate, FFP) were obtained from the Australian Red Cross Lifeblood for the study. EVs were isolated using size exclusion chromatography (SEC) and characterised based on international community guidelines: 1) Western blot using EV protein markers; 2) morphology verification using cryogenic electron microscopy; 3) particle size distribution and concentration determination by nanoparticle tracking analysis (NTA). Each sample underwent in solution digestion using trypsin and the resulting tryptic peptides injected into a liquid chromatography-mass spectrometer (LC-MS/MS). Proteomic data were acquired using data-independent acquisition (DIA) and processed using Spectronaut. Statistical comparison was conducted using the R package mass spectrometry downstream analysis pipeline (MS-DAP).

Results: Approximately 360 proteins were successfully identified and quantified across all sample groups. Principal component analysis and heatmaps revealed that both cryoprecipitate and FFP are similar. Similarly, EVs derived from cryoprecipitate and FFP are comparable. However, they differ between the originating fluids and their derived EVs. Utilising the statistical R package MS-DAP, we used a stringent process using multiple quantification models to identify differentially expressed proteins (DEPs) in pairwise comparisons between different sample types. The DEPs for all comparisons, when submitted for gene enrichment analysis, are involved in complement and coagulation pathways.

Conclusion: To the best of our knowledge, this is the initial proteomic investigation of cryoprecipitate and its derived EVs. Notably, there were distinct proteomic differences between the original fluids and their derived EVs. Key DEPs were predominantly involved in complement and coagulation pathways. These findings provide valuable clinical insights into the protein compositions of EVs from blood components, potentially enhancing therapeutic applications and diagnostic tools in transfusion medicine.

TP014

Laboratory Diagnosis Of Congenital Thrombotic Thrombocytopenia Purpura Using Two ADAMTS-13 Activity Testing Methods

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Background: Congenital Thrombotic Thrombocytopenia Purpura (cTTP) is a rare, potentially fatal, disorder caused by biallelic pathogenic variants in the *ADAMTS13* gene. TTP is characterised by a severe deficiency of the von Willebrand factor cleaving enzyme, ADAMTS13, resulting in accumulation of high molecular weight von Willebrand multimers and microthombi in the circulation, microangiopathic haemolytic anaemia and thrombocytopenia.

Case Report: A 35-week fetus was identified as being at risk of cTTP following an incidental finding of compound heterozygous likely pathogenic variants in the *ADAMTS13* gene on prenatal exome sequencing. Identification prior to birth allowed for appropriate laboratory testing to be planned, including out-of-hours ADAMTS13 levels.

Marked thrombocytopenia (platelet count $8x10^9$/L) on cord blood, was confirmed on a venous sample, also demonstrating hyperbilirubinaemia (120umol/L) elevated lactate dehydrogenase (2228 U/L), and schistocytes on the blood film. Two different ADAMTS13 testing methodologies where utilised; the HemosIL AcuStar ADAMTS13 Activity assay based on chemiluminescence technology and the Technozym ADAMTS13 Activity ELISA. Results of <0.2% and <1% were seen with the AcuStar and ELISA assays respectively on both cord and initial venous blood samples, confirming a diagnosis of cTTP.

Treatment was initiated immediately with fresh frozen plasma (FFP), and subsequently recombinant ADAMTS13 (rADAMTS13) was administered. rADAMTS13 was obtained on a compassionate use basis (from Takeda Development Center Americas). ADAMTS13 results post-FFP and rADAMTS13 showed excellent concordance, allowing subsequent monitoring with the AcuStar exclusively.

ADAMTS13 inhibitor testing using the Bethesda protocol and the ADAMTS13 ELISA were performed, due to the theoretical risk of ADAMTS13 inhibitor development during replacement therapy. ADAMTS13 antibodies were not detected.

Conclusion: An incidental finding of biallelic, likely pathogenic, variants in *ADAMTS13* on prenatal exome sequencing alerted the treating team to the risk of cTTP. Laboratory investigations after birth demonstrated evidence of microangiopathic haemolysis and marked thrombocytopenia. Diagnosis of cTTP was confirmed with ADAMTS13 activity <1% using two different methodologies. ADAMTS13 results post-FFP and rADAMTS13 showed excellent concordance between the two methods.

TP015

Design of a Human-derived Dual-domain Antifibrinolytic Protease inhibitor based on Aprotinin

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Aim: This study aimed to determine if the human dual domain, Kunitz-type inhibitor bikunin could be utilised as a scaffold to incorporate the canonical binding loop of the previous bovine-derived antifibrinolytic treatment aprotinin. The study would comprise of multiple inhibitors for each reside mutation within bikunin domain 1 and compared with aprotinin.

Method: *In vitro* kinetics assays were performed where inhibitors were incubated in a dilution series with plasmin (0.57 nM) and a chromogenic substrate (100 µM), reaction velocities were recorded for each inhibitor and each assay was completed in triplicate. Inhibition constants (K_i) were calculated and analysed using One-Way ANOVA in GraphPad Prism. *In vitro* fibrinolysis assays were also performed with a dilution of inhibitors incubated with plasmin (5 nM total), thrombin (30 nM total) and fibrinogen (1 mg/mL) in PBS and fibrin clot formation was measured over 3 hours. Clot formation and subsequent breakdown was compared between the inhibitors for determination of 50 % clot lysis time.

Results: The enzyme kinetics assays confirmed that there was a significant increase in inhibitor potency from the wild type K_i of 146.3 nM to 0.6788 nM ($p = <0.0001$) in the final bikunin variant. Compared to the aprotinin K_i value for plasmin (0.8087 nM) it showed no significant difference ($p = >0.9999$). In fibrinolysis assays, there was a similar increase in potency observed from the wild type inhibitor to the final bikunin variant. The final bikunin variant illustrating a high degree of similarity to aprotinin for clot retention over time.

Conclusion:
The final product of this study was a humanised version of aprotinin which showed significant improvements from the wild type bikunin molecule. This being a potential new antifibrinolytic treatment and a replacement for aprotinin with clinically relevant levels of inhibition.

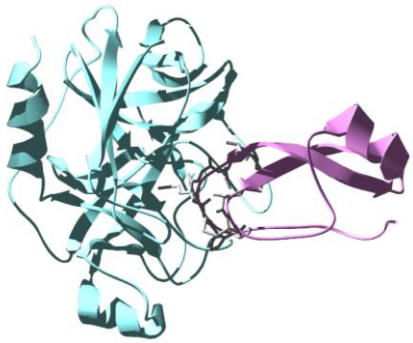

Figure 1: Bikunin domain 1 interacting with the plasmin active site

TP016

Extracorporeal Membrane Oxygenation (ECMO) causes early increased Fibrinolysis, with preservation of further Fibrinolytic potential which increases following the Discontinuation of ECMO; Results of the FOMO Pilot Study.

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Aim: Haemostatic complications remain the leading cause of morbidity and mortality in patients receiving ECMO. Haemorrhagic and thrombotic complications often co-exist in the same patient and often without a clear correlation to anticoagulation[1]. The changes to fibrinolysis during ECMO have not been extensively investigated. The 'Fibrinolysis On Membranous Oxygenation (FOMO)' Pilot study aimed to describe the changes to fibrinolysis in adult patients receiving veno-venous (VV) and veno-arterial (VA) ECMO.

Method: Platelet poor plasma was collected at regular intervals in eligible patients receiving ECMO at the Alfred Hospital intensive care unit from August - October 2022. Fibrinolytic parameters including plasmin-antiplasmin (PAP) complex, plasminogen, antiplasmin, tPA-activity and PAI-1 activity was measured. Fibrinolytic potential was also evaluated using our novel 'inducible PAP' assay on a subset of samples.

Results: Ten patients were included with a total of 86 samples. Fibrinolysis was increased, as reflected by elevated PAPs, during the first 24hr of ECMO commencement (mean 2,011 $\pm$ 1,184 ng/mL), with a trend towards a reduction from day 2 (1,334 $\pm$ 990 ng/mL) onwards on ECMO and a significant reduction in PAPs post decannulation (761 ng/mL $\pm$ 485 ng/mL) ($p < 0.05$). Fibrinolytic potential in response to *ex vivo* tPA was preserved in all samples with a significant increase in the samples post decannulation compared to the first 24 hours ($p<0.05$). There was no significant correlation between PAP levels and PAI-1 or tPA-activity.

Conclusion: ECMO results in a relative increase in fibrinolysis which is most marked within the first 24 hours of ECMO commencement compared to post decannulation. Interestingly, this increase does not appear to be related to changes in tPA or PAI-1 activity. Despite the increase in fibrinolysis, the fibrinolytic system maintains the potential for further activation. Whether this increase in fibrinolysis correlates with bleeding events requires evaluation in a larger observational study incorporating clinical data.

References

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TP017

Perioperative Management with Efanesoctocog Alfa in Adults, Adolescents, and Children with Severe Hemophilia A in the phase 3 XTEND clinical program

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Aim: To evaluate efficacy and safety of efanesoctocog alfa (formerly BIVV001), a first-in-class high-sustained factor VIII replacement therapy, for perioperative management in the Phase 3 XTEND clinical program.

Methods: XTEND-1 (NCT04161495) and XTEND-Kids (NCT04759131) studies assessed safety and efficacy of efanesoctocog alfa in previously treated patients ≥12 and <12 years old, respectively, with severe hemophilia A. Participants from each study could continue treatment in the XTEND-ed study (NCT04644575). Participants provided informed consent, and studies were approved by ethics committees. Participants undergoing surgery were to receive a pre-operative loading dose of efanesoctocog alfa 50 IU/kg. For major surgeries, post-operative doses of 30 or 50 IU/kg every 2–3 days were allowed. Surgery endpoints included dose, number of injections, hemostatic response, factor consumption, blood loss, and blood transfusions during the perioperative period. Interim data cut: January 17, 2023.

Results: Forty-one participants (<18 years, n=9; ≥18 years, n=32) underwent 49 major surgeries; 23 were orthopedic surgeries, with knee arthroplasty most common (n=12). All single 50 IU/kg pre-operative doses maintained hemostasis during major surgery. Median (range) number of doses per major surgery was 4.0 (1–7) during the perioperative period (Days −1 to 14). Hemostatic response was rated excellent for 43 surgeries and good for 5 surgeries. Median (range) blood loss was 20 (0–1000) mL during surgery (n=29); red blood cell transfusion was required for 1 total knee replacement. Of 32 minor surgeries among 28 participants, 27 were managed with 1 pre-operative dose and 5 with no pre-operative dose. Of those with an assessment (n=25), all hemostatic responses were rated excellent.

Conclusion: Efanesoctocog alfa was effective and well tolerated for perioperative management in patients with severe hemophilia A.

TP018

Efanesoctocog Alfa treatment outcomes in Subjects ≥50 years of age from the XTEND-1 trial

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Aim: The aging hemophilia population faces challenges compounded by limited data on factor therapy effectiveness. We performed post hoc assessment of patients ≥50 years old treated with efanesoctocog alfa, a first-in-class high-sustained factor VIII therapy, during XTEND-1 (NCT04161495).

Method: Patients received once-weekly efanesoctocog alfa (50 IU/kg) prophylaxis (52 weeks) in Arm A and efanesoctocog alfa (50 IU/kg) on-demand followed by once-weekly prophylaxis (26 weeks each) in Arm B. Endpoints included annualized bleed rate (ABR), factor consumption, Haemophilia Quality of Life Questionnaire for Adults (physical health), PROMIS Pain Intensity 3a T-score, Hemophilia Joint Health Score (HJHS), and safety.

Results: Twenty-nine patients ≥50 years old (range: 50–72 years) enrolled in XTEND-1 (Arm A: n=21; Arm B: n=8). Pre-study mean ABR was 3.89 (n=13; Arm A). Patients ≥50 years old had an overall mean ABR of 1.0 (Arm A) and 1.7 (Arm B) during once-weekly efanesoctocog alfa (50 IU/kg) prophylaxis. Arm A model-based mean (95% confidence interval [CI]) ABR was 1.05 (0.40–2.72) versus 0.71 (0.52–0.97) (n=133). One injection of efanesoctocog alfa (50 IU/kg) resolved 95% (n=19) of bleeds (Arm A) and all bleeds (n=89) during Arm B. Mean (standard deviation) annualized consumption per patient during prophylaxis was 2784 (137) and 2766 (91) IU/kg in Arms A and B. In Arm A, mean baseline HJHS scores were higher for those ≥50 years (41.1 vs 18.1 in the overall population); mean HJHS score improved by 4.0 (95% CI: −8.25, 0.25) points by Week 52. No patient developed inhibitors. Twenty (95%) patients in Arm A and 5 (63%) in Arm B had ≥1 treatment-emergent adverse event (TEAE). No thrombotic events or deaths occurred.

Conclusion: Prophylactic once-weekly efanesoctocog alfa (50 IU/kg) provided effective bleed protection in patients ≥50 years. ABR was comparable with the overall XTEND-1 population, and patients experienced joint health improvement.

TP019

Evaluation of DOAC-Stop to eliminate direct Oral Anticoagulant interference from Lupus Anticoagulant investigations.

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Aim:
This study was conducted to evaluate the use of DOAC-Stop and its efficacy in eliminating direct oral anticoagulant (DOAC) interference from lupus anticoagulant (LA) testing. It is well known that DOACs cause interference in clot-based assays and includes the detection of LA antibodies in patients with antiphospholipid syndrome (APS) resulting in a number of assays being rejected or demonstrating an equivocal finding.

Method:
A total of 95 (n=95) patient plasma samples in our laboratory were evaluated pre and post treatment to determine DOAC-Stops efficacy in removing DOACs that have interfering properties with LA assays (dRVVT-mix & SCT-mix). Testing performed to evaluate if anticoagulant levels significantly reduced post DOAC-Stop treatment and that treatment strictly removed only DOACs such that other coagulation proteins involved in the clotting mechanism were not affected. Averaged results were depicted in column charts to easily assess results pre and post treatment.

Results:
Plasma samples containing DOAC concentrations up to 428 ng/mL when treated with DOAC-Stop showed significantly reduced plasma drug levels. Subsequently, interferences on LA testing was mitigated and allowed for accurate result interpretation. It was confirmed DOAC-Stop strictly removed DOACs only.

Conclusion:
DOAC-Stop is a form of activated charcoal that removes commonly used DOACs from plasma and facilitate assessment of underlying coagulation. This study supports DOAC-Stops efficacy in mitigating DOAC interference in LA testing. Utilising DOAC-Stop with LA clot based assays will mitigate assays being rejected or the reporting of equivocal results, therefore allowing clinicians to make diagnoses from testing results and prevent delays in appropriate therapy for patients on these medications.

TP020

Human Liver Biopsy analysis shows decline in FVIII levels following AAV5-hFVIII-SQ Gene Therapy may be due to low RNA transcription levels despite persistence of full-length Episomal Vector Genomes

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Aim: Valoctocogene roxaparvovec, a gene therapy (GT) for severe hemophilia A, uses an AAV5 vector to deliver a B-domain–deleted factor VIII (FVIII-SQ) cDNA. We obtained liver biopsies from clinical trial participants to investigate safety, and mechanisms of FVIII expression variability and decline.

Method: In this sub-study of the phase 3, GENEr8-1 trial, liver biopsies were collected from 12 participants 2.1-4.1 years post-dosing. Standard-of-care biopsies in response to transient transaminitis were collected from 4 participants 0.1 to 1.1 years post-GT; 2 of these biopsies were from participants administered prophylactic corticosteroids (CS) prior to GT. Primary endpoints included liver histopathology, transduction efficiency, quantification of episomal vector DNA and transgene RNA transcripts.

Results: Liver histopathology revealed variable levels of steatosis common across Western populations. No evidence of abnormal architectural findings or dysplasia was noted. Similar levels of transduction were detected ±CS treatment. Full-length episomes correlated with FVIII activities and did not decrease over time (r=0.63, P=0.02). Two biopsies were from individuals with peak FVIII activities of 45.1 and 27.4 IU/dL, that declined to <3 IU/dL at biopsy. The remaining 14 biopsies were from participants with measurable FVIII activity at biopsy. FVIII activity levels positively correlated with FVIII-SQ RNA transcript levels (r=0.78, P=0.0016). In the 2 individuals with FVIII activity that declined to <3 IU/dL, full-length vector genomes were similar to those in participants with measurable FVIII activity; however, both biopsies had low FVIII-SQ RNA transcript levels, resulting in significantly lower RNA/DNA ratios (P=0.004).

Conclusion:
Efficient hepatocyte transduction of AAV5-hFVIII-SQ was detected regardless of CS treatment. The decline in FVIII over time may be due to reduced transcription of episomal vector DNA to RNA in hepatocytes.

TP021

Thromboprophylaxis in hospitalised COVID19 patients: A review of local practice.

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Aim: To assess compliance with institutional guidelines implemented for thromboprophylaxis in patients with COVID19.

Method: Retrospective, observational study of COVID19 positive inpatients at a quaternary referral centre from July 2020-March 2023. A random convenience sample of 500 patients were selected for screening. Patients were excluded for the following reasons: age <18 years, length of stay <24 hours, unclear COVID19 diagnosis (lack of documentation or incorrect coding), admitted under the community care pathway or taking pre-morbid anticoagulation. Electronic medical records were reviewed with data collected on demographics, venous thromboembolism (VTE) risk factors (malignancy, obesity, illness severity), thromboprophylaxis prescribed, contraindications to VTE prophylaxis, and clinical outcomes during admission (VTE, bleeding). Primary outcome was the percentage of patients who received appropriate thromboprophylaxis according to institutional guidelines. Descriptive statistics and chi-squared test were performed for analysis; a p-value <0.05 was considered significant.

Results: Overall, 267 patients were reviewed. The median age was 66 years (IQR 45-81), 43.8% (n=117) were female, and 77.5% (n=207) had mild COVID19 illness. Malignancy was present in 10.1% (n=27) of patients and 8.2% (n=22) had a BMI >30kg/m^2. Contraindications to thromboprophylaxis included pulmonary embolism on admission (n=5) and active bleeding (n=3). Appropriate thromboprophylaxis according to guidelines was assessed at 77.9% (95% CI: 72.4, 82.7). Non-compliance was driven by thromboprophylaxis not prescribed without a documented rationale in 47 (79.7%) cases. Subgroup analysis demonstrated guideline compliance for patients admitted to an inpatient unit was significantly higher compared with emergency department admissions (88.4% vs 5.7%, p<0.00001). The incidence of VTE was 4.9% (n=13) and bleeding 2.6% (n=7), all of which received appropriate thromboprophylaxis.

Conclusion: Compliance with local thromboprophylaxis guidelines for COVID19 patients was reasonable at nearly 80%. Future studies are needed to further assess reasons for deviations from guidelines to maintain low rates of VTE in this high-risk cohort.

TP022

Health-related quality-of-life outcomes 4 years after treatment with valoctocogene roxaparvovec

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Aim: Valoctocogene roxaparvovec, a gene therapy for severe hemophilia A (HA), helps prevent bleeding by providing the body with genetic instructions for making factor VIII (FVIII) protein. We report findings from the GENEr8-1 study 4 years after participants received valoctocogene roxaparvovec. The aim is to compare health-related quality-of-life (HRQOL) outcomes before and after treatment with valoctocogene roxaparvovec.

Method: In GENEr8-1, 134 adult men with severe HA received one infusion of valoctocogene roxaparvovec (6E13 copies of FVIII instructions/kg). To assess their HRQOL, participants completed questionnaires before receiving valoctocogene roxaparvovec and regularly afterwards. The Haemo-QOL-A, a questionnaire designed for HA and B, is being validated for gene therapy for HA. It produces a Total Score reflecting overall HRQOL and domain scores measuring impacts on specific aspects of life, such as Physical Functioning (eg, ability to carry out everyday tasks), Role Functioning (eg, relationships and ability to function in social roles), and Consequences of Bleeding (fear of having a bleed/what happens after you have a bleed). Here, Haemo-QOL-A results are presented for the 132 HIV-negative participants in total and by the participants' FVIII activity level at year 4. Other questionnaires will be included in the final presentation.

Results: Four years after treatment with valoctocogene roxaparvovec, the average Haemo-QOL-A Total Score increased by 6.2 points, an average improvement considered meaningful to people with severe HA. Improvements were also seen for Physical Functioning (4.8 points), Role Functioning (5.9 points), and Consequences of Bleeding (9.2 points). At year 4, average Haemo-QOL-A Total Score increased by 6.3, 5.8, and 6.9 points for year 4 FVIII activity in ranges ≥40%, ≥5% to <40%, and <5%, respectively.

Conclusion: Valoctocogene roxaparvovec provides HRQOL improvements considered meaningful for people with severe HA over 4 years, even for participants with FVIII levels below 5% at year 4.

TP023

Individual Pharmacokinetic evaluation of Fixed-sequence Single-dose Octocog alfa, Rurioctocog alfa pegol, and Efanesoctocog alfa in Adults with Severe Hemophilia A

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Aim: The Phase 1 sequential pharmacokinetic (PK) study (NCT05042440; EudraCT 2021-000228-37) assessed PK and safety outcomes for recombinant factor VIII (rFVIII) in previously treated patients following sequential single doses of standard half-life FVIII (SHL, octocog alfa), extended half-life FVIII (EHL, rurioctocog alfa pegol), and efanesoctocog alfa. This study evaluated individual patient-level PK profiles.

Method: The study included previously treated adult male patients (≥150 exposure days of prior FVIII treatment) with severe hemophilia A. Patients received sequential single 50 IU/kg doses of octocog alfa, rurioctocog alfa pegol, and efanesoctocog alfa. Demographics/baseline characteristics, time points above 10%, 15%, and 40% FVIII levels, and PK parameters (half-life [$t_{1/2}$], area under the curve (AUC), clearance [CL], maximum FVIII activity [C_{max}], incremental recovery [IR]) were assessed.

Results: Thirteen male patients aged 26–47 years with a mean standard deviation (SD) weight of 87.8 (18.9) kg were enrolled. Patients experienced a longer $t_{½}$ and greater AUC with efanesoctocog alfa (geometric mean [geometric SD] $t_{1/2}$: octocog alfa, 11.0 [1.5] h; rurioctocog alfa pegol, 15.4 [1.4] h; efanesoctocog alfa, 43.3 [1.3] h;). All patients experienced ~4 days above 40% FVIII activity with efanesoctocog alfa vs <1 and 1 day for octocog alfa and rurioctocog alfa pegol, respectively. Clearance was lower with efanesoctocog alfa indicating lower interpatient variability (geometric mean [geometric SD] CL: octocog alfa 3.0 [1.5] mL/h/kg; rurioctocog alfa pegol 1.8 [1.4] mL/h/kg; efanesoctocog alfa: 0.5 [1.2] mL/h/kg**)**. C_{max} and IR were similar for all 3 FVIII therapies. There were 3 treatment-emergent adverse events (TEAEs) while receiving efanesoctocog alfa in one patient. No TEAEs were serious or treatment related.

Conclusion: Consistent superiority regarding time over 40% FVIII activity, half-life, clearance, and FVIII exposure were observed with efanesoctocog alfa versus SHL and EHL FVIII in all patients. No serious TEAEs or inhibitor development were reported for efanesoctocog alfa.

TP024

First Interim Analysis of Clinical outcomes in Adults and Adolescents with Severe Hemophilia A receiving efanesoctocog alfa prophylaxis in XTEND-ed, a phase 3 long-term extension study

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Aim: Efanesoctocog alfa (formerly BIVV001) is a first-in-class high-sustained factor VIII (FVIII) replacement therapy designed to decouple FVIII from endogenous von Willebrand factor. In the Phase 3 XTEND-1 study (NCT04161495), once-weekly efanesoctocog alfa demonstrated superior bleed protection over prior prophylaxis, was well tolerated, and provided FVIII activity within the normal to near-normal (>40%) range for most of the week. The aim was to evaluate long-term safety and efficacy of efanesoctocog alfa in adults/adolescents with severe hemophilia A from XTEND-ed (NCT04644575; first interim analysis).

Method: Previously treated patients (≥12 years old) who completed XTEND-1 (Arm A/B) could continue once-weekly efanesoctocog alfa (50 IU/kg) prophylaxis in the multicenter, open-label, long-term XTEND-ed study. The primary endpoint is incidence of FVIII inhibitor development. Secondary endpoints include annualized bleed rates (ABRs), efficacy for bleed treatment, and safety. XTEND-ed was approved by local ethics committees; participants provided informed consent. Data cut: June 8, 2023.

Results: A total of 146 patients (including 1 female) rolled over from XTEND-1 to XTEND-ed (12–17 years, n=21; 18–64 years, n=120; ≥65 years, n=5). Mean (range) treatment duration in XTEND-ed was 82.5 (14.1–103.6) weeks. FVIII inhibitors were not detected. Mean (standard deviation) ABR during XTEND-ed for patients from XTEND-1 Arms A and B was 0.72 (1.26) and 0.42 (0.89), respectively, thus maintaining the low mean ABRs observed in the parent study (Arm A: 0.71; Arm B: 0.69). Most (94%; 142/151) bleeding episodes resolved with 1 injection of efanesoctocog alfa; response was rated by participants as excellent/good for 88% (108/123) of bleeds. Overall, 108 (74%) participants experienced ≥1 treatment-emergent adverse event (TEAE) and 17 (12%) experienced ≥1 serious TEAE.

Conclusion: Long-term results in adults/adolescents in XTEND-ed show that once-weekly efanesoctocog alfa continues to be well tolerated and highly effective. No inhibitors were detected and ABRs remained low.

TP025

GP1ba functional assay- A single centre comparative study of Functional Testing Methods on Von Willebrand Disease classification in a Tertiary Haematology Unit

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Background: The diagnostic algorithm of von Willebrand disease (VWD) requires measurement of VWF antigen (VWF:Ag) and VWF functional testing with ristoceitin cofactor (VWF:RicoF) or direct GPIba-binding assays. Multimer assessment and molecular genetics may be complementary.

Aims: Assessment of the INNOVANCE® VWF Ac assay against existing assays for accurate diagnosis of VWD.

Methods: Samples from patients with Type 1,2 VWD, acquired VWD and haemophilia were tested with the VWF:Ag assay, VWF:RicoF both turbidimetric assays on the Sta-R Max analyser and the INNOVANCE® VWF Ac assay, a turbidimetric latex based agglutination assay using recombinant GP1b with 2 gain of function mutations. A ratio of 0.7 was used to distinguish type 1 from type 2 VWD.

Results: 49 samples tested showed overall good correlation between VWF:RicoF and VWF: Ac (ROC curve 0.72) (Figure 1). 6 samples had discrepant ratios: 1 was classified Type 1 VWD using VWF:GP1bM/VWF Ag ratio versus Type 2 using VWF:RicoF/VWF Ag ratio (Table 1). This patient had Type 2 VWD and a mutation in exon 28 of VWF, in the A2 ADAMTS13 binding domain. 1 Haemophilia A patient had all assay levels within normal range. 4 remaining samples had VWF:RicoF/VWF Ag ratios close enough to 0.7 that classification would change if the VWF:RicoF result varied as much as the known CV of 13-34%.

Conclusion(s): The INNOVANCE® VWF Ac assay showed overall good correlation with the existing VWF: RicoF Assay. At low VWF Ag levels, small fluctuations in functional assay testing within the CV may cause misclassification between T1 VWD and T2VWD. The gain of function mutations in the GP1bM may compensate for certain mutations leading to normalisation of results and misclassification as Type 1 versus Type 2 VWD. Genetic testing could be employed to differentiate.

Figure 1: Correlation coefficient between vWF: RicoF and the VWF: Gp1bM assays

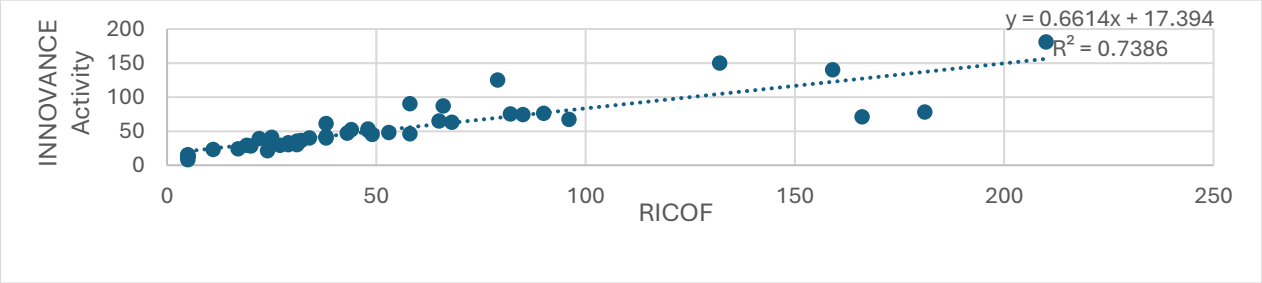

Table 1: Assay results from 6 samples with discrepant VWF:Gp1bM/vWF Ag ratio and vWF:RicoF/vWF Ag ratio

					INNOVANCE	RATIO		
Sample	FVIII	VWF	RICOF	CBA	VWACT	RICOF/VWF:Ag	INNOVANCE/VWF:Ag	DIAGNOSIS
1	51	17	5	15	15	0.29	0.88	Type 2M
2	92	60	38	58	61	0.63	1.02	Type I
3	326	196	166	123	71	0.85	0.36	Haemophilia A
4	83	31	20	32	28	0.65	0.90	Type I
5	81	36	25	35	30	0.69	0.83	Type I
6	61	34	24	32	21	0.71	0.62	Type 1

TP026

Registry-based 10-year review of real-world experience of acquired Haemophilia A in Western Australia

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Aim: Document clinical care of acquired haemophilia A (AHA) in Western Australia (WA), focussing on demographics, bleeding, precipitating factors, treatment options and outcomes.

Method: Retrospective population-based observational cohort study of acquired haemophilia A over 10-years (Jan 2014- Jan 2024) in Western Australia. Patients were identified using Australian Bleeding Disorders Registry (ABDR) and datapoints collected using ABDR and medical notes.

Results: 15 newly diagnosed AHA cases were identified, with median age 77 (range 16-87). All patients presented with bleeding, most commonly limb haematoma (7/15). Most cases (9/15) were idiopathic, 3/15 drug-related, 2/15 autoimmune associated and one post-partum. None had subsequent malignancy diagnosed. Immunosuppressive treatment was largely prednisolone and rituximab. Haemostatic treatment varied with activated prothrombin complex concentrate (APCC) used 11/15, recombinant activated factor VII (rFVIIa) 6/15 and 1/15 used recombinant porcine FVIII (rpFVIII). Time to complete response varied from 9-93 days, median 41 days. High-risk features such as Factor VIII (FVIII) coagulant activity (FVIII:C) < 1 IU/dL and FVIII inhibitor titre ≥ 20 BU/ml conferred the longest time to complete remission. Time to diagnosis was <1- 60 days, with 4/15 >1 week, and length of stay median 18 days (range 8-76). Mortality was 2/15 secondary to bleeding and infection.

Conclusion: Within WA, immunosuppressive management of AHA aligns with current guidelines recommending rituximab combined with steroids since 2015. Haemostatic management was heterogenous and may be based on availability and financial considerations. As expected, FVIII:C < 1 IU/dL and FVIII inhibitor titre ≥ 20 BU/ml were poor predictors of complete response. Prolonged doses of haemostatic treatment were required, suggesting limited efficacy of currently available haemostatic agents, with room for consideration of newer agents such as Emicizumab. Diagnostic delay remains a significant concern, potentially impacting morbidity and mortality. Prolonged hospital admission is a significant burden for patients.

Patient	Age	Site of bleeding	Precipitating factor	FVIII (%)	Inhibitor level (BU)	Time to diagnosis (days)	Length of stay (days)	Treatment	Haemostatic choice	ttCR (days)
1	18-70	GI	Idiopathic	<1	40	U	17+	Steroid Rituximab	APCC	78
2	18-70	Post-op epistaxis	Postpartum	11	<1.6	7	11	Steroid Rituximab	rFVIIa rpFVIII	42
3	18-70	Limb	Idiopathic	<1	71	<1	30	Steroid Cyclophos	rFVIIa	92
4	70+	Retroperitoneal	Autoimmune	1	11.4	7	76	Steroid Rituximab	APCC	27
5	<18	Post-op tonsil	Drug	9	7.4	2	8	Steroid	APCC	30
6	70+	Limb	Idiopathic	<1	64	<1	32	Steroid Rituximab	APCC	64

7	70+	Knee joint	Idiopathic	<1	37	6	26	Steroid Rituximab	APCC	21
8	70+	Retroperitoneal	Autoimmune	1	19	2	20	Rituximab	rFVIIa APCC	RIP
9	70+	Limb	Idiopathic	18	24	25	9	Steroid Cyclophos	rFVIIa	9
10	70+	Limb	Drug	1	47	20	22	Steroid Rituximab	rFVIIa	70
11	70+	Haematuria	Drug	14	1	17	31	Steroid Rituximab	rFVIIa APCC	40
12	70+	Retroperitoneal	Idiopathic	<1	15	3	U	Steroid Rituximab	APCC	U
13	70+	Limb	Idiopathic	<1	48.9	7	15	Steroid Rituximab	APCC	RIP
14	18-70	Limb	Idiopathic	6	3.1	5	10	Steroid Rituximab	APCC	33
15	18-70	Limb	Idiopathic	2	2	60	12	Steroid	APCC	93

Table 1: Patient demographics, disease characteristics, treatment, and outcomes

Abbreviations: U: unknown, Cyclophos: cyclophosphamide, rFVIIa: recombinant activated factor VII, APCC: activated prothrombin complex concentrate, rpFVIII: recombinant porcine FVIII, ttCR: time to complete response.

TP027

Australian experience of Haemostatic management in Acquired Haemophilia A

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Aim: Real-world data recording the haemostatic management of AHA in Australia over 5 years (2018-2023). Document the burden of bleeding complications (including duration of haemostatic treatment and length of stay in hospital) and accumulative cost comparison of choice of haemostatic agents.

Method: Retrospective population based observational cohort study of people with Acquired Haemophilia A (pwAHA) over a 5-year period (2018-2023) in Australia. Patients were identified on the Australian Bleeding Disorders Registry (ABDR) and datapoints collected using ABDR, National Blood Authority (NBA) and medical records.

Results: Interim data identified haemostatic management was heterogenous for patients with acquired haemophilia A. Haemostatic treatment included activated prothrombin complex concentrate (APCC) including FEIBA, recombinant activated factor VII (rFVIIa) often as NovoSeven and recombinant porcine FVIII (rpFVIII). Only one state had access to Emicizumab, as funding has not been agreed with NBA. Accumulative cost comparison of choice of haemostatic agents will be performed, including duration of haemostatic treatment and length of stay in hospital.

Conclusion: A mainstay of treatment is the use of bypassing agents to control active bleeding. Haemostatic therapies include recombinant activated factor VII (rFVIIa), activated prothrombin complex concentrate (APCC) or recombinant porcine FVIII (rpFVIII). Haemostatic therapy is expensive and is often required over an extended period of days to weeks. Choice of agent may be based on availability and financial considerations. Risks associated with haemostatic therapy include thrombotic complications. There is room for consideration of rpFVIII or Emicizumab in first line haemostatic management of AHA.

TP028

Registry-based review of bleeding events and use of Von Willebrand Factor concentrate prophylaxis in Type 3 von Willebrand disease in Australia

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Background: Type 3 von Willebrand disease (T3VWD) is a rare bleeding disorder caused by a marked deficiency or absence of von Willebrand factor (VWF). Autosomal recessive inheritance results in an even male/female distribution. The bleeding phenotype resembles that of severe Haemophilia A, except that affected females will often experience menorrhagia and dysmenorrhea. Patients with type 3 VWD with frequent or severe bleeding episodes may benefit from prophylactic treatment with VWF concentrate.

Aim: Quantify the bleeding events and use of von Willebrand Factor concentrate prophylaxis in patients with T3VWD in Australia to establish current standard of care.

Method: Registry-based retrospective Australia-wide observational cohort study of T3VWD. Patients will be identified from the Australian Bleeding Disorders Registry (ABDR) and datapoints collected using ABDR and medical records. Bleeding phenotype will be identified using ISTH BAT score and Haemophilia joint health score. Annualized bleeding rate and breakthrough bleeding rate will be described for those using on demand or prophylactic factor replacement.

Results: The 2021 ABDR annual report identifies 148 registered patients classified as having T3VWD, out of 2460 with VWD. Although accounting for 6% of VWD patients, 53% of total FVIII/ VWF IUs used in VWD is by T3VWD patients (average 1,436 IU/kg/yr useage) reflecting the significant bleeding phenotype. Of these, the majority (68%) is for prophylaxis, with 18% on demand usage and 13% for tolerization. Updated 2023 data including bleeding rates will be reviewed and presented.

Conclusion: Treatment of T3VWD is a changing landscape with various treatment options available, including on-demand and prophylactic treatment with VWF concentrate. Currently there is significant prophylactic factor usage. Given this, consideration of newer agents such as Emicizumab may be beneficial in this complex cohort.

TP029

Capturing Perioperative Anticoagulant management in Orthopaedics: a novel audit tool

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Aim: To develop an audit tool to capture and evaluate current trends in perioperative management of anticoagulation (PMA) for patients undergoing major orthopaedic procedures and conduct a preliminary audit to identify trends for further investigation.

PMA is complex with high bleed and thrombosis risks. Many local and international guidelines exist with varying levels of specificity and evidence, adding complexity. Identifying and evaluating current practice is essential to optimise PMA and reduce medication related harm. No standardised audit tool currently exists in Australia.

Method: The tool was developed from existing international literature, adapted to an Australian setting, then assessed for face validity by two experienced pharmacists with expertise in anticoagulation and perioperative medicine.

An audit of 10 patient charts at Ipswich Hospital tested useability and identified trends (Ethics approval HREC/2021/QTHS/76001). The proportion of compliance vs non-compliance to statewide guidelines was determined.

Results: The tool was streamlined based on face validity assessment and preliminary audit. Data collection identified that key information was not always available in a consistent location within the electronic record.

No emergency (3/10) but all elective (7/10) procedures documented a preoperative PMA plan. 20% of anticoagulants were withheld preoperatively at the recommended time, 70% withheld longer and 10% shorter. Bridging met recommendations in 80% of cases preoperatively and 60% postoperatively. 70% of postoperative notes overlooked therapeutic anticoagulation and recommended inappropriate VTE prophylaxis, 10% did not document PMA or VTE plans, 20% documented PMA plans meeting recommendations. Despite this, 70% restarted usual anticoagulant per recommended time, 20% withheld longer and 10% shorter.

Conclusion: Both clear guidelines and maintenance of the stages of prescribing are essential to optimise patient care. Consistent and easily accessible documentation assists busy clinicians with complex decisions. Further study including a larger audit is required to optimise PMA and inform future anticoagulant stewardship works to reduce the medication related harm burden.

References: Available upon request

TP030

Detection of Dabigatran Interference in an Activated Protein C Resistance EQA

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Aim: To review the results, methods, and the detection of dabigatran interference from an external quality assessment (EQA) survey sample of Activated Protein C Resistance (APCR), where the duplicate samples were issued seven years apart.

Method: Laboratories enrolled in the Activated Protein C Resistance (APCR) program were provided with an in-house preparation of lyophilised pooled plasma samples spiked with Dabigatran, which tested negative for APCR.

The results from sample APC-16-08a, issued in 2016, were compared with those from sample HA-APC-23-04, issued in 2023. The APCR ratio medians from both activated partial thromboplastin time (APTT) based and Russell viper venom test (RVVT) based assays were analysed. Trends and changes in favour of either APTT, RVVT or other more sensitive assays to detect dabigatran interference over 7 years were scrutinised.

Results: The breakdown of the APTT / RVVT methods showed no significant change over the seven years. In 2016, 21 participants submitted results using APTT-based methods and 12 using RVVT-based methods. Of these, 86% recorded normal APCR with APTT-based methods and 92% using RVVT-based methods.

In 2023, 18 participants (42%) detected the presence of Dabigatran along with a raised APTT upon testing compared to none in 2016. Of these, 39% used activated charcoal to neutralise the DOAC before performing the APCR tests and obtaining the expected APCR negative result.

Conclusion: The raised APTT in the presence of Dabigatran highlights increased awareness that DOACs can falsely elevate APCR ratios. This in vitro study using EQA samples, while limited, provides some evidence to support that Haemostasis measurement systems are now more sensitive in detecting the presence of Dabigatran than seven years ago.

TP031

Australia and New Zealand practice in the diagnosis and management of people with Bleeding Disorder of Unknown Cause (BDUC)

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Aim: We examined the current Australia and New Zealand (ANZ) and international approaches to the investigation, registration, and treatment of people with Bleeding Disorder of Unknown Cause (BDUC).

Method: BDUC was defined as a patient with a bleeding phenotype with normal laboratory tests. An online structured survey of health care providers (HCPs) using REDCap electronic data capture tool via the ISTH was sent to members of the associated Haemophilia Societies and professional associations. Ethical approval was granted by Cambridge University Hospital. Descriptive statistics are presented as frequencies and percentages rounded in whole numbers (n, %).

Results: Out of 314 responses, 216 were complete of which 31 were from ANZ. Most respondents utilised a bleeding assessment tool (BAT) (>80%) but assessed people less for hypermobility (55%). Initial haemostatic testing consisted of APTT, PT, fibrinogen in (>90%) but less VWF testing (84%), specific factor assays VIII, IX and XI (62%),fewer PFA-200 (37%) and platelet aggregation (26%). For second line testing, PFA-200 and platelet aggregometry was more frequently performed >60% as well as other specialised investigations. Registration of BDUC patients on national registries was less in ANZ (45%) than internationally (70%). Tranexamic acid was widely used (>70%) in major and minor procedures, heavy menstrual bleeding (>50%) and post-partum (58%) with/or without desmopressin and/or platelets or FFP. Around 50% advised avoiding regional anaesthesia for delivery. In BDUC patients without previous haemostatic challenge, 51% would give pre-emptive prophylactic haemostatic treatment.

Conclusion: Although BDUC is the most common mild to moderate bleeding tendency, there is a diversity of practice. The formal registration and recognition of BDUC patients will assist in the further understanding of the biological mechanisms that will contribute to a better diagnosis and personalised treatment.

TP032

Correlation of Factor VIII inhibitors when assessed by one stage and chromogenic VIII assays in patients not on Emicizumab treatment.

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Discrepancies between one stage (OSA) and chromogenic factor assays caused by missense mutations in Factor VIII are well documented. Some of these discrepancies are clinically significant (1). Emicizumab treatment is also known to cause similar discrepancies (2).

With the exception of recommendations for testing Emicizumab patients, there is little data on the correlation of Factor VIII inhibitors when assessed by OSA and chromogenic VIII assays.

The laboratory performed an internal study to collect data on all patients with Factor VIII inhibitor (Bethesda) requests, using both OSA and chromogenic VIII assays to assess inhibtor presence and titre.

This study revealed three cases where patients not on Emicizumab showed discrepancies between the results of their Factor VIII inhibitor assays when determined by OSA and chromogenic Factor VIII. The cases displayed either significantly different titres or discrepant results for the presence of inhibitors.

These case studies aim to start a discussion about when use of chromogenic VIII assay is warranted in inhibitor determination, and what these discrepancies mean for clinical management.

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TP033

Interim analysis of Real-world effectiveness and Usage of recombinant factor IX Fc for surgical haemostasis from the 24-month prospective, non-interventional B-MORE study

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Aim: B-MORE (NCT03901755) study assessed the real-world effectiveness/usage of extended half-life recombinant factor IX-Fc fusion protein (rFIXFc; Alprolix®) in patients with haemophilia B (PwHB) in perioperative setting.

Method: This descriptive interim analysis included PwHB≥1 surgery whilst on rFIXFc (no other FIX) during retrospective/prospective periods. Major surgery was any procedure involving general anaesthesia, and/or respiratory assistance, in which a major body cavity was penetrated/exposed while other surgeries were minor. Perioperative period was prior to, during, and post-surgery until return to usual treatment.

Result: B-MORE enrolled 151 PwHB (data cut-off: 6 October, 2022); 28 with 49 surgeries were included (20 severe, 5 moderate, 3 mild haemophilia; median [range] age: 20.1 [1–81] years; no inhibitor history).

Nine surgeries were major (n=8 PwHB; 7 severe; 1 moderate). Haemostatic efficacy was rated excellent/good for all 8 major surgeries with available data. Median (range) total perioperative rFIXFc consumption was 182.9 (70–524) IU/kg with 4.0 (1–13) injections (n=9 surgeries). Median (range) hospitalisation duration was 5.0 (2–10) days (n=8 surgeries). Median (range) estimated blood loss during the intra-/postoperative period was 0.0 (0–750) mL (n=7 surgeries). A total knee arthroplasty required 1 red blood cell unit transfusion.

Forty surgeries were minor (n=22 PwHB; 14 severe; 5 moderate; 3 mild). Haemostatic efficacy was excellent/good for all 34 minor surgeries with available data. Median (range) rFIXFc consumption was 89.3 (12–452) IU/kg with 1.0 (1–8) injection (n=36 surgeries). Median (range) hospitalisation duration was 2.0 (1–6) days (n=31 surgeries). No blood loss was reported in 23 minor surgeries with available data.

Thromboprophylaxis was given for 1 major and 1 minor surgery. Concomitant anti-fibrinolytic therapy was used in 5 major and 23 minor surgeries. No inhibitor development/or surgery-related serious adverse events were reported.

Conclusion: Interim data indicated that perioperative rFIXFc is efficacious and well-tolerated in PwHB.

TP034

Efficacy and safety of valoctocogene roxaparvovec 4 years after gene transfer in GENEr8-1

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Aim: Valoctocogene roxaparvovec (AAV5-hFVIII-SQ), a gene transfer therapy for severe hemophilia A, enables endogenous factor VIII (FVIII) production to prevent bleeding. The aim is to evaluate efficacy and safety outcomes 4 years post-valoctocogene roxaparvovec treatment.

Method: In the open-label, multicenter, phase 3 GENEr8-1 trial (NCT03370913), 134 adult men with severe hemophilia A (FVIII ≤1 IU/dL) without FVIII inhibitors received 6E13 vg/kg valoctocogene roxaparvovec (intention-to-treat [ITT] population). Bleeds and FVIII use were self-reported after regular prophylaxis cessation (scheduled week [W]4). The rollover population, which included 112 HIV-negative participants who enrolled from a non-interventional study, was used for comparisons with baseline FVIII use and bleeding rate. Chromogenic (CSA) and one-stage assay (OSA) FVIII activity was assessed in 132 HIV-negative participants (modified ITT [mITT] population). Safety was assessed in the ITT population.

Results: In the ITT population, 118/134 participants completed W208; 24/134 participants resumed prophylaxis. In the rollover population, mean annualized treated bleeding rate was 0.8 bleeds/y, mean annualized bleeding rate for all bleeds was 1.3 bleeds/y, and mean annualized FVIII infusion rate was 6.1 infusions/y over 4 years. During year 4, 81/110 (73.6%) participants had 0 treated bleeds and 68/110 (61.8%) participants had 0 bleeds regardless of treatment. At W208, mean CSA and OSA FVIII activity was 16.1 and 27.1 IU/dL, respectively, in the mITT population (18.0 and 25.5 IU/dL at W260 for the mITT subgroup dosed ≥5 years prior); 10/130 (7.7%), 68/130 (52.3%), 18/130 (13.8%), and 34/130 (26.2%) participants had CSA FVIII activity ≥40, ≥5 to <40, ≥3 to <5, and <3 IU/dL, respectively. During year 4, the most common adverse event was alanine aminotransferase (ALT) elevation (56/131 participants; ALT >upper limit of normal or ≥1.5x baseline); no participants initiated immunosuppressants for ALT elevation.

Conclusion:
Bleed control and FVIII expression were maintained 4 years post-valoctocogene roxaparvovec treatment. No new safety signals emerged.

TP035

Congenital factor XIII deficiency: a disease not to be forgotten - real world experience from Malaysia

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Aim: Factor XIII deficiency is a rare autosomal recessive coagulation disorder, which often leads to defective cross-linking of fibrin, manifesting in delayed haemorrhage. We report five cases of FXIII deficiency, summarizing the clinical spectrum and treatment types.

Method: This was a case-series of five patients diagnosed with FXIII deficiency in Malaysia. Demographic and clinical data were collected from electronic medical records. Quantitative determination of FXIII antigen was tested by latex enhanced immunoassay on ACL TOP automated analyzer using a commercial reagent kit(FXIII Antigen, Hemosil).

Results: Five patients were identified - four males and one female(Table1). All were diagnosed during first few years of life with FXIII level ranging from <1% to 1.3%. One had no family history, whereas the others had family members who succumbed to intracranial bleeds. The common bleeding phenotypes included intracranial, umbilical stump and muscle/joint bleeding, including delayed bleeding from a wound. The only female patient had antepartum haemorrhage during her first, twin pregnancy. She was commenced on FXIII concentrate 20IU/kg every 3 weeks from second trimester and the dose was increased to 20IU/kg fortnightly from 32 weeks gestation until delivery. This prophylactic regimen was able to keep the trough level at 4.3-8.49%. She received one dose of intravenous iron to correct iron deficiency. She had an uneventful spontaneous vertex delivery with no post-partum haemorrhage. Both babies had no bleeding manifestation and achieved appropriate developmental milestones. Prior to the advent of FXIII concentrate, most patients were given cryoprecipitate or plasma with some breakthrough bleeds. All five patients achieved zero bleeding events after commencement of FXIII concentrate prophylaxis. No thromboembolic events were reported.

Conclusion: FXIII deficiency is often underdiagnosed, possibly due to lack of awareness. Heightened clinical suspicion is crucial in cases with significant bleeding history despite normal standard coagulation assays. Targeted genetic analysis may be helpful in some scenarios.

** ICB, intracranial haemorrhage*

Patient No.	Age at diagnosis (years)	Gender	FXIII level at diagnosis	Family history	Bleeding phenotype (Year)	Treatment
1	4	Male	<1%	Parents and 2 brothers unaffected	- ICB* (1999) -Iliopsoas muscle haematoma (2002) - Post-traumatic muscle haematoma (2017) - Right ankle haemarthrosis (2019)	- Cryoprecipitate 8 units monthly until May 2020 - Started FXIII concentrate prophylaxis since June 2020 (22IU/kg every 4-6 weeks)
2	1	Male	1.273%	Younger sister passed away at 16 due to ICB* (unscreened)	- Delayed, prolonged bleeding from wound (1987) - Recurrent ICB* (2003, 2006, 2010)	- Cryoprecipitate 8 units monthly until April 2019 - Started FXIII concentrate prophylaxis since June 2019 (20IU/kg every 4-5 weeks)
3	At birth	Male	<1%	Elder sister passed away at birth due to umbilical stump bleeding; Younger brother had umbilical stump bleeding and succumbed at the age of 6 months due to ICB*	- Delayed umbilical stump bleed (1961) - Recurrent muscle haematoma (1981, 1986, 1992)	- Fresh frozen plasma on demand (1961, 1981, 1986) - Started FXIII concentrate prophylaxis since 1992 (15IU/kg every 3-4 weeks)
4	6	Male	<1%	One sister has FXIII deficiency; Parents unaffected	- Right ankle haemarthrosis (1999, 2018)	- Cryoprecipitate 8 units (on demand) - Not on prophylaxis
5	At birth	Female	1.3%	Elder brother (Patient no. 4) and mother have FXIII deficiency; mother succumbed to ICB* at 45	- Umbilical stump bleed (1994) - Menorrhagia (2020) -Threatened miscarriage with antepartum haemorrhage (2022) - Twin pregnancy	- No history of transfusion - FXIII concentrate started during pregnancy (2022) when presented with antepartum haemorrhage

TP036

Safety and efficacy of the Fitusiran revised antithrombin-based dose regimen (AT-DR) in people with Haemophilia (PwH) A or B, with or without inhibitors (ATLAS-OLE)

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Aim: Fitusiran, a subcutaneous (SC) investigational siRNA therapeutic, lowers AT to increase thrombin generation and rebalance haemostasis in PwH A/B, with/without inhibitors. We report interim safety and efficacy of the fitusiran AT-DR in ATLAS open-label extension study (NCT03754790).

Methods: Males (≥12 years) with severe haemophilia A/B, with/without inhibitors, completing fitusiran Phase 3 studies were enrolled. Original 80mg SC monthly (QM) dose regimen [ODR] was optimized to the AT-DR, targeting AT-levels:15–35% to mitigate adverse events (AEs). Participants received fitusiran prophylaxis 50mg or 20mg every other month (Q2M) or monthly (QM). Doses were individually adjusted to achieve AT:15–35%. Safety of AT-DR was compared to ODR across studies, and efficacy with control groups in the parent studies.

Results: 227 participants were enrolled. Mean (SD) AT-level was 23.5 (4.6) on AT-DR. 78% of participants were on Q2M regimens; 94% required zero or one dose adjustment to achieve AT:15–35%. Safety analyses included all participants exposed to fitusiran (n=270; ODR, n=286; AT-DR). Total patient (pt)-years of exposure were 306.8 and 486.0 for ODR and AT-DR, with ≥12 months exposure in n=101 and n=238, respectively. The exposure-adjusted incidence-rate of AEs was substantially reduced on AT-DR: thrombotic events (TEs) (ODR 2.28 versus AT-DR 0.82/100 pt-years), ALT/AST >3xULN (ODR 16.62 versus AT-DR 2.26/100 pt-years), and cholecystitis/cholelithiasis (ODR 14.67 versus 2.26/100 pt-years). All TEs had significant contributing risk factors. Median ABR (IQR) was 3.7 (0.0;7.5); 1.9 (0.0;5.6) and 3.8 (0.0;11.2) in PwH with and without inhibitors respectively. Superior bleed control was demonstrated versus on-demand CFC/BPA in PwH with/without inhibitors (73% and 71% reductions, $p<0.0006$, 0.0001, respectively). Bleed rate was reduced by 70% versus BPA prophylaxis ($p=0.0002$) and was comparable with CFC prophylaxis ($p=0.6$).

Conclusions: Fitusiran AT-DR (AT 15–35%) enhanced the safety profile and maintained bleed protection in PwH A/B, with/without inhibitors, mostly on Q2M SC dosing.

TP037

Impact of prophylactic-dose enoxaparin on anti-Xa levels, bleeding and extracorporeal circuit thrombosis in patients on intermittent haemodialysis

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Background: Therapeutic anticoagulation is required during intermittent haemodialysis (IHD) to prevent clotting of the extra-corporeal circuit. Unfractionated heparin (UFH) is the most common agent used for this, but low molecular weight heparin (LWNH) is increasingly being considered as an alternative. There is scant evidence for the safety and efficacy of LMWH in this setting.

Aims: 1. To assess anti-Xa levels with prophylactic-dose heparin in patients on intermittent haemodialysis

2. To assess the safety and efficacy of enoxaparin as an alternative to heparin in the prevention of thrombosis in dialysis circuits

3. To compare anti-Xa levels to clinical outcomes

Method: 20 outpatients (15 male, mean age 70+/-3.4 years) on three times weekly facility IHD (5hrs/session) were transitioned from UFH to LMWH 40mg (if weight 50-100kg) or 60mg (if weight > 100kg; 2 patients). APTT and enoxaparin anti-Xa measurements were measured at baseline, 2.5 and 5 hours for six consecutive dialysis sessions. Full blood count was also monitored at baseline (session 1) and at session 4 to monitor for potential complications. Dialysis unit nurses were asked to grade the degree of clotting in the dialysis circuit and to assess patients for access site bleeding or other bleeding events.

Results: With respect to safety, no episodes of minor or major bleeding were noted. Regarding efficacy, two patients had streaking of their dialyser which required a dose increase of their LMWH from 40mg to 60mg. Average anti-Xa levels anti-Xa levels across all 6 sessions at 0, 2.5 and 5hr were 0.038, 0.454 and 0.251IU/ml respectively. There was no evidence of accumulation of enoxaparin across the sessions (p=0.01).

Conclusion: In this limited study, LMWH did not result in increased bleeding complications when used as an alternative to heparin in IHD. Peak enoxaparin anti-Xa levels were comparable other small studies. Further investigation is required.

TP038

Case report of a Lymphoma patient with a strong Lupus Anticoagulant and its effect on Clotting factor assays

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Background: A 57-year-old woman with a new diagnosis of splenic marginal zone lymphoma and a background of antiphospholipid syndrome with high titre IgM and IgG anticardiolipin antibodies on warfarin therapy is noted to have markedly discordant INR results between recombinant and tissue-based thromboplastins. A falsely elevated INR with recombinant agent is identified. This led to more detailed investigation of coagulation results.

Aim: To present a case report demonstrating the effect of lupus anticoagulants on clotting factor assays prior to and following therapy with rituximab using different reagent sets.

Method: Plasma samples prior to and following therapy were tested for lupus anticoagulant using Hyphen APTT and Instrument Laboratory (IL) DRVVT reagents on neat plasma and with mixing tests with commercial pooled normal, reported as normalised ratios (NMR). Intrinsic factors were performed with LA-sensitive and LA-insensitive reagents. Extrinsic factors were performed with recombinant-based thromboplastin (Recombiplastin 2G from IL) and tissue factor-based thromboplastin (Thromborel S from Siemens).

Results: Pre-treatment LA NMR by APTT were 1.79 for neat plasma increasing to 4.34 at 1/4 mix with pooled normal, principally due to progressively reducing effect of the LA on the phospholipid rich APTT reagent with increasing dilution, namely 90.2s (neat), 43.1s (1/2) and 32.5s(1/4). The post-treatment NMR were 5.04, 4.59 and 3.50 at neat, 1/2 and 1/4 dilutions, indicating persistence of the LA. DRVVT results showed a similar pattern. Factor assays showed pronounced non-linearity with LA-sensitive APTT reagent but were linear with LA-insensitive APTT reagent.

Conclusion: It is important to consider the possibility of falsely elevated clotting times and falsely low factor levels in patients with a strong lupus anticoagulant, particularly when they are being used to modify therapy. Repeat testing using different reagent sets may be considered when discordant results are noted.

TP039

Krakow II Congenital dysfibrinogenaemia, Aα Gly13Glu, treated successfully with fibrinogen replacement during pregnancy: a case report

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Background: Congenital dysfibrinogenaemia (CD) is an inherited qualitive defect in fibrinogen commonly arising from a missense variant in the fibrinogen alpha, beta or gamma chain genes (FGA, FGB or FGG) on chromosome 4q28-q31. Clinical phenotypes vary broadly including asymptomatic carriers, thrombophilia, bleeding tendencies or pregnancy complications.(1) The previously reported missense variant NM_000508.4:c.95G>A; p.(Gly13Glu), arising in *FGA* exon 2 codes for fibrinogen Krakow II, and is associated with epistaxis and miscarriages.(2-4) Herein we describe a case of a 27 year old female with Krakow II CD presenting with consecutive first trimester miscarriages.

Case: The patient was referred with incidentally discovered low fibrinogen and two consecutive early pregnancy losses. She had an ISTH BAT score of 2 with no bleeding during prior non-obstetric haemostatic challenges and no thrombotic events. Coagulation studies showed a characteristically low Clauss fibrinogen (0.5g/L, normal 2- 4.5g/L), prolonged thrombin time (42 seconds, normal 16-23s), a prolonged reptilase time of >60s (normal 18-24s) but normal prothrombin time (PT), activated partial thromboplastin time (aPTT), PT-derived fibrinogen and immunological fibrinogen (3.8g/L, normal 1.8-3.5g/L). Commercially available *FGA* gene sanger sequencing confirmed the heterozygous variant NM_000508.4:c.95G>A; p.(Gly13Glu). Despite preconception planning the patient presented unexpectantly at 8 weeks gestation with a threatened miscarriage. She was commenced on twice weekly fibrinogen replacement, maintaining a trough level >1g/L, with no bleeding complications throughout the remainder of the pregnancy and vaginal delivery. Prophylactic dose low molecular weight heparin was administered for 6 weeks post-partum with no thrombotic complications.

Conclusion: This case demonstrates the safe and efficacious use of fibrinogen concentrate to a target >1g/L during pregnancy for patients with Krakow II CD. Interestingly this is the second case report of Krakow II CD displaying a solely obstetric bleeding phenotype. Careful phenotypic characterisation and publication of these extremely rare fibrinogen variants is critical to help inform management approaches for future cases.

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TP040

Major bleeding risk in elderly patients receiving anticoagulation for venous thromboembolism - a 10-year retrospective review

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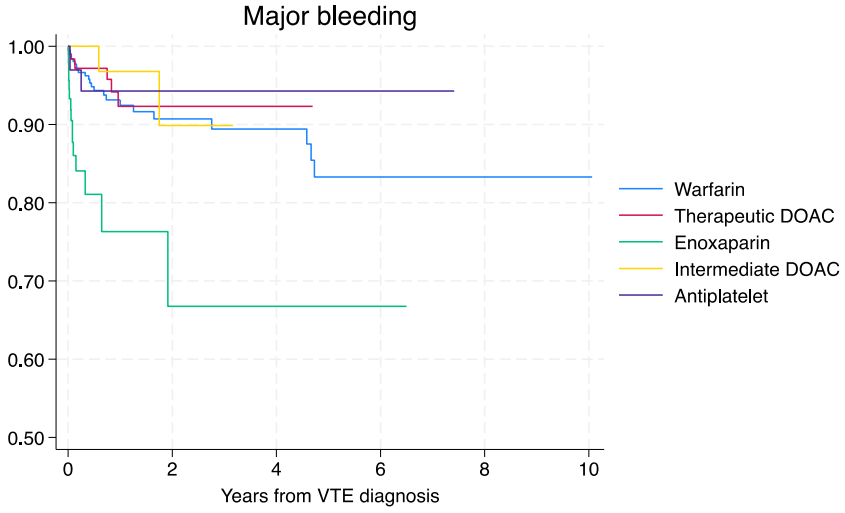
Aim: Elderly patients receiving anticoagulation for venous thromboembolism (VTE) are at increased risk of bleeding complications. There is limited real-world data to guide clinical management in this cohort. We aim to review the risk of major bleeding (MB) in elderly patients being anticoagulated for VTE at Northern Hospital, Victoria.

Method: This is a retrospective review of patients ≥75 years-old receiving anticoagulation for a new diagnosis of VTE from December 2010 to December 2020. Patients with active malignancy at time of VTE diagnosis were excluded. Univariate cox-regression analysis was performed, with MB (defined as per ISTH-SSC criteria) as the endpoint. Patients without MB were censored at the time of last follow-up or death.

Results: 674 patients (median age 82 years, 36.7% male) were identified. Over a total follow-up of 958.8 patient-years (PY), there were 54 MB events (5.6/100PY) including 17 gastrointestinal and 13 intracranial bleeds, leading to 13 (1.9% overall) bleeding-related deaths. The median time to MB was 1.9 months. MB was associated with previous history of bleeding (18.9% vs 6.8%, p=0.002), lower haemoglobin (114g/L vs 123.2g/L, p=0.002) and concurrent use of CYP3A4 metabolised medications (7.4% vs 2.3%, p=0.027). MB rate was highest for patients treated with enoxaparin (27.7/100PY) and compared to patients on DOAC, enoxaparin was more likely to lead to bleeding (hazard ratio (HR) 5.6, 95%CI 2.4-13.3,p<0.001). No significant differences for MB occurrence were found (figure 1) between patients on therapeutic DOAC (5.2/100PY), prophylactic DOAC (4.4/100PY), warfarin (4.4/100PY) or antiplatelets alone (1.37/100PY), logrank p=0.57.

Conclusion: Major bleeding was common (5.6/100PY) and occurred early in older patients being anticoagulated for non-malignancy related VTE regardless of type of anticoagulation, and is associated with a substantial risk of death. Enoxaparin was associated with the highest risk. Careful consideration is required when anticoagulating older patients with VTE.



Nursing Poster Presentations

NP001

Orange dot pilot – needle manipulation project

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Aim: To ensure only 1 needle manipulation during donor venesection, thereby reducing possibility of vein injury. Provide a better donor experience.

The orange dot is a visual tool on the donor's arm for staff to recognise when a needle manipulation has already taken place, so no further adjustments are made. Palmerston North donor centre piloted the project, based on previous work by Lifeblood.

Method: A pilot of 15 weeks (November 2023 till March 2024), testing one manipulation of the needle during donor venesection. When one needle manipulation occurs, it is visually shown with an orange dot on the lower tape.

Data collected: phlebotomy type, changeover, donation success, staff comment and donor adverse event. Donor and staff surveys.

Data analysis: Performed on phlebotomy success, injury rates and deferral data.

Results: 98 orange dot participants in total over the 15 weeks. 61 had a successful donation (62%).

NZ injury rate sits around 1.1-1.6% whereas Palmerston North during the pilot was 0.3-1.3%.

While the small sample sizes make the injury rate inconclusive, it does show an encouraging decrease during the pilot. Deferrals also decreased over the pilot period.

Donor experience survey results: 88% of participants were satisfied with their experience compared to their previous experience. 100% of participants were satisfied with the staff explanation of the project.

Staff experience survey results: Increased number of staff recognised the value of communication with the donor.

Conclusion:

- Potentially less phlebotomy injuries with the orange dot pilot.
- Orange dot shows a better experience for the donors and staff.
- No complaints about injury received since the start of Orange dot.
- Recommendation is to now roll out to rest of New Zealand, try at larger Donor Centre site first.

The data from this next phase will also be able to be shared at Blood 2024.

NP002

Use of Powerflow Implantable devices in Paediatric Sickle Cell Disease (SCD) for red cell exchange procedures: A nursing reflection

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Aim: To provide an overview of the use of the Powerflow device at QCH for red cell exchange in paediatric SCD and to evaluate care compared to other centres within Australia.

Method: A 12-month, qualitative retrospective review of the achievements and challenges in the QCH SCD paediatric cohort was undertaken, with experience compared to other centres.

Results: Two patients at QCH received red cell exchange procedures using a Powerflow™ device.

Challenges:

- Procedural pain and anxiety for the patients during port access.
- Devices only accessed by trained renal nurses (small team of only two trained nurses)
- Multiple attempts at port access - lack of experienced nurses
- Lack of knowledge and experience using Powerflow devices by surgical units, emergency physicians and nurses.

Achievements:

- Collaborative discussion and feedback resulted in a trial using 1% Lignocaine mixed with Sodium Bicarbonate (NaHCo3) to reduce the sting of the local anaesthetic. For procedural anxiety a trial of Midazolam and Entonox was used.Single needle red cell exchange procuredure
- Positive patient feedback including they were not as worried about the port access, and they experienced nil pain.

Conclusion: Benchmarking with other paediatric centres within the same field aids best practice and standardisation of care.

Improved outcomes for patients: feedback was positive.

Positive feedback from nursing team: reduced anxiety for patients and families made for a less stressful experience.

Recommendations for future practice: to develop a standard of care for all patients with a Powerflow™ device for red cell exchange.

The development of safety cards for families/patients in the event of an emergency presentation where intravenous access might be required.

NP003

South Australia's experience transitioning from Intragam to Privigen AU

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Aim: Optimise South Australian (SA) patient safety and minimise risks associated with the transition from Intragam to PrivigenAU and gain an understanding of change impacts.

Method: BloodSafe, with Immunoglobulin (Ig) Nurse Consultant, utilising Australasian Society of Clinical Immunology and Allergy (ASCIA) guidelines, developed SA specific guidelines for administration of PrivigenAU and standardised all IVIg administration guides within SA.

Data from public hospital incidents and near misses was collected using SA Health incident management system Safety Learning System (SLS) and the Ig nurse recorded, managed, investigated, and analysed incidents and consumer feedback. Data will be used to support education, and guide policy development.

Results: The BloodSafe Ig Nurse Consultant developed in consultation with CSLBehring a comprehensive framework to support the transition of patients to PrivigenAU. See Table 1.

Table 1: Transition Framework for SA patients, Intragam to PrivigenAU

Time Frame	Activities
5 Months (Dec 2022)	Stakeholder identification. Engagement Project planning. Initialisation. Resources
4 Months (Jan 2023)	Education, key stake holders Communication change management NBA communication. Neurology Patients transferred to Privigen Education Metro
3 Months (Feb)	Education Metro, Private PrivigenAU guideline development PrivigenAU Neonate guideline development
2 Months (Mar)	Education Metro, Private, Consumer
1 Month (Apr)	Education Metro
Week 1 17th April	**PrivigenAU available**
Week 2 24th April	Coordination Intragam usage SLS incident. PrivigenAU reaction
Week 3 1st May	Ongoing liaison, service centres Ongoing SLS collection
Week 4 8th May	Reaffirming education, Rural settings Ongoing service centre liaison Co-ordinate weekly Intragam stock usage
Week 5 15th May	SLS incident
Week 6 22nd May	SLS incident
Week 7 29th May	SLS incident
Ongoing	Stock-level management

Conclusion: The framework for change management provided a successful transition from Intragam to PrivigenAU and an opportunity to learn about good change processes. This was evident with limited incidents reported and positive feedback provided from patients and clinicians.

NP004

Nursing at Australian Red Cross Lifeblood – It's unique and diverse.

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Nursing is one of the most trusted professions in Australia[1]; with this comes considerable responsibility and expectations from patients, donors, the public and the healthcare sector. The Australian Health Practitioner Regulation Agency (AHPRA) 2022/23 Annual report showed that across Australia 480,070 nurses have registrations[2] (including those with endorsements and dual registrations), and approximately 912[3] (0.2%) are employed by Australian Red Cross Lifeblood (Lifeblood). Lifeblood nurses' work is unique - unlike traditional nursing roles, we apply our knowledge and skills with healthy volunteers who enable Lifeblood to deliver life-giving blood products, breast milk and other biological products to where they are needed.

Lifeblood nursing is specialised and expanding in response to demand, technology, new products, and research. Our dedicated frontline nursing team facilitate the 1.7 million donations collected annually[4]. They are supported by a multidisciplinary team who work in compliance with good manufacturing practice and a focus on excellent customer service. Lifeblood nurses also help facilitate special collections from platelet donors, anti-D plasma donors and research participants. Lifeblood's nursing workforce includes donor eligibility, transfusion and infectious disease nurses, lactation consultants and midwives to support our milk collections for pre-term babies. Additionally, in WA our nurses are screening and collecting faecal microbiota for transplant (FMT) for clinical trials. Further, we have nurses who facilitate research initiatives and innovation.

Lifeblood has come a long way in over 90 years, and so have its nurses, whose roles require unique skill sets applied in a diverse, trusted, and essential service. Lifeblood nurses work extensively with our colleagues across Lifeblood to ensure that safe, regulatory compliant products of the highest quality are available. Our nurses strive to provide excellent, informed and evidence-based care, in recognition of our generous volunteer donors, and in support of patients, the public and the Australian healthcare sector.

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NP005

Validation of the Steroid Symptom Questionnaire Multiple Myeloma (SSQ-MM) with concurrent symptom and quality of life measurement (EORTC QLQ-C30 and MY20)

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Aim: Psychometric evaluation of the SSQ-MM to support use in clinical practice and research settings.

Method: Multi-centre cross-sectional study of 140 MM patients taking dexamethasone as part of treatment. Participants completed the SSQ-MM, QLQ-C30 and MY20 PROMs. SSQ-MM was repeated 1-week later. Internal consistency reliability was tested with Cronbach's alpha >0.8 for individual patient decision-making. Test-retest using intraclass correlation coefficient >0.7 evaluated SSQ-MM stability reliability. Construct validity was tested with factor analysis and spearman ρ rank-order correlation coefficients for similar domains between the PROMs (high, r > 0.7; moderate, r 0.3-0.7; low, r < 0.3).

Results: Participants were aged between 38-89yrs (Mean: 69.7, SD: 9.9), 54% male, average 4.5 yrs since diagnosis (range 4mths to 22yrs). Average dexamethasone dose was 26mg/week (range, 4-80), or 84mg/cycle (range, 12-180) and an average of 4.0 (SD: 3.0) prior lines of treatment completed. Internal consistency reliability was high: Cronbach's alpha 0.84, and test-retest indicated SSQ-MM stability (ICC: 0.846). Factor analysis supported a total score reflecting overall symptom bother associated with steroids. Moderate positive correlations were observed between SSQ-MM total scores and MY20 symptom and treatment side-effect scores (r = .466 and .682) providing evidence towards construct validity.

Frequently reported symptoms were disturbed sleep, fatigue, and fragile skin. Patients typically experienced 10 symptoms concurrently (range, 0-19) with four symptoms rated severe (range, 0-12). Longer time since diagnosis (r= 0.239; p=0.005), female gender (r= 0.194; p=0.022) and higher ECOG (r=0.169; p=0.048) were associated with higher SSQ-MM total scores.

Descriptive findings highlight Social/Role functioning is impacted by steroid use, which in other studies has been shown to correlate with lower QOL.

Conclusion: This study provides evidence in support of the validity and reliability of the SSQ-MM. It is suitable for clinical use to detect steroid toxicity and improve treatment outcomes for MM patients and for use in research settings to assess the impact of steroids in MM.

NP006

Transfusion Audit Data and Informatics- Initiatives that support data-driven decisions to improve practice

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Aim: Transfusion Audits may have started as an academic exercise that is necessary as key performance indicators that help guide practice improvements. But these days a booming and fast changing IT platform makes changing traditional transfusion auditing methods innovative, practical, and exciting.

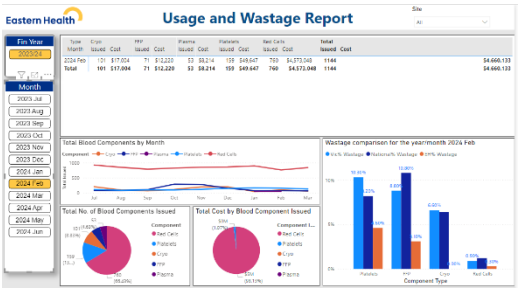
Even if you have never seen Power BI reporting before, learn how to start with concise, practical tips on how your Transfusion audits can be transformed.

Method: Access to data can be challenging with respect to information being held in multiple systems E.g. National Blood Authority, ARC Lifeblood and internal IT systems within an organisation. This results in those responsible for Scorecards being developed to gather and integrate information from multiple sources. E.g Blood Management Scorecard

The process always requires manual interpretation of data. This is person dependant and errors can occur if there is lack in concentration E.g. not identifying duplicate information when auditing. This can result in inaccurate results. There is also the potential for inconsistencies if the process for data auditing is not clearly defined and documented. When reports are provided, staff often need to simply “trust the integrity” of the data.

Given the time consuming nature of gathering and presenting performance data, there is an opportunity to provide real-time audit data that is reported monthly. There is also the opportunity that the data can be accessed from anywhere and anytime.

Results: Power BI Reports provide an automated way of showing what is needed for accreditation readiness and could be used to communicate the information in a timelier and effective way. There is increasing awareness of its existence with further collaboration and combining informatics, auditing data and presentation of this data in a meaningful way to members of the healthcare system.



Conclusion: You will see how Power BI reports can be developed. You can gain a new way of thinking about how audits are conducted and how results can be presented to provide feedback and evidence for key performance indicators in real-time to influence and improve practice.

NP007

Australian Red Cross Lifeblood Rh Program – The need for new donors to support Australian newborns

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Since 1967, pregnant Rh negative Australian women have received Rh(D) Immunoglobulin to prevent haemolytic disease of the foetus and newborn (HDFN). HDFN can have serious health outcomes for the foetus or newborn, including anaemia, jaundice, brain damage or death. Since the introduction of the Rh Program (RhP) at Australian Red Cross Lifeblood (Lifeblood), an estimated 2 million pregnant women in Australia have received Rh (D) Immunoglobulin and mortality from HDFN has significantly reduced[1].

Rh(D) immunoglobulin is available with the help of our volunteer RhP donors and our partners at CSL Behring. There are two RhP donor categories. Those rare donors with preformed antibodies and others that are Rh negative and consent to being transfused with Rh (D) positive red cells. In June 2023, there were 107 active donors within the program, who donated 219 litres of plasma[2]. To maintain the active panel to meet demand, in 23/24FY, we set ourselves a target of securing 90 new donors to the RhP.

Finding donors to recruit and immunise into our program can be tricky. Our staff work as a multidisciplinary team to search our databases, talk to donors in centre, review donor records and reach out to those few that fit the criteria. Potential donors are interviewed by Medical Officers, and then they're introduced into the RhP. Specialised teams across Australia provide donors with continued support on their journey to becoming a valued RhP donor.

Keeping Australia self-sufficient in Rh(D) Immunoglobulin injections relies on growing the panel. By April 2024, we are well on the way with meeting our targets of 90 new donors growing our active panel to 160 donors, and increased plasma volume to 314 litres collected as part of the RhP[3]. Lifeblood celebrates, respects and thanks this small but growing number of special donors who have a huge impact on newborn health outcomes.

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NP008

Evaluation of nurses' attitudes toward patients with sickle cell disease in South Brisbane, Australia

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Aim: This study aimed to evaluate the attitude of nurses caring for sickle cell disease (SCD) patients in South Brisbane, Australia.

Method: A descriptive, observational convergent-parallel mixed-method design was conducted in a tertiary teaching hospital between July 2022 and August 2022. Purposive sampling was used in sample (N=40) selection. A survey questionnaire was used to determine the demographic profile and nursing attitudes. Concurrently, in-depth interviews were undertaken to evaluate nurses' lived experiences.

Results: There were 34 participants in the online survey (n=34) and six in-depth interviews (n=6). The majority of the respondents were female nurses (67.6%), with a median age of 25 (IQR:21-30), and Bachelor of Nursing (BN) graduates (64.7%) with 1 to 5 years of clinical experience (52.9%). The attitude of the nurses towards patients with SCD is seldom evident (mean: 2.76). A positive attitude is high (mean:3.61); a negative attitude is low (mean:2.38; SD=1.04); concern-raising behaviour is moderate (mean:2.74; SD=0.95), while red-flag behaviour is low (mean of 2.31 (SD=0.87). Overall, the nurses' attitudes do not significantly differ across sex (p=.504), age (p=.931), education (p=.811), and years of practice as a nurse (p=.968). However, there are significant differences in the concern-raising and red-flag behaviours of the nurses based on their education (p=.038) and sex (p=.020). Furthermore, the lived experiences of the nurses caring for SCD patients highlighted key themes: knowledgeable about the disease, dealing with different patients' emotions, and finding SCD patients easy to manage. These experiences have also shaped nurses' attitudes toward SCD patients, leading to themes such as being happy in the profession, being glad to look after SCD patients, and enabling nurses to reflect on their values.

Conclusion: Some nurses' attitudes toward SCD patients differ. Therefore, it is recommended that further research on SCD be conducted to address the identified attitude that affects patient care delivery. Improving education and training for all nurses about SCD is vital.

NP009

Technology and documentation changes in clinical trials – a decade snapshot.

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Aim: The changes in clinical trial requirements over the past decade have impacted on site management in order to continue to be competitive in the global market.
Increased requirements impact on site resources but does it really achieve better productivity or just a change in responsibilities and skill requirements.

Method: The length and content of documentation has increased as have electronic systems which impact on all trial participants - site staff, sponsor and patient.

Trial Documentation - Protocols, Patient Information Sheets and Consent forms, and supportive clinical trial requirements (manuals and training) have been reviewed over a 10 year span - 2013 – 2023 in regards to length or complexity, and changes in information technology. This review seeks to demonstrate the increased requirements and impact on site resources and patient burden and commitment.

Results: Over the period of review, increases in required documents (number or length) and in additional site resource or patient commitment requirements.
External sponsor supported studies have demonstrated significant changes in the following areas:
- Protocol and PICF length has increased significantly

- Increase in external service providers - 80% of studies require additional training, electronic uploads etc.
- Increase in patients time requirements to participate - length of time to read the PICF, additional medication / side effect / QOL diaries.

Conclusion: Increased site requirements impact on site resources but does it really achieve better productivity or just a change in responsibilities and skill requirements.
Predicting the impact of increased site responsibilities and tools are difficult to measure quantitatively and flexible and adaptable processes are required to meet this need.
The time to manage start up efficiently has increased hand in hand with the number of documents and external service providers.