Lymphoma/Leukaemia RESEARCH REVIEW™

Making Education Easy

Issue 52 – 2020

In this issue:

Abbreviations used in this issue
AML = acute myeloid leukaemia
ALL/B-ALL = (B-cell) acute lymphoblastic leukaemia
CAR = chimeric antigen receptor
CLL = chronic lymphocytic leukaemia
CR = complete remission
CRS = cytokine-release syndrome
DFS = disease-free survival
DLBCL = diffuse large B-cell lymphoma
ECOG = Eastern Cooperative Oncology Group
MDS = myelodysplastic syndrome
MRD = minimal residual disease
NK = natural killer
OS = overall survival
PFS = progression-free survival
Ph+/Ph– = Philadelphia chromosome-positive/-negative
RFS = relapse-free survival
RT = radiotherapy
SCT = stem-cell transplantation

Welcome to issue 52 of Lymphoma/Leukaemia Research Review.

This issue begins with research reporting good tolerability of BR (bendamustine, rituximab) in patients aged ≥80 years with CLL, with efficacy and safety similar to that seen in younger patients as long as carefully adapted dosing is applied. There is also a phase 2 trial of dasatinib plus glucocorticoids followed by two cycles of blinatumomab as first-line therapy for adults with newly diagnosed Ph+ ALL. Other research has found that patients with ALL are still at risk of relapse beyond 3 years, although patients who relapse at this later stage tend to have better outcomes than those who relapse earlier. The year concludes with research showing that adding venetoclax to BR increased toxicity and reduced the dose intensity of BR in patients with relapsed/refractory follicular lymphoma.

We hope you enjoy our final selection for 2020, and we look forward to bringing you more interesting research next year. We remain more than happy to receive your comments and feedback in the meantime.

Kind regards,

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LEUKAEMIA SELECTION

Risk-adapted bendamustine + rituximab is a tolerable treatment alternative for elderly patients with chronic lymphocytic leukaemia

Authors: Mattsson A et al.

Summary: This retrospective study reported the effectiveness and safety of risk-adapted BR in 141 elderly (median age 72 years) Swedish real-world patients with CLL; 84 and 57 of the patients received BR as first- and later-line therapy, respectively, 49% had Binet stage C, 40% had a Cumulative Illness Rating Scale score of ≥6, 20% had an ECOG score of 2, and none had del(17p). For the respective age groups of <73, 73–79 and ≥80 years, the proportions who received full-dose bendamustine were 36%, 21% and 15%, and the proportions who delayed rituximab until cycle two were 33%, 63% and 65%. The overall response rate associated with first-line BR was greater than for later-line BR (83% vs. 67% [p<0.022]), with similar results seen among age subgroups. Factors significantly associated with PFS were ECOG score, *IGHV* mutation status and cytogenetics, but not treatment line or age. The rates of infections and neutropenia/thrombocytopenia (grade ≥3) did not differ significantly among the age subgroups.

Comment (LB): Although BR is offered as second-line or as an alternative treatment to younger patients, there is reluctance to use this front-line, especially in patients aged over 80 years due to perceived lack of tolerability. Although a smaller group, in this study patients aged over 80 years had a similar overall response rate at 83% to the <80-year age group, despite the median number of cycles being four as opposed to five or six in the younger patients. Only 15% received full-dose BR at 90 mg/m^2 and 65% had their initial rituximab postponed until the second cycle. Second-line BR had a 63% response rate. OS was not informative, as many got ibrutinib at disease recurrence. Of note, the safety profile did not differ across age groups with respect to severe infections or neutropenia/thrombocytopenia. The authors are suggesting that dose-reduced BR is an alternative and possibly more effective treatment to obinutuzumab and chlorambucil in CLL in patients >70 years of age. It is possible that further studies exploring BR for CLL may not be completed, as future trials in CLL are likely to focus on either BTK inhibitor- or bcl2 inhibitor-based therapy.

Reference: Br J Haematol 2020;191:426–32
Abstract

LEUKAEMIA SELECTION *continued*

Dasatinib-blinatumomab for Ph-positive acute lymphoblastic leukemia in adults

Authors: Foà R et al., for the GIMEMA Investigators

Summary: This phase 2 trial of dasatinib plus glucocorticoids followed by two cycles of blinatumomab was conducted in 63 patients (median age 54 years) with newly diagnosed Ph+ ALL. The primary endpoint of sustained molecular response in bone marrow was achieved in 29% of participants at the end of dasatinib induction therapy (day 85), and increased to 60% after two cycles of blinatumomab. CR was observed in 98% of the participants. After median follow-up of 18 months, the OS rate was 95% and the DFS rate was 88%. DFS was shorter among patients with *IKZF1* deletion plus other genetic aberrations (*CDKN2A/CDKN2B*, *PAX5*); six participants had *ABL1* mutations and increased MRD during induction therapy – all these mutations were cleared by blinatumomab. Six patients relapsed, 21 grade ≥3 adverse events occurred, 24 patients received a stem-cell allograft and there was one death related to transplantation.

Comment (CH): Sixty-three patients received this chemotherapy-free induction and consolidation as first-line treatment for Ph+ ALL. The age range of patients was 24–82 years. Patients received a minimum of two cycles of blinatumomab, but could receive a further three cycles. Also 12 intrathecal chemotherapy doses were given over the course of therapy. Complete molecular and positive nonquantifiable response rates increased with the addition of a third and then a fourth cycle of blinatumomab (from 60% to 70% to 81%). With a median follow-up of 18 months, OS was 95% and DFS 88%, which compares favourably with other trials. This was achieved as there was just one induction death in an elderly patient. Twenty-four patients went on to receive a transplant, and there was just one transplant-related death (4% treatment-related mortality rate) despite a median age of 52 years, suggesting that the omission of systemic chemotherapy may reduce the risk of transplant-related complications. The most common adverse event of grade ≥3 was cytomegalovirus reactivation in six patients (9.5%). This is likely related to the high-dose steroids received during the first month of induction. Monitoring is therefore essential.

ABL1 mutations are the usual cause of relapse in Ph+ ALL, and were assessed in 15 patients with an increase in MRD levels. Six patients had a *T315I* and one an *E255K* mutation; the rest were wild-type. These developed during induction and were all cleared by subsequent blinatumomab. Recurrent deletions in diagnostic genomic DNA were also assessed. *IKZF1* deletions were the most frequent aberration. A total of 11/46 patients were classified as *IKZF1*^{plus}; i.e. had an *IKZF1* mutation associated with *PAX5* deletions and/ or *CDK2A/B* deletions. These patients had reduced molecular response rates and lower DFS and OS, and may need to be considered for alternative therapies. Longer follow-up is required to confirm that results are maintained. This is likely, as relapses usually occur within 1.5–2 years. Follow-up of the nontransplant patients will also be interesting. Access to blinatumomab remains an ongoing issue, as Amgen does not feel it is commercially viable to bring to NZ.

Reference: N Engl J Med 2020;383:1613–23
Abstract

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LEUKAEMIA SELECTION *continued*

At three years, patients with acute lymphoblastic leukaemia are still at risk for relapse

Authors: Ganzel C et al.

Summary: These researchers used data from the international MRC UKALLXII/ECOG E2993 trial to investigate the incidence and characteristics of late relapse in 1909 adult participants with ALL. Among the 92% of participants who achieved CR, the relapse rate was 43.2%, most (91.3%) within 3 years. The 66 participants who relapsed after 3 years did so in a median of 47 months, and they represented 3.8% of all participants who achieved CR. The cumulative 3-, 5- and 10-year relapse rates were 40%, 43% and 45%. Among participants who achieved CR, 11.7% and 40.6% underwent autologous and allogeneic transplantation, respectively, while in first CR. Among autologous transplant recipients, the early and late relapse rates were 43.2% and 3.4%, respectively, while among allogeneic transplant recipients, they were 13.2% and 1.3%. The respective 5-year OS rates after early and late relapse were 5.8% and 20%.

Comment (CH): This UK/US collaborative trial remains one of the largest (1909 patients) prospective adult ALL trials. This paper focuses on late relapses, with a median follow-up now of 8 years. In patients achieving a CR, 11.7% received an autologous transplant, 40.6% an allogeneic transplant and 47.6% chemotherapy only. Ph+ and Ph– patients received the same treatment until an amendment in 2003 added imatinib. Patients up to age 55 years received an allogeneic transplant if a suitable donor was identified (matched sibling in Ph– and matched sibling or unrelated donor in Ph+ patients). Of the 757 relapses after achieving a CR, 91.3% were within 3 years, with a median time to relapse of 9 months. There were 8.7% who relapsed beyond 3 years and 2.8% were very late relapsers (beyond 5 years). The median time to relapse in the late and very late relapsers was 47 months (range 37–144). Late relapses occurred in 1.3% of allogeneic transplant patients and 3.4% and 5.9% of autologous transplant and chemotherapy only patients, respectively. These late relapses occurred in equivalent numbers of high-risk and standard-risk cytogenetic patients, so all cytogenetic risk patients require follow-up beyond 3 years. Median survival after relapse was just 11.3 months with 5-year OS of 20%, compared with 5.4 months and 5.8%, respectively, in the early-relapse patients. This is significantly worse than in smaller adult trials and paediatric trials. Unfortunately, relapse treatment was not collected within the study to understand the effects of newer treatment modalities. The disease recurrences are assumed to be relapses versus second leukaemias. Molecular studies looking at the original clones present and relapsed clones will confirm this. This study remains relevant in NZ because of the lack of access to novel therapies up front, apart from in adolescent/young adult patients within the COG trials.

Reference: Br J Haematol 2020;191:37–43
Abstract

A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS patients

Authors: Oran B et al.

Summary: Patients aged 18–75 years with AML/MDS in CR were randomised to receive twelve 28-day maintenance cycles of subcutaneous azacitidine 32 mg/m^2/day for 5 days (n=93) or no intervention (n=94) in this trial; 87 of those assigned to azacitidine started treatment, and a median of four cycles were received. Twenty-nine participants experienced disease relapses during the study, and 23 withdrew from the study for a variety of reasons. There was no significant difference between the azacitidine versus control arm for median RFS duration (2.07 vs. 1.28 years [p=0.19]) or median OS duration (2.52 vs. 3.56 years [p=0.43]).

Comment (CH): This is a negative study after promising phase 2 data. The study took 7.5 years to enrol 187 high-risk AML/MDS patients and closed early due to slow accrual. Roughly 50% of patients did not consent due to concerns regarding an ongoing year of treatment post-transplant. Failing eligibility criteria also hampered recruitment. Only 24 (27.6%) of 87 patients received the planned 12 cycles of maintenance. The median number of cycles received was just four. The dose chosen was 32 mg/m^2 for 5 days every 4 weeks. In the nontransplant older patient maintenance setting, the phase 3 randomised Hovon-97 trial (50 mg/m^2 for 5 days every 4 weeks for 12 cycles) reported significant improvements in RFS, and in the AML16 trial (75 mg/m^2 for 5 days every 6 weeks for nine cycles) there were significant OS improvements, but only in patients who were MRD-negative (data not published). Therefore, the dose and schedule may be critical. The QUAZAR trial using oral azacitidine in the nontransplant maintenance setting has also recently reported RFS and OS benefits across key patient groups. This is the first completed phase 3 maintenance study post-transplant; many others will follow, using targeted agents (FLT3 and IDH1/2 inhibitors) and oral azacitidine/decitabine with or without venetoclax. We have been recruiting to a phase 3 post-transplant gilteritinib (FLT3 inhibitor) placebo-controlled study in NZ, and have encountered the same difficulties with recruitment.

Reference: Blood Adv 2020;4:5580–8
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.

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 leukaemia and lymphoma.

LEUKAEMIA SELECTION *continued*

Anti-CD19 chimeric antigen receptor T-cell therapy in acute lymphocytic leukaemia

Authors: Anagnostou T et al.

Summary: This was a systematic review with meta-analysis of 35 studies (17 and 18 at low and moderate risk of bias, respectively) reporting outcomes for 953 adult or paediatric patients with B-ALL who were treated with anti-CD19 CAR T-cells. The CR rate was 80%, with respective rates of 75% and 81% for adult and paediatric participants, respectively. CR did not differ significantly by anti-CD19 CAR T-cell construct type or single-chain variable fragment clone, but a greater CR rate was seen for treatments with an autologous versus allogeneic T-cell origin (83% vs. 55% [p=0.018]). The grade ≥3 CRS rate was 26% and the grade ≥3 neurotoxicity rate was 12%. The different anti-CD19 CAR T-cell constructs did not differ significantly in terms of the proportions of participants who achieved CR or who experienced CRS or neurotoxicity.

Comment (CH): Thirty-five studies containing 953 patients met the eligibility criteria for inclusion in this meta-analysis. The pooled CR rate was an impressive 80% (75% in adult and 81% in paediatric studies), with 1-year PFS rates dropping to 37%. The CAR T-cell construct type (4-1BB vs. CD28 costimulated) or the single chain variable fragment clone did not affect CR or 1-year PFS rates, but autologous CAR T-cell therapy had higher CR rates then allogeneic CAR T-cell therapy (83% vs. 55%). Third- or fourth-generation constructs were associated with lower 1-year PFS than 4-1BB costimulated constructs. MRD-negative rates were higher with 4-1BB costimulated constructs than with CD-28 costimulated constructs. Preclinical data suggest the former results in memory-like CAR T-cells, which ameliorate T-cell exhaustion and improve persistence, whereas CD28 costimulation yields mainly effector CAR T-cells with rapid antitumour responses but poor persistence. CRS and neurotoxicity rates also did not differ between autologous CAR T-cell constructs, but neurotoxicity was less with allogeneic constructs. It should however be noted that different studies used four different CRS grading systems, making comparisons difficult. There are currently scarce data comparing different constructs, so these data are potentially useful for current choice of CAR T-cell therapy prior to comparison studies being available. It should also be noted that in some studies, patients proceeded to allogeneic transplantation, but others did not, which will clearly impact on PFS and OS. There is ongoing debate with regards to the need for a consolidation allograft, and this is likely to be dictated by CAR T-cell persistence. These products are only potentially funded centrally for NZ patients under the age of 25 years for relapsed B-ALL, and transfer to Australia is necessary for CAR T-cell manufacture and infusion.

Reference: Lancet Haematol 2020;7:E816–26
Abstract

LYMPHOMA SELECTION

Real-world efficacy of brentuximab vedotin plus bendamustine as a bridge to autologous hematopoietic stem cell transplantation in primary refractory or relapsed classical Hodgkin lymphoma

Authors: Pinczés LI et al.

Summary: The efficacy and safety of 1–6 (median 3) cycles of brentuximab vedotin 1.8 mg/kg on day 1 plus bendamustine 90 mg/m^2 on days 1–2 every 4 weeks as a bridge to autologous SCT were reported for 41 real-world patients who received such therapy for primary refractory or relapsed classical Hodgkin's lymphoma. The objective response rate was 78%, with a CR rate of 70.7%. The post-transplant relapse rate was 29.3% with two deaths and two patients lost to follow-up. After median follow-up of 17 months post-transplant, the respective estimated 2-year OS and PFS rates were 93% and 62%. Significant predictors of an unfavourable outcome were features of advanced disease at recurrence and stage IV disease at relapse. The any-grade adverse event rate was 58.5%, with no grade 4 toxicities recorded.

Comment (LB): The premise of this study is that incorporating brentuximab vedotin with bendamustine will be both effective and relatively less toxic in the multiple relapsed patient with Hodgkin's lymphoma in order to become eligible for autologous SCT. PET negativity before autologous SCT is associated with improved outcomes, and is the standard of care guideline in Hungary and elsewhere. I note that only 2% developed peripheral neuropathy, which is in stark contrast to the 54% in the original phase 2 study published by LaCasce. It is notable that 22% of those proceeding to autologous SCT were still PET-positive. PET-positive patients were eligible for brentuximab vedotin following autologous SCT but only 2/12 received brentuximab vedotin maintenance. By contrast, 13/26 patients in remission post-SCT received brentuximab vedotin maintenance. The latter will obviously impact on the PFS of the group as a whole. NZ haematologists are aware that bendamustine and vinorelbine (BEGEV) is now available in this setting. The outcome data for the BEGEV protocol are similar to the brentuximab vedotin and bendamustine-treated group in this paper, so it is a good option for relapsed Hodgkin's lymphoma failing to respond to first-line salvage in the NZ setting. Currently brentuximab therapy salvage for relapsed Hodgkin's lymphoma is only available as a bridge to allogeneic SCT in NZ.

Reference: Ann Hematol 2020;99:2385–92
Abstract

Prediction and prevention of central nervous system relapse in patients with extranodal natural killer/T-cell lymphoma

Authors: Kim H et al.

Summary: These researchers reported the incidence of CNS relapse, identified its predictors and assessed the need for CNS prophylaxis with intermediate-dose methotrexate for training (n=399) and validation (n=253) cohorts of patients with extranodal NK/T-cell lymphoma treated with non-anthracycline-based chemotherapy. The patients were stratified according to whether their chemotherapy regimen included methotrexate >2 g/m^2. A new model (CNS-PINK) was developed based on the sum of scores of PINK (Prognostic Index of NK; hazard ratio 2.908 [p=0.030]) and extranodal involvement ≥2 (4.161 [p=0.001]), with high-risk defined as 2 points. The cumulative CNS relapse incidence differed between the CNS-PINK risk groups in both the training (p<0.001) and validation (p=0.038) cohorts. In the training cohort, patients who were high risk according to CNS-PINK and were treated with SMILE or SMILE-like regimens with intermediate-dose methotrexate had a lower incidence rate of CNS relapse than those who received other regimens without intermediate-dose methotrexate (p=0.029).

Comment (LB): This is a useful paper that can be used to guide which patients with NK/T-cell lymphoma are at risk of CNS relapse. The CNS-PINK score is a merger of the PINK score and the number of extranodal sites. The variables in the PINK score are age >60 years, stage III or IV disease, distant lymph-node involvement and non-nasal type disease. Those with an intermediate to high PINK score and 2 or more extranodal sites were considered high risk. In this study, patients who were in the high-risk CNS-PINK group were treated with SMILE or SMILE-like regimens with intermediate-dose methotrexate (>2 g/m^2). The methotrexate recipients displayed a lower incidence rate of CNS relapse than those who received other regimens without intermediate-dose methotrexate in the training cohort. Looking to the future, this work needs validation in larger trials. The dose of methotrexate for CNS prophylaxis is >3 g/m^2 for DLBCL, so the intermediate dose used in this study also needs further validation.

Reference: Blood 2020;136:2548–56
Abstract

LYMPHOMA SELECTION *continued*

Outcomes in patients with DLBCL treated with commercial CAR T cells compared with alternate therapies

Authors: Sermer D et al.

Summary: This retrospective, observational study compared outcomes in 69 patients with relapsed/refractory DLBCL treated with CAR T-cell therapy versus a historical population treated with alternative therapies (n=146). Compared with patients treated with alternative therapies, CAR T-cell recipients had a higher complete response rate (52% vs. 22% [p<0.001]), longer median PFS duration (5.2 vs. 2.3 months [p=0.01]) and longer median OS duration (19.3 vs. 6.5 months [p=0.006]). After adjustment for pretreatment disease characteristics, the superior response rate in CAR T-cell recipients persisted, but PFS and OS differences did not. Patients responding to alternative therapies had prolonged remission durations that were similar to those of CAR T-cell therapy responders.

Comment (LB): CAR T-cell therapy is the latest innovation for relapsed lymphoma, but difficult to access and very expensive. Our patients often perceive CAR T-cell therapy as the holy grail. This paper looked at real-world patient outcomes after CAR T-cell therapy, and found that they closely resembled the data from landmark phase 2 trials. The benefit of CAR T-cells over alternative therapies is less clear after adjusting for baseline risk factors for unfavourable disease. Despite the encouraging response rates, PFS and OS in the CAR T-cell cohort, greater than two-thirds ultimately progressed after CAR T-cell therapy. Patients who received alternative therapies had a significantly increased incidence of elevated LDH (lactate dehydrogenase) levels and refractory disease compared with patients who were referred for CAR T-cell therapies. The subgroup analysis performed on patients with elevated LDH levels and bulky disease demonstrated that CAR T-cell therapy did not significantly improve PFS or OS. Future trials need to concentrate on the best sequencing of available therapies, as in some instances, alternative chemoimmunotherapy may have equivalent outcomes to CAR T-cell therapy.

Reference: Blood Adv 2020;4:4669–78
Abstract

Consolidation radiotherapy could be safely omitted in advanced Hodgkin lymphoma with large nodal mass in complete metabolic response after ABVD

Authors: Gallamini A et al.

Summary: The role of consolidation RT was assessed in this final analysis of participants from the GITIL/FIL HD0607 trial with advanced-stage Hodgkin's lymphoma who had a large nodal mass (≥5cm) at presentation and who were PET-negative after two and six cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy. The 296 participants were prospectively randomised to consolidation RT at a median dose of 30.6Gy over their large nodal mass or no further treatment. Baseline mass diameters of 5–7, 8–10 and >10cm were present in 34%, 32% and 33% of the patients, respectively. A residual mass after chemotherapy was present in 88% of the patients. After median follow-up of 5.9 years, there was no significant difference between the consolidation RT and no further treatment groups for the 6-year PFS rate for patients with baseline masses 5–7cm (91% vs. 95% [p=0.62]), 8–10cm (98% vs. 90% [p=0.24]) or >10cm (89% vs. 86% [p=0.53]).

Comment (LB): Most patients who presented with a large nodal mass had a residual mass following chemotherapy (ABVD). Those who were negative at PET-2 and PET-6 were randomly assigned to receive consolidation RT at a dose of 30Gy to the site of the original large nodal mass or to no further treatment. This was suggested to be safe practice from data gathered retrospectively from GHSG-15 and is already creeping into our current algorithms. This prospective trial confirms that a residual mass regardless of size does not require involved-field RT. Interesting points include that there was no difference in outcome with this approach between masses with maximal diameters of 5–7cm, 7–10 cm or >10 cm.

Reference: J Clin Oncol 2020;38:3905–13
Abstract

Venetoclax-rituximab with or without bendamustine vs bendamustine-rituximab in relapsed/refractory follicular lymphoma

Authors: Zinzani PL et al.

Summary: Patients with relapsed/refractory follicular lymphoma were randomised to receive 12 cycles of venetoclax plus rituximab (evaluable n=52; arm A), or six cycles of BR (bendamustine, rituximab) with (evaluable n=51; arm B) or without (evaluable n=51; arm C) venetoclax after a safety venetoclax run-in, in this open-label phase 2 study. A smaller proportion of participants from arm B received ≥90% of the planned bendamustine dose (90 mg/m^2 on days 1 and 2) compared with arm C (61% vs. 96%), as a result of more reduced dosing and treatment discontinuations secondary to greater haematological toxicity. The respective complete metabolic/complete response rates in arms A–C were 17%, 75% and 69%, and the respective grade 3–4 adverse event rates were 51.9%, 93.9% and 60.0%.

Comment (LB): This study looked at the addition of venetoclax to rituximab or BR in relapsed follicular lymphoma (median of 3 prior therapies). More patients receiving venetoclax plus BR than BR withdrew from study treatments or underwent dose modifications, driven by haematological and gastrointestinal toxicities. Only 27% of patients achieved ≥90% venetoclax dose intensity in the venetoclax plus BR arm, showing the limited tolerability of this regimen at the given dose and schedule. The conclusion is that the bcl2 inhibitor venetoclax shows activity in follicular lymphoma, which was difficult to confirm as many patients in the venetoclax plus BR arm discontinued therapy due to side effects. The dosage of venetoclax in combination with bendamustine was likely too high at 800 mg/day for 6 months. A lower dosage may have shown a different result altogether, as more patients would have achieved the intended dose density. There was a follicular lymphoma arm in the CAVALLI study that looked at noncontinuous dosing of venetoclax for example. Future trials exploring the role of venetoclax in follicular lymphoma are underway.

Reference: Blood 2020;136:2628–37
Abstract

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