Lymphoma & Leukaemia Research Review™

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In this issue:

Abbreviations used in this issue:

ALL = acute lymphoblastic leukaemia; **AML** = acute myeloid leukaemia; **CLL** = chronic lymphocytic leukaemia; **CMML** = chronic myelomonocytic leukaemia; **CSF** = cerebrospinal fluid; **DLBCL** = diffuse large B-cell lymphoma; **EOT** = end-of-treatment; **GIV** = venetoclax-obinutuzumab-ibrutinib; **GV** = venetoclax-obinutuzumab; **HCT** = haematopoietic cell transplantation; **iCPSS** = international CMML Prognostic Scoring System; **iNHL** = indolent non-Hodgkin lymphoma; **NOL** = number of lesions; **NPV** = negative predictive values; **PPV** = positive predictive value; **R^2** = lenalidomide plus rituximab; **RAdR** = romidepsin, azacitidine and dexamethasone; **RV** = venetoclax-rituximab; **TLRpeakmean** = tumorSUVpeak/liverSUVmean; **TMLI** = total marrow and lymphoid irradiation; **TTNLT** = time-to-next lymphoma treatment.

Welcome to issue 105 of Lymphoma & Leukaemia Research Review.

The review begins with a phase 1-2, open-label, multicentre, nonrandomised trial that explored the efficacy of oral decitabine-cedazuridine. Another notable inclusion is the phase 3 CLL13/GAIA trial, which compared several medication combinations, including venetoclax-rituximab, venetoclax-obinutuzumab, and venetoclax-obinutuzumab-ibrutinib, to chemoimmunotherapy, yielding significant findings. The review concludes with the phase II FLUORO study, which investigated the efficacy of obinutuzumab paired with PET-adapted ultra-low dose nodal radiotherapy.

We hope you enjoy this update in lymphoma and leukaemia research, and we look forward to receiving comments and feedback.

Kind Regards,

Dr Shafqat Inam
shafqat.inam@researchreview.com.au

All-oral treatment of newly diagnosed acute myeloid leukemia

Authors: Roboz GJ et al.

Summary: In this phase 1-2, open-label, multicentre, nonrandomised trial, investigators evaluated the efficacy of oral decitabine-cedazuridine. Eligible participants were 75 years or older with newly diagnosed acute myeloid leukaemia (AML) who were ineligible for intensive chemotherapy. Each participant received oral decitabine-cedazuridine plus oral venetoclax. Of the 189 patients included, 30 participated in phase 1, 58 in phase 2a, and 101 in phase 2b. No drug-drug interactions were reported between decitabine-cedazuridine and venetoclax. Within phase 2b, the complete response rate was 47% (95% CI 36 to 57), and the rate of complete response or complete response with partial incomplete haematologic recovery was 63% (53 to 73), with a median OS of 15.5 months (7.6 to could not be estimated). For these phase 2b patients, common grade 3 or higher adverse events included anaemia (30%), neutropenia (26%), and febrile neutropenia (25%). Overall, oral decitabine-cedazuridine plus venetoclax demonstrated no drug interactions and achieved a complete response in nearly half of the cohort.

Comment: The combination of venetoclax and azacitidine has transformed the treatment landscape for patients with AML who are not candidates for intensive chemotherapy. Azacitidine requires frequent outpatient visits for administration, while the oral formulation of decitabine–cedazuridine is now available in Australia for selected patients with myeloid malignancies. ASCERTAIN-V was a phase I/II trial evaluating an all-oral combination of decitabine–cedazuridine and venetoclax in patients with AML aged >75 years who were ineligible for intensive chemotherapy. Response rates were comparable to those reported with venetoclax and azacitidine (recognising the limitations of cross-trial comparisons), with a similar expected safety profile. Importantly, these outcomes were achieved with an oral regimen that maximises time at home and would provide a valuable option to patients who have difficulty routinely attending an infusion centre.

Reference: N Engl J Med. 2026;4;394(21):2107-2116.
Abstract

Molecular-based ecosystem to improve personalized medicine in chronic myelomonocytic leukemia

Authors: Lanino L et al.

Summary: This study aimed to integrate genomic features into the clinical decision-making process for patients with chronic myelomonocytic leukaemia (CMML). The analysis included a retrospective cohort of 3,013 patients (training set) and a prospective population of 516 patients (validation set). Utilising an innovative framework for multimodal data analysis, the authors established a molecular-based disease taxonomy and prognostication system. Unsupervised clustering identified nine distinct entities characterised by unique genomic features and clinical outcomes ($p<0.001$), specifically involving the splicing machinery, transcription factors, signal transduction, tyrosine kinase pathways aberrations, and high-risk molecular signatures. Integrating these data into an international CMML Prognostic Scoring System (iCPSS) revealed five risk groups with distinct probabilities of overall and leukaemia-free survival across both the training and validation cohorts ($p<0.001$). Furthermore, applying this model resulted in the risk reassignment of 55% of patients to either a higher or lower category. These findings demonstrate that incorporating molecular information significantly improves CMML risk classification.

Comment: CMML is a heterogeneous disorder in which outcomes are influenced by clinical, cytogenetic and molecular factors. Several existing scoring systems provide prognostic information, with particular utility in guiding treatment initiation and decisions regarding suitability and timing of allogeneic stem cell transplantation in fit, eligible patients. This international collaboration developed the iCPSS using innovative statistical approaches applied to a large retrospective patient cohort. The model demonstrated improved prognostic discrimination, including for transplant decision-making, in an independent validation cohort. As molecular testing is now incorporated into standard diagnostic pathways this model has the potential for immediate clinical application, though further analysis of its incremental clinical utility over existing prognostic models is necessary.

Reference: J Clin Oncol. 2026;10;44(17):1608-1623.
Abstract

Total marrow and lymphoid irradiation in combination with cyclophosphamide and etoposide before haematopoietic cell transplantation for relapsed or refractory acute leukaemia: a single-centre, open-label, phase 2 trial

Authors: Stein A et al.

Summary: The efficacy of total marrow and lymphoid irradiation (TMLI) plus high-dose cyclophosphamide and etoposide as a conditioning regimen prior to allogeneic haematopoietic cell transplantation (HCT) was investigated in this single-centre, open-label, phase 2 trial. Conducted in the USA, the study enrolled patients 16 to 60 years old with relapsed/refractory AML or acute lymphoblastic leukaemia (ALL). Among the 106 patients (46% female, 68% were White, 21% were Asian or Pacific Islander) included, TMLI was administered on days -9 to -5, etoposide 60 mg/kg on day -4, and cyclophosphamide 100 mg/kg on day -2. Overall, patients had a median follow-up of 1.8 years, while those who were alive at last contact had a median follow-up of 3.1 years. Across the entire cohort, the 2-year estimated PFS was 34% (95% CI 25 to 43), and none of those in the safety lead-in (n=6) reported any unacceptable toxicity. The most frequently reported adverse events of grade 3-4 were cytopenias (n=96; 91%), metabolic disorders (n=83; 78%), oral mucositis (n=45; 42%), diarrhoea (n=25; 24%), nausea (n=21; 20%) and palmar-plantar erythrodysesthesia syndrome (n=11; 10%). These results suggest that TMLI could be safely used in combination with high-dose etoposide and cyclophosphamide.

Comment: Total body irradiation is a common component of transplant conditioning regimens but can cause a range of acute and late toxicities. As transplant survival outcomes have improved, increasing attention has focused on reducing long-term treatment-related sequelae. Advances in radiation technology allow targeted delivery to the haematopoietic compartment while sparing critical organs. This phase II study, with recruitment occurring over 10 years, reports outcomes of a conditioning regimen incorporating TMLI. Although the 2-year outcomes were reasonable, prolonged recruitment, highly selected patients and the absence of a comparator arm make it difficult to determine the incremental benefit of TMLI over contemporary TBI-based conditioning. Longer-term toxicity data will also be important to clarify the benefits of this approach.

Reference: Lancet Haematol. 2026;13(6):e365-e375.
Abstract

Venetoclax combinations in untreated CLL: 5-year results and patient-reported outcomes analysis of the CLL13/GAIA trial

Authors: Fürstenau M et al.

Summary: This phase 3 trial, CLL13/GAIA, compared venetoclax-rituximab (RV), venetoclax-obinutuzumab (GV), and venetoclax-obinutuzumab-ibrutinib (GIV) to chemoimmunotherapy. Fit patients with chronic lymphocytic leukaemia (CLL) without TP53 aberrations (n=926) were randomly allocated to receive either 6 cycles of chemoimmunotherapy (n=229; 150 of whom received fludarabine-cyclophosphamide-rituximab and 79 received bendamustine-rituximab), or 12 cycles of GIV (n=231), GV (n=229), or RV (n=237). After a median observation time of 63.8 months, patients receiving GIV achieved a 5-year PFS of 81.3% compared to 69.8% for GV, 57.4% for RV, and 50.7% for chemoimmunotherapy. PFS was superior for patients receiving GV and GIV in comparison to chemoimmunotherapy and RV ($p<0.001$ in each case), and GIV prolonged PFS in contrast to GV ($p=0.0046$). Similar overall survival rates were seen among the treatment groups, with 5-year rates of 94.3% (GIV), 93.6% (GV), 94.7% (RV) and 90.7% (chemoimmunotherapy). Overall, when compared to chemoimmunotherapy, GV and RV led to the greatest improvements in quality-of-life.

Comment: The long-term outcomes of the CLL13/GAIA study, which compared several frontline treatment strategies for CLL, continue to inform clinical practice. Chemoimmunotherapy was clearly inferior to all targeted therapy-containing comparators and should no longer be considered a standard of care. Obinutuzumab was superior to rituximab as the preferred CD20-targeting monoclonal antibody partner. There was no survival difference between GV and the triplet combination incorporating ibrutinib. However, the addition of ibrutinib improved PFS, particularly among patients with higher-risk disease defined by unmutated IGHV status. This benefit came at the cost of increased cardiac events and additional toxicity, reflected in patient-reported quality-of-life outcomes. Although the ibrutinib-containing triplet is not currently available in Australia, these findings may help guide patient selection for future BTK inhibitor-based triplet combination strategies as regimens incorporating second-generation BTK inhibitors become available.

Reference: Blood. 2026;18;147(25):3025-3038.
Abstract

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Radiotherapy for indolent primary cutaneous B-cell lymphoma: an international multicenter ILROG analysis

Authors: Oertel M et al.

Summary: Within this international multicentre ILROG analysis, researchers examined radiotherapy use among patients with low-grade primary cutaneous B-cell lymphoma. Twenty-two institutions participated in this study, which included individuals diagnosed with limited (T1/T2) primary cutaneous marginal zone or follicle centre lymphoma who were treated with radiotherapy between 1995 and 2023. Of the 535 patients examined, the majority were treated in the head (40%) and trunk (36%), receiving a median radiotherapy dose of 24 Gy in fractions of 2 Gy. After a median of 3.6 months following radiotherapy, 91% of patients achieved a complete response. There were no statistically significant differences between ≤4 Gy and >4 Gy treatments in terms of complete or overall response rates (p=0.077 and p=0.056, respectively). However, an inferior duration of local control was seen for ≤4 Gy (5-year local control 73% ± 12% versus 96% ± 2%; p<0.001). In summary, while these treatments have a shorter duration of local control, they have a favourable toxicity.

Comment: This international multicentre retrospective study confirms that indolent primary cutaneous B-cell lymphomas are exquisitely sensitive to radiotherapy and associated with excellent outcomes. Ultra-low-dose radiotherapy has become increasingly attractive because of its convenience and negligible toxicity, but concerns have remained regarding durability. Lower-dose radiotherapy (4 Gy) was associated with a higher rate of recurrence at 5 years compared with higher-dose approaches; however, a substantial proportion of patients remained in remission (70%), with no difference in overall survival. These findings support continued use of radiotherapy for this disease and suggest that an initial 4 Gy strategy remains reasonable for carefully selected patients.

Reference: Blood. 2026;18;147(25):3051-3060.
Abstract

Diagnosis of primary CNS lymphoma through molecular and immune biomarkers in cerebrospinal fluid (PRICELUS): a multicentre, prospective, cohort study

Authors: van Rooij JLM et al.

Summary: Researchers aimed to validate the diagnostic utility of emerging cerebrospinal fluid (CSF) biomarkers in this multicentre, prospective, cohort study, PRICELUS. Eligible participants were 18 years or older with suspected primary CNS lymphoma who underwent CSF analysis. They were enrolled across five hospitals in the Netherlands between March 1, 2021, and May 1, 2025, with investigators specifically focusing on MYD88 and chemokines with reported diagnostic value. Of the 255 patients (median age 61 years, 67% male) included, 50 were diagnosed with CNS lymphoma; among these, 44 had primary CNS lymphoma and six had secondary CNS lymphoma. Within the univariable analysis, six out of the seven chemokines demonstrated significant diagnostic value (AUC 0.67 to 0.96). For those with CNS lymphoma (n=50) 28 (56%) had MYD88, yielding a sensitivity of 56.0% (95% CI 41.3 to 70.0) and a specificity of 98.5% (198 of 201; 95.7 to 99.7). Factors such as MYD88, interleukin-10, and C-X-C motif chemokine ligand 13 were all independently associated with a CNS lymphoma diagnosis. In summary, CSF biomarker testing could serve as a non-invasive diagnostic approach for this patient population.

Comment: Confirming a tissue diagnosis of primary CNS lymphoma can be challenging, as patients may present with rapidly progressive neurological symptoms requiring urgent treatment, and biopsy may carry significant procedural risk depending on lesion location. CSF-based molecular diagnostic approaches have previously been explored; however, the diagnostic performance of standard assays such as cytology and flow cytometry remains limited. This prospective cohort study assessed the diagnostic utility of MYD88 L265P mutation testing combined with a panel of chemokines, demonstrating that the addition of interleukin-10 and CXCL13 achieved a sensitivity of 54% and specificity of 100%. With further validation, this CSF-based diagnostic algorithm may reduce the need for biopsy in carefully selected patients with the appropriate clinicoradiological context. As biologically informed therapies become increasingly important, tissue diagnosis is likely to remain preferred whenever feasible.

Reference: Lancet Haematol. 2026;13(6):e376-e385.
Abstract

Lenalidomide plus rituximab for relapsed/refractory indolent non-Hodgkin lymphoma: 5-year follow-up and subgroup analyses from the phase III AUGMENT trial

Authors: Leonard JP et al.

Summary: In follow-up and subgroup analyses of the phase III AUGMENT trial, researchers explored the long-term outcomes of lenalidomide plus rituximab (R^2) compared to rituximab plus placebo. A total of 358 patients with relapsed/refractory indolent non-Hodgkin lymphoma (iNHL) were included, including those 70 years or older, of which 295 had FL (≥70 years, n=66). Participants were randomly allocated (1:1) to receive R^2 or rituximab plus placebo. After a median follow-up of 65.9 months, patients receiving R^2 demonstrated improvements in both PFS (HR 0.50, 95% CI 0.38 to 0.66) and overall survival (0.59, 0.37 to 0.95), in comparison to placebo. The safety findings within the long-term follow-up were consistent with the primary analysis. Overall, these findings support the use of R^2 as a standard of care for this patient population.

Reference: J Clin Oncol. 2026;44(16):1483-1489.
Abstract

Lenalidomide plus rituximab for previously untreated advanced follicular lymphoma: the 10-year RELEVANCE trial analysis

Authors: Gower N et al.

Summary: This analysis of the multinational, phase 2 trial, RELEVANCE, explored the 10-year outcomes of R^2 compared to rituximab-based immunochemotherapy. A total of 1,030 patients with previously untreated FL were included for analysis and randomly allocated to receive either R^2 (n=513) or rituximab-based immunochemotherapy (R-Chemo; n=517). After 120 months of follow-up, patients receiving R^2 (110.6 months) demonstrated a comparable PFS to those receiving R-Chemo (102.8 months), with 10-year PFS rates of 46.4% and 46.6%, respectively. Moreover, the median overall survival and time-to-next lymphoma treatment (TTNLT) were not reached in either group, with 10-year overall survival rates of 82.4% for R^2 and 81.1% for R-Chemo, and 10-year TTNLT rates of 62.2% and 66.3%. These results indicate that R^2 is a viable chemotherapy-free alternative to immunochemotherapy.

Reference: Blood. 2026;18;147(25):3061-3068.
Abstract

Comment: The combination of rituximab and lenalidomide (R^2) is an established treatment strategy for FL (although not PBS funded in Australia!), and as it is increasingly incorporated as a partner regimen with newer immunotherapies, it is timely to revisit the foundational studies supporting its use. The long-term outcomes of the AUGMENT study confirm a sustained benefit in relapsed disease compared with rituximab alone, including among older patients aged >70 years. The 10-year analysis of the RELEVANCE study confirms the comparability of R^2 with immunochemotherapy in frontline treatment, with no additional long-term safety signals, including no increase in second primary malignancies. These studies provide important benchmarks as the field moves towards chemotherapy-free strategies and survivorship-focused care with substantially improved patient outcomes.

A phase 1 trial of romidepsin, azacitidine, dexamethasone, and lenalidomide in relapsed or refractory T-cell lymphoma

Authors: Gordon MJ et al.

Summary: Researchers explored whether multiagent combinations of romidepsin, azacitidine, dexamethasone, and lenalidomide could lead to deep responses among patients with relapsed/refractory T-cell lymphoma in this phase 1 trial. Twenty-six patients were included, receiving escalating doses of lenalidomide combined with romidepsin, azacitidine, and dexamethasone (RAdR). The primary outcome of this trial was to determine the maximum tolerated dose of lenalidomide that could be safely utilised in combination with RAdR. Of the 26 patients, 21 were evaluable for response. Reported adverse events were generally gastrointestinal and haematologic, with 19% of patients experiencing grade 3/4 thrombocytopenia and 21% experiencing neutropenia. The maximum tolerated dose of lenalidomide was 20 mg; among the 9 participants receiving this dose, the objective response rate was 89% and the complete response rate was 22%. After one year of treatment, patients had an estimated PFS of 14% and an overall survival rate of 66%. In summary, RAdR demonstrated clinical activity in this patient population; however, responses were not durable.

Comment: Relapsed T-cell lymphoma remains a challenging clinical scenario, with poor responses to conventional cytotoxic chemotherapy. This phase I study combines several agents with demonstrated activity in T-cell lymphoma that target recognised biological vulnerabilities, including epigenetic dysregulation, aberrant proliferation and immune dysfunction. The overall response rate was 88%; however, most responses were not durable, with an estimated 1-year PFS of only 14%. Nevertheless, the regimen enabled some patients to proceed to allogeneic stem cell transplantation. There were no unexpected toxicities, and the maximum tolerated dose of lenalidomide was 20 mg. The authors also present correlative studies highlighting the importance of developing biologically informed treatment strategies for this challenging disease subtype.

Reference: Blood Adv. 2026;26;10(10):3398-3408.
Abstract

Improving the predictive value of end-of-treatment PET/ CT in diffuse large B-cell lymphoma

Authors: Bes AL et al.

Summary: In this study, researchers aimed to determine whether combining quantitative PET parameters with clinical data could improve the prediction of treatment failure in end-of-treatment (EOT) PET-positive patients. A total of 138 patients in Deauville score groups 4-5 were included and analysed, with lesions segmented utilising a semi-automated adaptive method. Model 1 combined clinical data and EOT PET, whereas model 2 combined baseline, EOT, and delta values. The models were evaluated for classification across various risk-of-progression cutoffs, determining their sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV). Specifically, model 1 included two variables: the number of lesions (NOL) and the tumorSUVpeak/liverSUVmean (TLRpeakmean) at EOT (AIC=690.072, c-index=0.747), while model 2 included NOL, TLRpeakmean (EOT) and baseline SUVmean (AIC=687.064, c-index=0.762). Overall, PPV improved to 85% without compromising the NPV. These results suggest that these models could enable more accurate response-adapted treatment decisions.

Comment: Interpretation of EOT PET/CT imaging in diffuse large B-cell lymphoma (DLBCL) is frequently complicated by false-positive findings, resulting in patient anxiety and additional investigations, including serial imaging and biopsy. The authors incorporated multiple radiomic parameters from baseline and EOT imaging to develop predictive models that substantially improved positive predictive value. It is encouraging that these improvements can be achieved using existing imaging technology, though before routine implementation, external validation and integration into reporting workflows will be required; better end of treatment assessments may be particularly valuable in the era of effective, but costly, second-line immunotherapy strategies.

Reference: Haematologica. 2026;1;111(6):2087-2096.
Abstract

Checkpoint inhibitors, obinutuzumab plus PET-adapted ultra-low dose nodal radiotherapy yield high efficacy in treatment-naïve follicular lymphoma: Results from the phase II 'FLUORO' study

Authors: Martynchyk A et al.

Summary: The phase II FLUORO study evaluated the efficacy of obinutuzumab and PET-adapted ultra-low dose nodal radiotherapy. Sixteen patients (median age 53 years) were identified, and 15 were included in the final analysis, 94% of whom had an intermediate/high Follicular Lymphoma International Prognostic Index score. Participants received combination checkpoint inhibition (atezolizumab) and obinutuzumab (6 cycles) along with PET-adapted ultra-low dose radiotherapy (4Gy) to all PET-avid sites after cycle 2, followed by 2 years of obinutuzumab maintenance. A complete response was achieved by 93% of participants (95% CI 70% to 99%), with an overall objective response rate of 100% (75% to 100%). After a median follow-up of 41 months, the 3-year PFS was 80% (55 to 93) and the overall survival rate was 100% (79.6 to 100). A grade 3-4 adverse event was reported among 31% of those included. In summary, these results suggest that the study regimen demonstrates promising efficacy and safety for this patient population.

Comment: Immune checkpoint inhibitors have demonstrated limited single-agent activity in FL, although combination strategies may overcome potential mechanisms of resistance. This innovative Australian investigator-led study combined the PD-L1 inhibitor atezolizumab with obinutuzumab while also harnessing the immunostimulatory effects of radiotherapy. Among patients with untreated high-volume disease, there was a complete response rate of 93%, and 3-year progression-free and overall survival rates of 80% and 100%, respectively. Treatment was well tolerated, with a low incidence of immune-related adverse events. Importantly, correlative immunological studies may help identify biomarkers to guide patient selection for this interesting chemotherapy-free approach.

Reference: Br J Haematol. 2026;208(6):2026-2035.
Abstract

Independent commentary by Dr Shafqat Inam

Dr Shafqat Inam is a consultant haematologist working in Sydney. His clinical and research focus is the application of cell and immune therapies in the treatment of lymphoma, leukaemia, and myeloma.

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