# Lymphoma/Leukaemia RESEARCH REVIEW™

Making Education Easy

Issue 1 – 2020


## In this issue:

### Leukaemia selection



### Lymphoma selection



**Abbreviations used in this issue**

**AML** = acute myeloid leukaemia
**B-ALL/ETP-ALL/T-ALL** = B-cell/early T-cell precursor/T-cell acute lymphoblastic leukaemia
**BTK** = Bruton's kinase
**CLL/SLL** = chronic lymphocytic leukaemia/small lymphocytic lymphoma
**CML** = chronic myeloid leukaemia
**CR/CRi** = complete remission (with incomplete count recovery)
**ENKTL** = extranodal natural killer T-cell lymphoma
**HR** = hazard ratio
**HSCT/SCT** = (haematopoietic) stem-cell transplantation
**ITD** = internal tandem duplication
**MRD** = minimal residual disease
**OS** = overall survival
**PFS** = progression-free survival
**QALY** = quality-adjusted life-year
**TKI** = tyrosine kinase inhibitor

# Welcome to the latest issue of Lymphoma/Leukaemia Research Review.

This winter issue begins with 5-year follow-up of the RESONATE-2 trial, reporting sustained PFS and OS benefits with single-agent ibrutinib versus chlorambucil, as well as increased depth of response over time. There is also a paper reporting real-world patient outcomes for blinatumomab in the treatment of B-ALL. The lymphoma research also includes real-world patient outcomes, this time with the use of intensive immunochemotherapy in the treatment of Burkitt's lymphoma. The issue concludes with a cost-effectiveness analysis from Canada of three induction strategies for primary CNS lymphoma, concluding that the MATRix regimen of methotrexate, cytarabine, thiotepa and rituximab was the optimal strategy in most of the simulations evaluated.

We trust you find the research selected for this issue enlightening. Please keep sending us your comments and feedback.

Kind regards,


**Claire Hemmaway (CH)**
clairehemmaway@researchreview.co.nz

**Leanne Berkahn (LB)**
leanneberkahn@researchreview.co.nz


## LEUKAEMIA SELECTION

## Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL

**Authors:** Burger JA et al.


**Summary:** These authors reported 5-year follow-up data from the phase 3 RESONATE-2 study, in which 269 patients aged ≥65 years with CLL/SLL were randomised in a 1:1 ratio to receive oral ibrutinib 420mg once daily until disease progression or unacceptable toxicity or up to twelve 28-day cycles of chlorambucil 0.5–0.8 mg/kg on days 1 and 15. Over median follow-up of 60 months, ibrutinib retained superiority over chlorambucil for the estimated 5-year PFS and OS rates (70% vs. 12%; HR 0.146 [95% CI 0.098, 0.218] and 83% vs. 68%; 0.450 [0.266, 0.761], respectively), including in high prognostic risk participants (respective HRs 0.083 [0.047, 0.145] and 0.366 [0.181, 0.736]). The investigator-assessed overall response rate was 92% for the ibrutinib arm with a complete response rate of 30% (11% at primary analysis). Common grade ≥3 adverse events included neutropenia (13%), pneumonia (12%), hypertension (8%), anaemia (7%) and hyponatraemia (6%); most events and adverse event-related discontinuations decreased over time. At the time of reporting, 58% of the patients were still receiving ibrutinib.


**Comment (LB):** This trial now has 5 years of follow-up. The reduced OS in the chlorambucil arm persists despite the majority of patients crossing over to ibrutinib, thereby supporting the use of BTK inhibitors as first-line therapy. The complete response rate deepened with time to 30% (MRD rates are not given) implying that treatment should probably be continued. The presence of del(11q) was a good prognostic feature with BTK inhibitors, despite its adverse prognosis with chemo-immunotherapy. There have been no concerning late effects emerging, but the incidence of atrial fibrillation continues to drift up, and is now 16%, which makes later-generation BTK inhibitors more appealing. Also, the drug discontinuation rate of 41% is high and hints at persistent low-level toxicity. In summary, ibrutinib is a highly effective drug in the upfront setting and notably missing from our arsenal in NZ.


***Reference: Leukemia 2020;34:787–98***

Abstract

LEUKAEMIA SELECTION *continued*

## Molecular patterns of response and treatment failure after frontline venetoclax combinations in older patients with AML

**Authors:** DiNardo CD et al.

**Summary:** These authors reported molecular response patterns and treatment failure for 81 patients with AML treated with venetoclax plus hypomethylating agents or low-dose cytarabine. Patients with *NPM1* or *IDH2* mutations typically had high response rates and durable remissions, with prolonged molecular remissions also frequent for those with *NPM1* mutations. Primary and adaptive resistance to these regimens was characterised mostly by acquisition or enrichment of clones that activate signalling pathways, such as FLT3 or RAS, or bi-allelically perturbing TP53. The polyclonal nature of intratumoural resistance mechanisms was seen in some cases. Among primary refractory cases, heterogeneous and sometimes divergent interval changes in leukaemic clones were seen within a single therapy cycle. FLT3 ITD gain and TP53 loss were associated with cross-resistance to both venetoclax and cytotoxic-based therapies.

**Comment (CH):** The MD Anderson Cancer Center and the Alfred Hospital have combined over 80 trial samples of elderly AML patients treated with venetoclax and azacitidine/decitabine (hypomethylating agents) or venetoclax and low-dose cytarabine, respectively, to look at the mutational profiles of those who have prolonged remissions with the combination, those who have adaptive resistance and those who are refractory. Molecular response was predicted by the presence of *NPM1*, *IDH1*, *IDH2* or *DNMT3* mutation, and *NPM1* and *IDH2* mutations were the strongest predictors of sustained remissions – the 2-year OS rates with these mutations were 71.8% and 79.5%, respectively, which compares favourably with intensive induction in the >60-year age group (2-year OS <40%). This will be tested in a randomised study in *NPM*-mutated patients in the VICTOR trial, which will open in NZ later this year. MRD negativity was achieved in *NPM*-mutated AML, whereas the majority of *IDH2*-mutated cases remained MRD-positive and despite this had excellent outcomes. Outcomes in *IDH2*-mutated patients may be further improved by the addition of an IDH2 inhibitor to clear MRD.

In the response and then relapse group, amplification or less frequently emergence of FLT3 ITD signalling pathways was a strong predictor of relapse, and therefore there is a strong rationale for combining venetoclax and low-dose cytarabine or a hypomethylating agent with an FLT3 inhibitor in the amplification group, as will be done in the INTERVENE and EVOLVE studies, respectively. Bi-allelic TP53 defects, not present at diagnosis, were also enriched in the relapse group. TP53 dysfunction or loss in both alleles appears to blunt the effectiveness of venetoclax combinations and remains a significant unmet need in the treatment of elderly AML. Single-cell sequencing at presentation, response and relapse identified the outgrowth of resistant subclones and could be potentially used to identify actionable targets. Primary refractoriness was associated with bi-allelic loss or dysfunction of TP53, *RUNX1* mutations without a co-existing *IDH2* or *SRSF2* and activating kinase mutation (*FLT3*-ITD, *N/KRAS*, *CBL* or *KIT*).

***Reference: Blood 2020;135:791–803***
Abstract

## Real-world outcomes of adult B-cell acute lymphocytic leukemia patients treated with blinatumomab

**Authors:** Badar T et al.

**Summary:** The safety and efficacy of blinatumomab were reported for a retrospective cohort of real-world patients with B-ALL, including 227 with relapsed/refractory disease and 12 with MRD; 26% of the patients had received ≥3 prior therapies and 19% had undergone allogeneic HSCT prior to receiving blinatumomab. For the patients with relapsed/refractory disease, the CR/CRi rate was 65% (MRD-negativity rate, 47%) and the respective median relapse-free survival and OS durations (after blinatumomab) were 32 months and 12.7 months. In the MRD group, 75% achieved MRD negativity, median relapse-free survival was not reached (2-year MRD-negativity rate, 54%) and OS duration was 34.7 months. Among patients who achieved CR/CRi, consolidation therapy with allogeneic HSCT retained favourable prognostic significance for OS (HR 0.54 [95% CI 0.30, 0.97]). The respective grade ≥3 cytokine-release syndrome, neurotoxicity and hepatotoxicity rates were 3%, 7% and 10%.

**Comment (CH):** This paper looked at the outcomes of 227 relapsed/refractory and 12 MRD-positive B-ALL patients in academic centres across the USA. Response rates were higher in this real-world setting than in the phase 3 TOWER trial. However, 60% of patients in the TOWER trial were treated at second salvage or beyond, and 30% had undergone prior SCT compared with 47% and 19%, respectively, in the current study. The response rate (CR/CRi) was 65% with 47% achieving MRD negativity by flow cytometry in the relapsed/refractory patients, and 75% achieved MRD negativity in the 12 MRD-positive patients. The Philadelphia chromosome-positive group, who were treated with blinatumomab and a TKI, had a particularly promising CR/CRi rate of 83%, compared with those treated with blinatumomab alone (CR/CRi 69%), whereas B-ALL patients with extramedullary disease outside of the CNS had a response rate of only 20% (ten patients only). Over one-third of patients were successfully bridged to transplantation, which is required for long-term survival, as blinatumomab responses were short-lived without consolidation.

More studies are required to look at the combination of blinatumomab and a TKI in Philadelphia chromosome-positive disease, as there is a theoretical risk of the TKI reducing the effect of blinatumomab (and reducing the risk of cytokine-release syndrome) by Src inhibition reducing T-cell proliferation. This and other studies however do not demonstrate a reduction in activity of blinatumomab when it is combined with a TKI (dasatinib or ponatinib). Unfortunately, blinatumomab is not available in NZ, either within the upfront ALLG trial setting or in the relapsed/refractory setting. Amgen feels it is commercially not viable, as the hurdle to obtaining Pharmac approval is too high. We have recently set up an ALLG medicines access committee to address this.

***Reference: Blood Adv 2020;4:2308–16***
Abstract



**Independent commentary by Dr Claire Hemmaway**

Claire is a Consultant Haematologist at Auckland City Hospital. Her main research interests are acute leukaemias and lymphomas, with a particular interest in these diseases in teenagers and young adults. She moved to New Zealand in 2016, having trained and worked in London prior to that as both a paediatric and adult haematologist. Her research was in mouse models of infant leukaemia at the Institute of Child Health.

## LEUKAEMIA SELECTION *continued*

### Risk of molecular recurrence after tyrosine kinase inhibitor discontinuation in chronic myeloid leukaemia patients

**Authors:** Dulucq S et al.

**Summary:** This systematic review and meta-analysis of CML studies published over the last decade (up until April 2019) estimated the likelihoods of molecular recurrence within various time periods after first and second TKI discontinuations, and re-acquisition of subsequent deep molecular response after molecular recurrence. The respective probabilities of molecular recurrence within 0–6, 6–12, 12–18 and 18–24 months after a first attempt at TKI discontinuation were 35%, 8%, 3% and 3%, whereas after a second attempt, they were 48%, 27% and 12% for 0–6, 6–12 and 12–18 months. The deep molecular response re-acquisition rate was 90%.

**Comment (CH):** This meta-analysis of over 3000 patients can inform CML physicians and patients in deep molecular remission of the likely outcome of TKI discontinuation on first and second attempts. The studies within the meta-analysis had different eligibility criteria and different definitions of molecular recurrence. However, the probability of molecular recurrence on a first attempt is similar to that in another meta-analysis: 49% at 2 years, with 38% of molecular recurrences occurring in the first 6 months. With a second attempt at discontinuation, molecular recurrence occurs in 87% of patients at 18 months and the bulk of relapses occur over a longer time window: 48% within 6 months, 27% within 6–12 months and 12% within 12–18 months. The total number of patients included in this part of the meta-analysis was only 124. Re-acquisition of a deep molecular remission was similar to previous studies at 90% at first and second attempts. Late relapses are described beyond the study period in this meta-analysis: 1.6% in eight first attempt studies between 25 and 52 months, and 7.6% between 25 and 72 months in three second attempt studies. This underlies the importance of long-term follow-up in both situations. This paper potentially questions the validity of a second attempt at stopping a TKI with 87% having molecular recurrence within 18 months and clear evidence of late relapses beyond this time.

***Reference: Br J Haematol 2020;189:452–68***
Abstract

### Clinical experience with venetoclax combined with chemotherapy for relapsed or refractory T-cell acute lymphoblastic leukemia

**Authors:** Richard-Carpentier G et al.

**Summary:** These authors performed a retrospective review on the efficacy and safety of venetoclax combined with chemotherapy in 13 patients with relapsed/refractory T-ALL (38% with ETP-ALL) treated at their institution. The patients had received 1–11 (median 2) prior therapy lines. The median dosage of venetoclax was 200 mg/day for 21 days. Among patients evaluable for bone marrow response (n=10), 60% achieved remission with bone marrow blasts <5%, including three with complete haematological recovery. The respective median OS and relapse-free survival durations were 7.7 months and 4.0 months. There were no early deaths or cases of clinically significant tumour lysis syndrome. The respective median times to neutrophil recovery and platelet recovery were 15 days and 44 days; cytopenias were prolonged with venetoclax 400 mg/day or when the agent was given for >14 days per cycle.

**Comment (CH):** This is a small study of 13 patients with relapsed T-ALL (an area of unmet need) treated with various salvage venetoclax-containing chemotherapy regimens. Preclinical studies have shown activity in T-ALL cell lines that are dependent on BCL-2 for survival, particularly ETP-ALL cell lines. Five of 13 patients had ETP-ALL and 2/13 had a complex karyotype as adverse risk features. Of the 13 patients, three had <5% blasts at initiation of venetoclax and are therefore not included in the 60% (6/10) bone marrow responses (CR/CRi/morphological leukaemia-free state) with 10% (1/10) MRD negativity, but are included in the survival figures. This response rate compares favourably with standard chemotherapy (20–40%) and nelarabine alone (31–36%). The numbers were too small to assess *TP53* and *NOTCH1* mutational status effects on response. The estimated 1-year OS rate was 44%. The combinations are safe with no tumour lysis observed, but there was significant myelosuppression, which was more marked with higher doses of venetoclax (>200mg) given for >14 days per cycle. The only two long-term survivors both had ETP-ALL, at 5.8 and 8.3 months; one had received a consolidation allograft. There are currently three trials looking at different venetoclax combinations and dosing in relapsed/refractory T-ALL and one upfront trial in elderly patients. These are early data in a small number of patients, but could represent a treatment option for relapsed/refractory ETP-ALL in order to achieve a remission prior to a consolidation allograft, as remission lengths appear to be short-lived.

***Reference: Clin Lymphoma Myeloma Leuk 2020;20:212–8***
Abstract

## LYMPHOMA SELECTION

### Rituximab/bendamustine and rituximab/cytarabine induction therapy for transplant-eligible mantle cell lymphoma

**Authors:** Merryman RW et al.

**Summary:** These researchers analysed data pooled from two phase 2 trials (n=41) and an off-trial cohort (n=47) of treatment-naïve patients with mantle cell lymphoma who received three cycles of RB (rituximab, bendamustine) and three cycles of RC (rituximab, high-dose cytarabine) followed by autologous SCT; 92% of the patients had completed induction therapy, and 84% underwent their planned consolidative autologous SCT. Among trial participants, grade 3–4 adverse events included lymphopenia (88%), thrombocytopenia (85%), neutropenia (83%) and febrile neutropenia (15%). There were no treatment-related deaths during induction therapy and two after autologous SCT. Among patients evaluable for response (n=87), the respective overall and complete response rates at the end of induction were 97% and 90%, and after median follow-up of 33 months, the respective 3-year PFS and OS rates were 83% and 92%. Prolonged MRD negativity after autologous SCT was seen in patients who underwent MRD testing, with MRD emerging in only one patient, who subsequently relapsed.

**Comment (LB):** With a median follow-up of 3 years, the PFS of 83% is an excellent outcome in mantle cell lymphoma. This practice has already been adopted by many NZ centres with the recent funding of bendamustine. The initial phase 2 trial used 3 g/m$^2$ of cytarabine, which caused more toxicity without improved outcomes. The study observed delayed platelet recovery in some patients after autologous SCT, particularly in those who received cytarabine 3 g/m$^2$ and/or alternating cycles of RB/RC. Since neither higher cytarabine doses nor alternating cycles of RB/RC were associated with improvement in response rate or PFS, the authors recommend sequential cycles of RB/RC with 2 g/m$^2$ dosing of cytarabine for clinical practice and for future trials that adopt this regimen. Also under study is the addition of a BTK inhibitor to the induction therapy, possibly removing the need for autologous SCT.

***Reference: Blood Adv 2020;4:858–67***
Abstract

LYMPHOMA SELECTION *continued*

## Minimal relapse risk and early normalization of survival for patients with Burkitt lymphoma treated with intensive immunochemotherapy

**Authors:** Jakobsen LH et al.

**Summary:** Real-world outcomes were reported for a retrospective cohort of 264 adults with Burkitt's lymphoma treated with intensive immunochemotherapy (47% R-CODOX-M/IVAC, 25% R-BFM/GMALL, 16% R-hyper-CVAD, 11% DA-EPOCH-R and 2% other); most of the patients had advanced-stage disease and elevated lactate dehydrogenase levels. The overall response rate was 89%, and the respective 2-year OS and event-free survival rates were 84% and 80%. For patients who achieved CR (including unconfirmed), the 2-year relapse rate was 6%, but this was only 0.6% for those who had achieved event-free survival 12 months after remission (the loss of lifetime for this group was 0.4 months).

**Comment (LB):** This study has all the caveats of a retrospective multicentre study, but its strength lies in the real-world nature of the patient cohort. Very old patients (two patients over 85 years) and HIV-positive patients were included. The 2-year relapse risk was only 6%, but dropped dramatically to 0.6% for those reaching the 12-month postremission timepoint. This is better than most of us quote our patients and provides further impetus to go hard with front-line therapy (R-CODOX-M/IVAC seemed a winner). Dose intensity may be relevant, but was not studied here, although older patients, more prone to time delays and dose modifications, did worse than younger patients. Unfortunately, at this time, there is no effective salvage therapy for the unfortunate few who do relapse, adding further incentive to go hard with induction therapy.

***Reference: Br J Haematol 2020;189:661–71***
Abstract

## Survival outcomes of patients with extranodal natural-killer T-cell lymphoma

**Authors:** Fox CP et al.

**Summary:** This was a substudy of 166 patients with ENKTL (extranodal natural killer T-cell lymphoma) from the global, prospective T-cell Project cohort study of consecutively diagnosed adults with newly diagnosed, untreated mature T-cell or NK lymphomas (n=1553). After median follow-up of 44 months, the respective 5-year OS rates in the ENKTL cohort with nasal disease (n=98) and extranasal disease (n=68) were 54% and 34%.

**Comment (LB):** This is a prospective study of the management of ENKTL from the Italian study group. The important role of radiotherapy in the management of early-stage ENKTL was highlighted by this study. In patients with early-stage disease, combined modality therapy with chemotherapy plus radiotherapy was associated with improved survival (median survival not reached); chemotherapy alone was associated with poor outcomes (12% survival at 5 years) – radiotherapy alone featured in between. Analysis of treatment type showed a 5-year PFS and OS of 42% and 50% in patients receiving an L-asparaginase-based regimen, compared with 26% and 31% in those receiving an anthracycline-based regimen, and 59% and 66% in those not receiving either drug (largely platinum-based regimens). SMILE was the most popular regimen; GDP presumably fits into the latter group and continues to be a reasonable upfront chemotherapy option for advanced disease.

***Reference: Lancet Haematol 2020;7:e284–94***
Abstract

### Independent commentary by Dr Leanne Berkahn, FRACP, FRCPA.

Leanne Berkahn is a consultant haematologist at Auckland City Hospital and senior lecturer in the Department of Molecular Medicine and Pathology at the University of Auckland School of Medicine. Her current research interests are new therapeutic approaches in the management of leukemia and lymphoma.

## Cardiovascular adverse events in patients with non-Hodgkin lymphoma treated with first-line cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP with rituximab (R-CHOP)

**Authors:** Linschoten M et al.

**Summary:** This systematic review and meta-analysis of 137 studies (n=21,211) evaluated the CV toxicity of first-line CHOP or R-CHOP regimens in patients with non-Hodgkin's lymphoma. Median follow-up was 39 months. The pooled proportion for all grade 3–4 CV adverse events was 2.35%; for heart failure it was 4.62%. There was a significant increase in reported heart failure from 1.64% to 11.72% when cardiac function was monitored after chemotherapy.

**Comment (LB):** The proportion of patients developing severe CV adverse events in this study is low (pooled proportion, 2.35%) and discontinuation of CHOP or R-CHOP due to treatment-related heart failure was rare. Female sex and older age (≥65 years) were independently associated with an increased risk of severe CV adverse events. The proportion of patients with heart failure increased significantly from 1.64% to 11.72% when cardiac function was evaluated at the end of treatment. Clearly heart failure is underdiagnosed; note that in the current CTCAE (Common Terminology Criteria for Adverse Events) for phase 3 studies, the patient has to be breathless at rest or have a symptomatic drop in left-ventricular ejection fraction to qualify as severe heart failure. Patients with heart failure due to either anthracycline or cyclophosphamide are likely to decline in performance status over the first year after treatment, therefore end-of-treatment echocardiography will likely pick up cases who have not yet developed symptoms. Perhaps this should be performed in those at higher risk, e.g. female patients and those >65 years of age where the risk is highest, likely greater than 10%.

***Reference: Lancet Haematol 2020;7:e295–308***
Abstract

## Cost-effectiveness analysis of rituximab with methotrexate, cytarabine and thiotepa for the treatment of patients with primary central nervous system lymphoma

**Authors:** Beca JM et al.

**Summary:** The cost-effectiveness of three induction strategies for primary CNS lymphoma was evaluated using a Markov model, based on the IELSG32 trial, over a 20-year time horizon and from the perspective of the Canadian healthcare system. Compared with methotrexate plus cytarabine, the MATRix (methotrexate, cytarabine, thiotepa, rituximab) regimen was associated with 3.05 QALYs gained at added costs of (Can)$75,513, resulting in an incremental cost-effectiveness ratio of $24,758 per QALY gained. Methotrexate, cytarabine plus rituximab was inferior to the methotrexate-cytarabine and MATRix regimens. MATRix was determined to be the optimal strategy for most simulations (98% probability at willingness-to-pay of $50,000 per QALY gained), with robust results across sensitivity analyses.

**Comment (CH):** The addition of thiotepa to the induction treatment of primary CNS lymphoma adds to the cost (NZ$1700 per cycle × 4) and significantly increases the grade 4 neutropenia and thrombocytopenia without increasing grade ≥3 neutropenic infections. The clinical outcomes, however, were significantly better with the addition of rituximab and thiotepa, with a more than doubling of the response rate, tripling of the 5-year FFS and doubling of the 5-year OS. As one of the authors of the first randomisation of the IELSG32 trial that compared MATRix with the previous standard of care, this complex cost-effectiveness analysis within the Canadian healthcare system further validates its use as first-line induction for patients aged under 70 years in NZ since 2017.

***Reference: Leuk Lymphoma 2020;61:1097–107***
Abstract