Malignant Haematology RESEARCH REVIEW™

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Issue 11 – 2025

In this issue:

Abbreviations used in this issue
CAR = chimeric antigen receptor
CLL = chronic lymphocytic leukaemia
CR/PR = complete/partial remission
HR = hazard ratio
MCL = mantle cell lymphoma
MM = multiple myeloma
MRD = measurable residual disease
NKTL = natural killer/T-cell lymphoma
ORR = overall response rate
OS = overall survival
PD-1 = programmed cell death-1
PFS = progression-free survival
SCT = stem-cell transplantation

Welcome to the eleventh issue of Malignant Haematology Research Review.

This issue has an analysis of a phase 3 trial comparing the addition of venetoclax to ibrutinib, when compared with ibrutinib alone or the FCR regimen (fludarabine, cyclophosphamide, rituximab), in patients with CLL. A trial subset analysis has compared the addition of nivolumab or brentuximab vedotin to the AVD regimen (doxorubicin, vinblastine, dacarbazine) for treating older participants with classical Hodgkin lymphoma. There is also a comparison of NZ and Australian patients with MM revealing significant inferior survival for kiwis. We conclude with an analysis of the DREAMM-7 and DREAMM-8 trials of managing ocular toxicities from belantamab mafodotin using dose delays and modifications.

Thank you for the comments and feedback you have sent us – they are appreciated.

Kind regards,

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P3-GemOx as a novel immunochemotherapy candidate in NK/T-cell lymphoma management

Authors: Zhang Y et al.

Summary: This paper reported on 11 patients with NKTL who received 1–4 cycles (median 3) of the P3-GemOx regimen (Plm60 [pegylated liposomal mitoxantrone], anti-PD-1 antibody, pegaspargase, gemcitabine, oxaliplatin) every 3–4 weeks, and eleven who received 2–6 cycles (median 4) of the regimen without Plm60. Among P3-GemOx regimen recipients, the ORR was 100% (nine CRs and two PRs), compared with 63.6% among PP-GemOx recipients; seven P3-GemOx regimen recipients underwent haematopoietic SCT, compared with none of the PP-GemOx recipients. Adverse events were manageable and resolved.

Comment (LB): In this retrospective study of advanced NKTL, a rare Epstein-Barr virus-associated malignancy with poor prognosis despite asparaginase-based regimens, the novel P3-GemOx protocol – incorporating Plm60 alongside anti-PD-1 blockade, pegaspargase, gemcitabine and oxaliplatin – demonstrated superior efficacy over PP-GemOx, achieving a 100% ORR with an 81.8% CR rate, versus a 63.6% ORR and an 18.2% CR rate, in matched cohorts of 11 patients each. The control arm response rates seem remarkably low, even for this entity, and a randomised study is therefore needed. The findings suggests that Plm60's immunomodulatory synergy in overcoming PD-1 resistance and primary refractoriness should be taken further given the abysmal outcome of most patients with advanced NKTL.

Reference: Front Med 2025;12:1666601

Abstract

INDEPENDENT COMMENTARY BY
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Rituximab, bendamustine, and cytarabine followed by venetoclax in older patients with high-risk mantle cell lymphoma (FIL_V-RBAC)

Authors: Visco C et al., on behalf of the Fondazione Italiana Linfomi

Summary: In this phase 2 study, 54 patients with high-risk untreated MCL received four cycles of RBAC (rituximab 375 mg/m^2 on day 1, bendamustine 70 mg/m^2 on days 1 and 2, cytarabine 500 mg/m^2 on days 1, 2 and 3) followed by 4 months of consolidation oral venetoclax 800 mg/day and 20 months of maintenance oral venetoclax 400 mg/day; the study also enrolled 86 patients with low-risk untreated MCL who received six 4-week cycles of intravenous RBAC. Outcomes for the high-risk group were reported. After a median 45 months of follow-up, the 2-year PFS rate (primary endpoint) was 60%, with a median PFS duration of 37 months. The most frequent grade ≥3 adverse event during venetoclax consolidation was neutropenia (28%), followed by thrombocytopenia and skin reactions (7% each). During venetoclax maintenance, neutropenia remained the most frequent grade ≥3 adverse event (19%), followed by thrombocytopenia and anaemia (5% each). There was one treatment-related death recorded.

Comment (LB): The Italian FIL group showed that the RBAC regimen was highly effective in untreated MCL. The current study is designed to further improve outcomes with the addition of venetoclax maintenance (800mg for 4 months before reducing to 400 mg/day) in high-risk patients. Despite this measure, high-risk patients still did worse. Venetoclax monotherapy is known to have activity in relapsed/refractory MCL, but it is not clear if the high-risk patients are the ones who benefitted. Novel agents are useful in *TP53* aberrant diseases as they avoid the risk of cytotoxic agents creating additional mutations, but it is not clear that sequential treatment with a BCL2 inhibitor is beneficial. BCL2 inhibitors are possibly more effective in combination, and randomised studies are required.

Reference: Lancet Haematol 2025;12:e777–88
Abstract

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Measurable residual disease-guided therapy for chronic lymphocytic leukemia

Authors: Munir T et al., for the UK CLL Trials Group

Summary: Patients with CLL were randomised to receive ibrutinib plus venetoclax (n=260), ibrutinib alone (n=263) or FCR (n=263) in this open-label phase 3 trial. For the two primary endpoints, ibrutinib-venetoclax was associated with: i) a higher proportion of participants with undetectable MRD in bone marrow within 2 years versus the ibrutinib-only arm (66.2% vs. 0% [p<0.001]); and ii) a lower proportion with disease progression or death after a median 62.2 months of follow-up versus the FCR arm (6.9% vs. 42.6%; HR 0.13 [95% CI 0.08, 0.21]), with a higher 5-year PFS rate (93.9% vs. 58.1%). For PFS, ibrutinib-venetoclax was also superior to ibrutinib alone. The mortality rate was significantly lower in the ibrutinib-venetoclax arm compared with the ibrutinib-only and FCR arms (4.2% vs. 9.9% and 14.8%, respectively; HRs 0.41 [95% CI 0.20, 0.83] and 0.26 [0.13, 0.50]).

Comment (LB): The FLAIR study has evolved from a two-, four- and now three-arm study. This paper describes the latest iteration, and shows that ibrutinib with venetoclax is superior to ibrutinib alone, and both are better than FCR. Rather than fixed duration, the study was MRD-guided, and extended treatment was needed, i.e. up to 6 years to achieve these excellent MRD results. Similar to the GLOW study, older patients had increased toxicity with the ibrutinib-venetoclax arm. The MRD rates are much higher than the recently published AMPLIFY study using acalabrutinib and venetoclax, but the latter was better tolerated. The zanubrutinib and sonrotoclax regimen is very well tolerated and has very high MRD rates. Oral regimens appear to be gaining favour over rituximab-venetoclax or venetoclax-obinutuzumab in CLL. Several approaches are available for upfront treatment, and salvage is effective.

Reference: N Engl J Med 2025;393:1177–90
Abstract

Acalabrutinib-obinutuzumab improves survival vs chemoimmunotherapy in treatment-naive CLL in the 6-year follow-up of ELEVATE-TN

Authors: Sharman JP et al.

Summary: Results after a median 74.5 months of follow-up were reported for ELEVATE-TN trial participants with CLL who had been randomised to acalabrutinib-obinutuzumab (n=179), acalabrutinib (n=179) or chlorambucil-obinutuzumab (n=177). Compared with chlorambucil-obinutuzumab, acalabrutinib-obinutuzumab and acalabrutinib were associated with longer median PFS (not reached and not reached, respectively, vs. 27.8 months [both p<0.0001]), with higher estimated 72-month PFS rates (78.0% and 61.5% vs. 17.2%) and acalabrutinib-obinutuzumab outperforming acalabrutinib monotherapy (HR 0.58 [p=0.0229]). Among participants with unmutated *IGHV*, del(17p) and/or mutated *TP53* or a complex karyotype, PFS was significantly better in both the acalabrutinib arms compared with the chlorambucil-obinutuzumab arm. None of the arms reached median OS duration, although this was significantly longer with acalabrutinib-obinutuzumab than with chlorambucil-obinutuzumab (HR 0.62 [p=0.0349]); the estimated 72-month OS rates in the respective acalabrutinib-obinutuzumab, acalabrutinib and chlorambucil-obinutuzumab arms were 83.9%, 75.5% and 74.7%. Adverse events that emerged after 4 years were mostly grade 1–2, with the acalabrutinib-containing arms having similar rates (including serious and clinical interest events).

Comment (LB): This study showed that acalabrutinib with or without obinutuzumab was superior to chlorambucil-obinutuzumab. With extended follow-up, the PFS still favoured the addition of obinutuzumab; the OS was better with acalabrutinib-obinutuzumab than with chlorambucil-obinutuzumab, but did not reach statistical superiority compared with acalabrutinib alone. Looking at subgroup analyses, the patients with *TP53* aberrant disease did not seem to benefit from the addition of obinutuzumab, so this high-risk population can have acalabrutinib alone. Given the additional toxicity, inconvenience and resource associated with adding obinutuzumab, the 'juice may not be worth the squeeze'. The BTK inhibitor plus BCL2 inhibitor combinations seem more appealing.

Reference: Blood 2025;146:1276–85
Abstract

Nivolumab-AVD versus brentuximab vedotin-AVD in older patients with advanced-stage classic Hodgkin lymphoma enrolled on S1826

Authors: Rutherford SC et al.

Summary: This was a subset analysis of 99 eligible participants aged ≥60 years with newly diagnosed advanced-stage classical Hodgkin lymphoma from the phase 3 S1826 trial, in which they had been randomised to receive six cycles of AVD with either nivolumab or brentuximab vedotin. After a median 2.1 years of follow-up, the 2-year PFS rate was greater with nivolumab-AVD than brentuximab vedotin-AVD (89% vs. 64%; HR 0.24 [95%CI 0.09, 0.63]), as was the 2-year OS rate (96% vs. 85%; 0.16 [0.03, 0.75]) and the proportion of participants who received all six treatment cycles without needing a dose reduction (69% vs. 26%); the nivolumab discontinuation rate was lower than the brentuximab vedotin discontinuation rate (14% vs. 55%), as was the nonrelapse mortality rate (6% vs. 16%). Nivolumab-AVD was associated with a greater neutropenia rate, whereas brentuximab vedotin-AVD was associated with higher rates of febrile neutropenia, peripheral neuropathy and sepsis/infections; the toxicity profile of nivolumab-AVD was confirmed to be better based on patient-reported key adverse events.

Comment (LB): Hodgkin lymphoma is a disease with a bimodal age distribution, but the death rate is higher in the older population. The ECHELON-1 study showed replacing bleomycin with brentuximab-vedotin was beneficial, although the older patients, who struggle most with bleomycin, failed to benefit. In this study, the PD-1 inhibitor nivolumab and AVD was associated with statistically superior PFS and OS. Treatment was deliverable and better tolerated, with less neuropathy and infections. Properties of both the host and the tumour may account for this, but nivolumab-AVD was superior. Other PD-1 inhibitors are likely to be combined with AVD with the expectation of similar outcomes.

Reference: J Clin Oncol 2025;43:2968–73
Abstract

Phase 1/2 trial of anti-CD7 allogeneic WU-CART-007 for patients with relapsed/refractory T-cell malignancies

Authors: Ghobadi A et al.

Summary: This phase 1–2 trial examined the use of WU-CART-007 (CD7-targeting, allogeneic, fratricide-resistant CAR T-cell product) in patients with T-cell acute lymphoblastic leukaemia/lymphoma following lymphodepleting chemotherapy. The recommended phase 2 dose (900×10^6 cells) was administered to 13 of 28 enrolled participants. Cytokine-release syndrome was the most frequent treatment-related adverse event, occurring in 88.5% of patients (19.2% grade 3–4). ICANS (immune effector cell-associated neurotoxicity syndrome) occurred in two participants (both grade 1), one participant experienced acute graft versus host disease (grade 2), and one participant experienced immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome (grade 2). Among the eleven evaluable participants who received WU-CART-007 at the recommended phase 2 dose with enhanced lymphodepleting chemotherapy, the composite CR rate was 72.7% and the ORR was 90.9%.

Comment (NC): Despite the advances in CAR T-cell therapy in many malignancies, it remains a challenge for T-cell malignancies due to potential autologous product contamination and T-cell fratricide. These early results from a Chinese group using an allogeneic CAR T-cell product overcomes these issues, and shows promising results in an area where new therapies have been sparse. However, despite early promising results, there continue to be challenges, which include prolonged aplasia due to enhanced leucodepletion required prior to CAR T-cell infusion and short CAR T-cell persistence. This means the CAR T-cell therapy is used as a bridge to allogeneic SCT, rather than a standalone therapy.

Reference: Blood 2025;146:1163–73
Abstract

New Zealand multiple myeloma patients demonstrate inferior outcomes when compared to Australian counterparts

Authors: Li J et al.

Summary: Patient and disease-related demographics, access to treatment and OS were reported for a retrospective cohort of patients with MM from Aotearoa NZ (n=1160) or Australia (n=3871) enrolled in the MRDR (Myeloma and Related Diseases Registry) between 2012 and 2023. Compared with the Australian patients, those from NZ were older, were more likely to have cardiac disease and had worse performance status at diagnosis, and regarding outcomes, they had a shorter median OS duration (65.3 vs. 79.8 months). Predictors of better survival were undergoing autologous SCT (adjusted HR 0.59 [95% CI 0.51, 0.68]), frontline combination proteasome inhibitor plus immunomodulatory drug (0.63 [0.55, 0.72]) and receipt of anti-CD38 monoclonal antibody therapy at first relapse rather than VTD (bortezomib, thalidomide, dexamethasone; 0.61 [0.44, 0.83]). After adjusting for confounders, NZ patients less frequently underwent transplantation, irrespective of age group.

Comment (NC): This real-world registry result shows sobering results for NZ myeloma patients. The lower autologous SCT rate is somewhat unexpected and may require further investigation, as it remains the cornerstone of front line therapy internationally. The lack of new antimyeloma therapy funding is almost certainly contributing to the worse outcome, and the gap will only widen.

Reference: Clin Lymphoma Myeloma Leuk; Online Oct 18, 2025
Abstract

Modification of belantamab mafodotin dosing to balance efficacy and tolerability in the DREAMM-7 and DREAMM-8 trials

Authors: Mateos M-V et al.

Summary: These researchers used descriptive analyses to assess the impact of belantamab mafodotin dose modifications for managing ocular events in participants from the DREAMM-7 and DREAMM-8 trials whose vision was normal prior to initiating this treatment. Dose modifications, which almost all responders needed, led to increases in dosing intervals to a median of 8–12 weeks by 9 months. The greatest prevalences of reduced vision to bilateral 20/50 or worse and ocular adverse reactions were seen during the first 3 months of treatment, remaining low at later timepoints. Grade ≥2 ophthalmic examination findings resolved in a median of 12 weeks. Ocular events led to only low rates of belantamab mafodotin discontinuation. A response was achieved by most patients prior to needing a dose delay of >2 cycles, and most of those who didn't subsequently achieved or deepened their response. The median PFS duration for DREAMM-7 participants who had ≥1 dose delay of ≥12 weeks was 36.6 months, and for DREAMM-8 participants it was not reached.

Comment (NC): Ocular toxicity is common (80–90% of patients) in patients treated with belantamab mafodotin. This study combined patients treated on the DREAMM-7 and -8 trials, and showed that keratopathy was common and manageable with dose delays and modifications without compromising efficacy. Most patients could continue to read and drive, which is important from a quality of life perspective. From a clinician's perspective, administration of this drug will involve significant involvement from the eye specialists, and how this can be maintained practically will need to be explored in different jurisdictions.

Reference: Blood Adv 2025;9:5708–19
Abstract

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Safety and efficacy of a dexamethasone-sparing regimen with daratumumab and lenalidomide in patients with frailty and newly diagnosed multiple myeloma (IFM2017-03)

Authors: Manier S et al.

Summary: Patients aged ≥65 years with newly diagnosed MM and an Eastern Cooperative Oncology Group proxy frailty score of ≥2 were randomised to 28-day cycles of subcutaneous daratumumab 1800mg plus oral lenalidomide 25mg daily for 21 days and dexamethasone 20mg weekly for two cycles (dexamethasone-sparing arm; n=200) or lenalidomide 25mg daily and oral dexamethasone 20mg weekly (control arm; n=95) in this open-label phase 3 trial. After a median 46.3 months of follow-up, median PFS duration (primary endpoint) was significantly longer in the dexamethasone-sparing arm than in the control arm (53.4 vs. 22.5 months; HR 0.51 [95% CI 0.37, 0.70]). The most common grade 3–5 adverse events were neutropenia (55% and 24% in the dexamethasone-sparing and control arms, respectively) and infection (19% and 21%), with serious adverse event rates of 63% and 69% in the respective arms, fatal adverse event rates of 12% and 13%, and a grade 5 treatment-emergent event rate of 2% in each arm.

Comment (NC): The superior efficacy in the investigational arm in this study is perhaps not a surprise given the addition of daratumumab. There has been considerable effort in reducing the use of dexamethasone in myeloma treatment to reduce steroid-induced toxicity and infectious risks. It is somewhat disappointing to see similar rates of cytopenia and infection in the two arms. However, this underlines the difficulty in the treatment of frail patients. The authors also attempted to make comparisons between the daratumumab and lenalidomide arm in this trial and the DRD (daratumumab, lenalidomide, dexamethasone) arm of the MAIA trial, which showed similar efficacy but less infection risks with omission of dexamethasone. However, cross-trial comparisons are always difficult given the different trial populations. Overall, the study does show the proof of concept of a steroid-sparing regimen, but future efforts will be needed to further reduce toxicity of antimyeloma regimens in older and frail populations.

Reference: Lancet Oncol 2025;26:1323–33
Abstract

Long-term (≥5-year) remission and survival after treatment with ciltacabtagene autoleucel in CARTITUDE-1 patients with relapsed/refractory multiple myeloma

Authors: Jagannath S et al.

Summary: These researchers reported outcomes from the CARTITUDE-1 trial of single-dose ciltacabtagene autoleucel (cilta-cel) at a target dose of 0.75×10^6 CAR T-cells/kg in patients with heavily pretreated relapsed/refractory MM. After a median 5 years of follow-up, the median OS duration was 60.7 months and the 5-year PFS rate was 33%. Analysis of long-term efficacy revealed that around half the participants had progressive disease, 20% died, and about one-third had a durable remission lasting ≥5 years without further treatment or maintenance therapy. The finding of sustained MRD-negativity and complete metabolic response by imaging for ≥5 years post-therapy in all twelve participants who attained a stringent complete response prompted the study authors to suggest that cilta-cel may be curative in a subset of patients. No new safety concerns were noted with longer follow-up.

Comment (NC): These long-term follow-up results are particularly impressive, especially given that the patients in this trial were heavily pretreated. CAR T-cell therapy is one of the most significant breakthroughs in the last decade. While it is not yet a curative treatment for myeloma, the long-term follow-up showing around 30% of patients still in remission more than 5 years later is extremely encouraging. CAR T-cell therapies are currently undergoing trials in the earlier phase of disease, including in frontline treatment and the results of these trials are eagerly awaited.

Reference: J Clin Oncol 2025;43:2766–71
Abstract

INDEPENDENT COMMENTARY BY
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Dr Chien is a consultant haematologist at Auckland City Hospital. She completed her haematology training in Auckland region and undertook fellowship in bone marrow transplant and multiple myeloma at Vancouver General Hospital Canada. Her main area of research interest is in therapy for plasma cell disorders.