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Congress Report ASH 2023

A GLOBAL CONGRESS DIGEST ON TARGETED THERAPIES IN B-CELL MALIGNANCIES

Report from the American Society of Hematology (ASH) Annual Meeting, December 9–12, 2023

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Preface

Dear Colleagues,

The 65th Annual Meeting of the American Society of Hematology (ASH) took place as a hybrid event that hosted participants both online and on-site in San Diego, California, USA. Among the multitude of updates and new insights presented from December 9th to 12th, 2023, attendees had access to thousands of scientific abstracts highlighting cutting-edge research in hematology. In this issue of memo inHaematology, you are invited to explore the forefront of hematologic oncology, focusing on the latest advancements and therapeutic strategies in the treatment of various B-cell malignancies.

In mantle cell lymphoma (MCL), several targeted, chemotherapy-free combinations have demonstrated promising efficacy in patients with relapsed/refractory disease, including ibrutinib plus venetoclax and mosunetuzumab plus polatuzumab vedotin. The highly selective, non-covalent BTK inhibitor pirtobrutinib was proposed as a new standard of care for patients with MCL after prior covalent BTK inhibitor treatment. In the setting of *TP53*-mutant MCL, the BOVen triplet, i.e., zanubrutinib, obinutuzumab and venetoclax, has emerged as a promising treatment option.

Subsequently, the focus shifts to Waldenström macroglobulinemia, and data on outcome optimization in both the first and subsequent lines of treatment are summarized. The following chapter highlights strategies to improve responses and overcome resistance in multiple myeloma such as the addition of anti-CD38 antibodies to established combination regimens. The novel Bcl-2 inhibitor sonrotoclax is being evaluated in various B-cell malignancies, with multiple myeloma being one of them.

Moreover, trial evidence obtained with bispecific antibodies and BTK inhibitors is outlined in the context of newly diagnosed and relapsed/refractory follicular lymphoma, offering insights into how these approaches are reshaping therapeutic landscapes. The results reported in this issue support the further development of agents such as odronextamab and epcoritamab.

A special focus is drawn to updated findings in CLL where the combination of ibrutinib and venetoclax is widely investigated, as well as the second-generation BTK inhibitors zanubrutinib and acalabrutinib as monotherapies and combination partners, among others. MRD-guided strategies such as the one used in the CLL2-BAAG study are considered valuable as they can help to ensure the suitable amount of treatment in the individual patient.

Potential advances are further described in the setting of diffuse large B-cell lymphoma (DLBCL). For decades, the

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CHOP regimen has been the first-line standard of care for patients with newly diagnosed DLBCL. Data on promising chemotherapy-free approaches in the untreated and pretreated settings are summarized in chapter six.

Finally, this issue concludes with a discussion of innovative agents in marginal zone lymphoma and other B-cell malignancies, highlighting the continued search for more effective and less harmful treatment modalities.

Whether you are seeking to update your knowledge on current practices or looking for inspiration for future research, this issue offers a wealth of information on the cutting edge of B-cell malignancy treatment.

Happy reading,

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University of Cologne,
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Mantle cell lymphoma: emerging treatment regimens and new standards

SYMPATICO: venetoclax plus ibrutinib

Based on promising results of early-phase studies, the multinational, double-blind, placebo-controlled phase III SYMPATICO trial is evaluating the concurrent administration of the BTK inhibitor ibrutinib and the Bcl-2 inhibitor venetoclax in the setting of relapsed/refractory mantle cell lymphoma (MCL) [1, 2]. Patients after 1–5 prior therapies who had received ≥ 1 rituximab/anti-CD20-containing regimen were randomized to either ibrutinib plus venetoclax (n = 134) or ibrutinib plus placebo (n = 133). Venetoclax and placebo were used for 24 months; after that, ibrutinib was continued as a single agent until disease progression or unacceptable toxicity. The primary endpoint is progression-free survival (PFS) by investigator assessment.

According to the findings reported at ASH 2023 by Wang et al. after a median follow-up of 51.2 months, ibrutinib plus venetoclax improved PFS in a statistically

significant manner vs. ibrutinib alone (31.9 vs. 22.1 months; HR, 0.65; p = 0.0052; **Figure 1**) [3]. The Kaplan-Meier PFS curves separated early on. All sensitivity analyses showed a robust PFS benefit. Moreover, the combination demonstrated significant superiority in terms of time to next treatment (not reached vs. 35.4 months; HR, 0.60; p = 0.0096) and the complete response (CR) rate (54 % vs. 32 %; p = 0.0004). The overall response rates (ORR) did not differ (82 % vs. 74 %; p = 0.1279). Duration of response was significantly longer with ibrutinib plus venetoclax than with ibrutinib plus placebo (42.1 vs. 27.6 months). For overall survival (OS), the analysis revealed numerical improvement (44.9 vs. 38.6 months; HR, 0.85; p = 0.3465).

The safety profile of the combination was consistent with the known adverse events (AEs) of each agent. Any-grade AEs primarily included diarrhea (65 % vs. 34 %), neutropenia (34 % vs. 14 %), nausea (31 % vs. 17 %), fatigue (29 % vs. 27 %), anemia (22 % vs. 12 %) and cough (20 % vs. 27 %). Among grade ≥ 3 AEs, neutropenia was most common (31 % vs. 11 %), followed by pneumonia (13 % vs. 11 %), thrombocytopenia (13 % vs. 8 %) and anemia (10 % vs. 3 %). At 5 %, the rates of grade ≥ 3 atrial fibrillation were identical across the arms. AEs leading to discontinuation of treatment occurred in 31 % vs. 36 %; AE-related dose reductions were necessary in 36 % vs. 22 %.

Ten patients in each arm died due to COVID-19. These fatalities had no meaningful impact on the PFS and OS benefits of the combination. After censoring of COVID-19–related deaths, median PFS was 36.4 vs. 22.1 months (HR, 0.63; p = 0.0042), and median OS was 58.2 vs. 49.4 months (HR, 0.84; p = 0.3257). Overall, the addition of venetoclax to ibrutinib demonstrated a favorable risk-benefit profile in patients with relapsed/refractory MCL. The authors emphasized that this combination represents a new standard of care in this setting.

Fixed-duration mosunetuzumab and polatuzumab vedotin

Initial safety and efficacy data were presented from an ongoing phase II expansion cohort of 20 patients with relapsed/refractory MCL who are being treated with the CD20xCD3 T-cell–engaging bispecific antibody mosunetuzumab and the anti-CD79b antibody-drug conjugate polatuzumab vedotin [4]. Mosunetuzumab is administered subcutaneously in 21-day cycles with step-up dosing in cycle 1 for a total of 17 cycles, while polatuzumab vedotin 1.8 mg/kg is administered intravenously on day 1 of cycles 1–6. Prior to each dose in cycle 1, all patients received corticosteroid premedication, and hospitalization was not mandatory. The study participants had previously been treated with ≥ 2 therapies including an anti-CD20 antibody, anthracycline or bendamustine therapy, and BTK inhibition. All patients had received prior BTK inhibitors, while 35 % had undergone CAR T-cell therapy. High-risk features abounded in this population; *TP53* aberrations were present in 42 %, blastoid/pleomorphic histology was found in 50 %, and 60 % of patients had Ki-67 index ≥ 50 %.

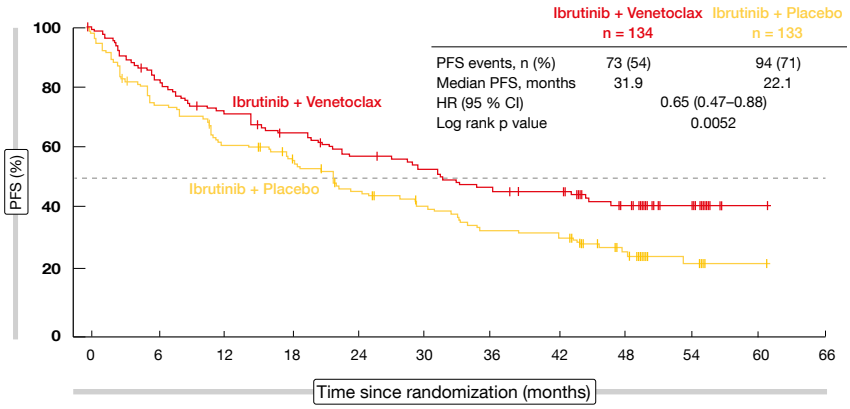


Figure 1: SYMPATICO trial: significantly improved progression-free survival with ibrutinib plus venetoclax vs. ibrutinib plus placebo

The study identified no new safety signals in this heavily pretreated cohort. Mosunetuzumab plus polatuzumab vedotin demonstrated a manageable safety profile that was consistent with that of the individual agents in the setting of relapsed/refractory MCL, including disease with high-risk features. Treatment-related AEs (TRAEs) mostly included injection site reactions, all of which were grade 1 or 2, as well as fatigue, cytokine release syndrome (CRS), diarrhea, and dyspnea. CRS events were reported in 45 %, with 40 % and 5 % classified as grade 1 and 2, respectively. Almost all cases occurred in cycle 1, and median CRS duration was 3 days. In 5 % each, corticosteroids or tocilizumab and low-flow oxygen were required to manage CRS. TRAEs led to discontinuation in 10 %. No patient died due to TRAEs.

Regarding efficacy, the combination was shown to induce an ORR of 75 % according to the investigators, with 70 % of patients obtaining CR. The ORR rates were generally consistent across high-risk MCL subgroups including those who had relapsed within 12 months of the first prior therapy, the group that had undergone CAR T-cell therapy before enrolment, and those with *TP53* aberrations, among others. CRs were achieved early on and proved durable. After a median follow-up of 15.8 months, 11 of 14 patients with CR remained in remission; median duration of response was estimated at 13.3 months. Median OS and PFS were 17.9 and 15.8 months, respectively. At 9 months, 74.1 % of patients were alive, and 68.8 % were progression-free.

The authors concluded that the fixed-duration outpatient regimen of mosunetuzumab plus polatuzumab vedotin has promising efficacy in a population with relapsed/refractory MCL pretreated with BTK inhibitors. The long-term follow-up will inform the utility of this combination in the treatment landscape.

Pirtobrutinib: update from BRUIN

Likewise, the highly selective, non-covalent BTK inhibitor pirtobrutinib has demonstrated efficacy in patients with MCL after covalent BTK inhibition (cBTKi) [5, 6]. Pirtobrutinib was investigated in 166 patients with relapsed/refractory MCL in the phase I/II BRUIN study. Among these, 152 had previously

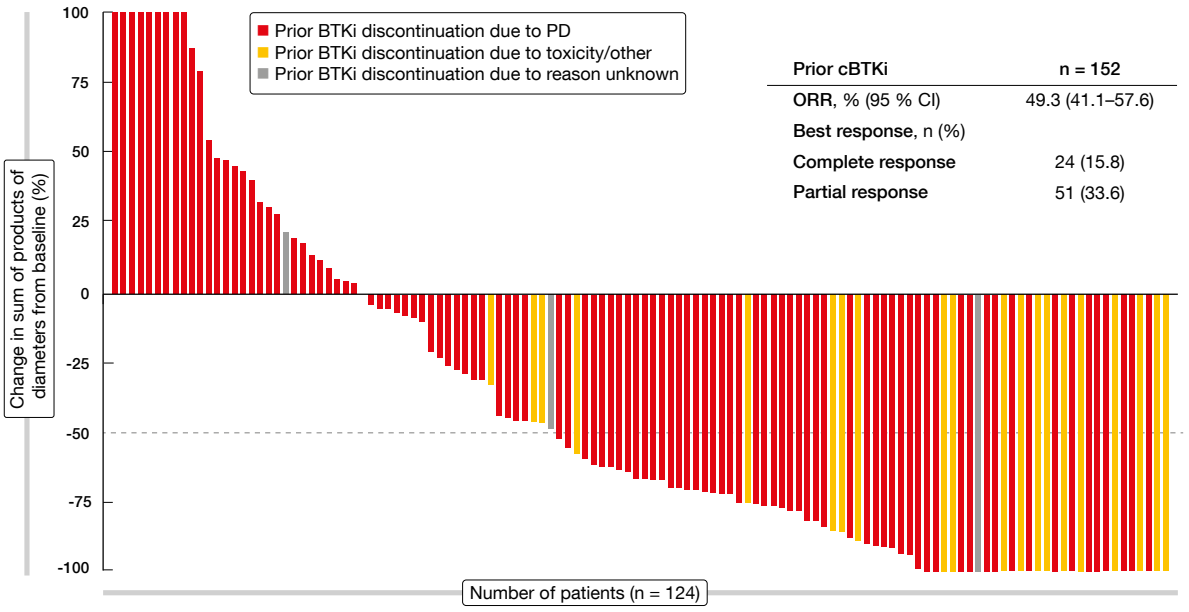


Figure 2: Efficacy of pirtobrutinib in patients who received prior covalent BTK inhibitor (cBTKi) therapy

been treated with cBTKi, whereas 14 were cBTKi-naïve. Updated results reported at ASH 2023 by Cohen et al. continued to demonstrate promising efficacy [7]. In the cBTKi-pretreated group, the ORR was 49.3 %, with 15.8 % of patients achieving CR (**Figure 2**). Median duration of response, median OS and median PFS were 21.6 months, 23.5 months and 5.6 months, respectively. Clinically meaningful ORRs resulted in a variety of MCL subgroups including those with high-risk features such as Ki-67 index ≥ 30 % and bone marrow and gastrointestinal involvement. In the group that had discontinued prior BTK inhibitor therapy due to toxicity, the ORR was very high at 90.5 %, while this was 43.0 % in the cohort of patients who had switched treatment due to progression.

The cBTKi-naïve group showed an ORR of 85.7 %; here, 42.9 % of remissions were classified as CRs. At 24 months, 92.3 % of patients were alive, and 83.9 % were progression-free. Although this cohort is small, these data were deemed encouraging by the investigators. Moreover, pirtobrutinib was well tolerated, with low dose reduction and discontinuation rates due to TRAEs (5 % and 3 %, respectively). Infections, bruising and rash constituted the most common TRAEs of interest (any grade, 15.7 %, 11. 4 %, and 9.0 %, respectively). According to the authors, pirtobrutinib represents a new standard of care for patients with MCL after prior covalent BTK inhibitor treatment. The randomized, global, phase III BRUIN MCL-321 trial is currently comparing pirtobrutinib with covalent BTK inhibitor therapy at the investigator's discretion in BTK-inhibitor–naïve patients with relapsed MCL (NCT04662255).

BOVen for patients with *TP53*-mutant disease

No standard frontline approach has been established to date for patients with MCL harboring *TP53* mutations. Survival on treatment with chemoimmunotherapy is poor in this group [8]. Kumar et al. therefore tested the BOVen triplet, i.e., zanubrutinib, obinutuzumab and venetoclax, in a multicenter phase II trial based on the assumption that this regimen will be well tolerated and efficacious in untreated patients with *TP53*-mutant MCL [9]. Obinutuzumab was administered for a total of 8 cycles, while oral zanubrutinib and venetoclax were continued for a minimum of 24 cycles. Venetoclax was introduced with a standard ramp-up starting on cycle 3, after 2 cycles of obinutuzumab and venetoclax.

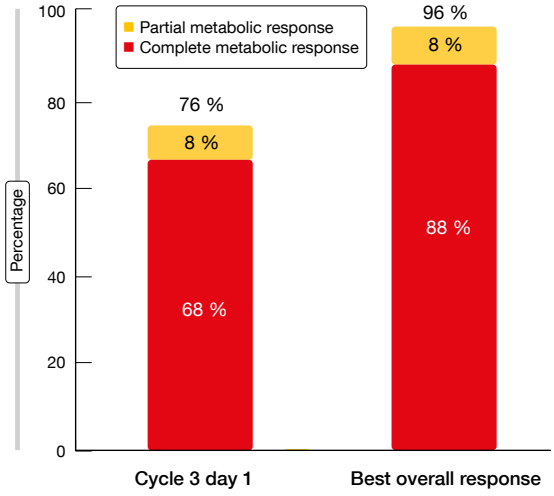


Figure 3: Response rates after two cycles of zanubrutinib and obinutuzumab (left) and best overall response with zanubrutinib, obinutuzumab and venetoclax (right)

At cycle 24, an MRD-driven approach was utilized to limit treatment duration in selected patients. Those who had CR and undetectable minimal residual disease (uMRD) discontinued treatment, while those with < CR and/or detectable MRD continued on zanubrutinib and venetoclax. At two sites, a total of 25 patients were enrolled substantial proportions of whom showed high-risk features such as Ki-67 index ≥ 50 % and high MIPI score. PFS at 2 years was defined as the primary endpoint. As the authors pointed out, this is the first dedicated study for *TP53*-mutant MCL.

Overall, BOVen proved to be a well-tolerated and safe outpatient regimen. The most frequent AEs comprised diarrhea (any grade, 60 %), COVID-19 infection (48 %), neutropenia (32 %), and infusion-related reactions (24 %). Grade 3 neutropenia occurred in 16 % of patients and resolved with growth factor support. Diarrhea was predominantly grade 1 and manageable. Among serious AEs that were reported in 48 % of patients, COVID-19 infections prevailed (20 %). At cycle 3, only three patients were at high risk for tumor lysis syndrome (TLS) and required initial inpatient venetoclax ramp-up. No clinically significant TLS was observed during ramp-up, although one grade 4 TLS event occurred after the initial administration of obinutuzumab.

uMRD in 80 %

With 72 % of patients being progression-free at 2 years, the primary endpoint of the study was met. This result compared favorably to the 2-year PFS rates observed with standard-of-care regimens in the NORDIC MCL-2 and MCL-3 trials as well as the findings of the SHINE study conducted with bendamustine, rituximab and ibrutinib [8, 10]. At 2 years, 75 % of patients were alive, and 88 % were disease-free. Analyses by baseline factors did not reveal any significant associations between DFS and morphology, age, Ki-67 index, or *TP53* mutation/deletion 17. Neither median PFS nor median DFS or OS had been reached at the time of the analysis.

The treatment gave rise to high metabolic response rates already after 2 cycles of zanubrutinib and obinutuzumab **(Figure 3)**. The best ORR on the triplet therapy was 96 %, with CRs achieved in 88 %. All patients had detectable MRD at baseline. By cycle 13, uMRD at the 10^{-6} level was present in 95 %. Eleven patients completed 24 cycles of therapy, and 100 % of them achieved CR. One patient without MRD results due to the lack of a baseline tumor specimen continued on zanubrutinib and venetoclax. Eight of the 10 remaining patients achieved uMRD and were able to stop treatment. In 6 and 2 of these, uMRD was obtained at sensitivity levels of 10^{-6} and 10^{-5}, respectively. One patient restarted treatment due to MRD becoming detectable at two time points and another due to clinical relapse. In their summary, the authors noted that BOVen emerges as a promising treatment option for patients with *TP53*-mutant MCL.

Indirect comparison of zanubrutinib and orelabrutinib

A previous indirect comparison of the next-generation BTK inhibitors zanubrutinib and orelabrutinib in Chinese patients with relapsed/refractory MCL has shown that PFS and CR favored zanubrutinib over orelabrutinib [11]. Song et al. reported an updated analysis to indirectly compare the long-term efficacy of the two agents using an unanchored matching-adjusted indirect comparison (MAIC) based on individual patient data from the single-arm BGB-3111-206 and ICP-CL-00102 studies [12]. These two studies included 86 and 106 patients, respectively. Response evaluations were both PET- and CT-based in the zanubrutinib trial and CT-based only in the orelabrutinib trial. After matching, the baseline characteristics were well balanced between the two groups; the effective sample size was 70 for the zanubrutinib cohort.

According to MAIC, zanubrutinib gave rise to statistically significant longer PFS compared to orelabrutinib (not reached vs. 22.0 months; HR, 0.54; p = 0.009). PFS rates were numerically higher for zanubrutinib at 12 months (80.1 % vs. 65.1 % after matching) and 24 months (67.3 % vs. 46.5 %). Although the PET-based assessment is more sensitive than CT in terms of detection of disease progression, PFS according to PET was significantly longer for zanubrutinib than PFS according to CT for orelabrutinib (HR, 0.63; p = 0.044). For OS, a trend was observed in favor of zanubrutinib (HR, 0.68; p = 0.223). The sensitivity analysis results were consistent with the comparative findings. ■

REFERENCES

1 Tam CS et al., Ibrutinib plus venetoclax for the treatment of mantle-cell lymphoma. N Engl J Med 2018; 378(13): 1211-1223
2 Wang M et al., Concurrent ibrutinib plus venetoclax in relapsed/refractory mantle cell lymphoma: the safety run-in of the phase 3 SYMPATICO study. J Hematol Oncol 2021; 14(1): 179
3 Wang M et al., Ibrutinib combined with venetoclax in patients with relapsed/refractory mantle cell lymphoma: primary analysis results from the randomized phase 3 SYMPATICO study. ASH 2023, abstract LBA-2
4 Wang ML et al., Fixed-duration mosun-pola has promising efficacy and a manageable safety profile in patients with prior-BTKi treated relapsed/refractory mantle cell lymphoma: initial results from a phase Ib/II study. ASH 2023, abstract 734
5 Hess LM et al., Outcomes among patients with mantle cell lymphoma post-covalent BTK inhibitor therapy in the United States: A real-world electronic medical records study. Adv Hematol 2022; 2022: 8262787
6 Mato AR et al., Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet 2021; 397 (10277): 892-901
7 Cohen J et al., Pirtobrutinib in relapsed/refractory mantle cell lymphoma patients with prior cBTKi: Updated safety and efficacy including high-risk subgroup analyses from the phase 1/2 BRUIN study. ASH 2023, abstract 981
8 Eskelund CW et al., TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. Blood 2017; 130(17): 1903-1910
9 Kumar A et al., A multicenter, phase 2 trial with zanubrutinib, obinutuzumab, and venetoclax (BOVen) in patients with treatment-naïve, TP53-mutant mantle cell lymphoma. ASH 2023, abstract 738
10 Wang ML et al., Ibrutinib plus bendamustine and rituximab in untreated mantle-cell lymphoma. N Engl J Med 2022; 386(26): 2482-2494
11 Song Y et al., Indirect comparisons of efficacy of zanubrutinib versus orelabrutinib in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma or relapsed or refractory mantle cell lymphoma. Invest New Drugs 2023; 41(4): 606-616
12 Song Y et al., Indirect comparison of efficacy of zanubrutinib versus orelabrutinib in patients with relapsed or refractory mantle cell lymphoma: An updated analysis with long-term follow-up. ASH 2023, abstract 1682

Waldenström macroglobulinemia: optimizing outcomes in the first and later lines

Effects of transition from ibrutinib to zanubrutinib

The randomized phase III ASPEN study compared the next-generation BTK inhibitor zanubrutinib with ibrutinib in patients with symptomatic, *MYD88*-mutated Waldenström macroglobulinemia (WM), demonstrating a trend towards better response quality and decreased toxicity in the zanubrutinib arm [1]. Eligible patients who participated in trials of zanubrutinib for the treatment of B-cell malignancies could enroll in the BGB-3111-LTE1 study. This long-term extension was accessible to individuals from comparator arms as well. At ASH 2023, Garcia-Sanz et al. presented results for 47 patients who had transitioned from the ibrutinib arm of the ASPEN trial to zanubrutinib in the LTE1 study [2]. At the time of the analysis, treatment with zanubrutinib had been ongoing for at least 1 year. The outcome assessment included the recurrence of adverse events (AEs) that had emerged on ibrutinib treatment.

As the safety analysis showed, the majority of ibrutinib-emergent AEs did not recur or continue with zanubrutinib despite increasing patient age (**Figure**). Worsening of ibrutinib-emergent AEs of interest after the switch to zanubrutinib included three COVID-19 infections and one case each of anemia and neutropenia. Two deaths occurred that were due to COVID-19. Grade ≥ 3 and serious treatment-emergent AEs (TEAEs) were observed in 23 % and 13 %, respectively. The severity of ongoing hypertension did not increase after the switch, and no new or recurrent episodes of hypertension were reported. Likewise, no resolved atrial fibrillation/flutter that had emerged on ibrutinib recurred, and ongoing atrial fibrillation/flutter did not worsen following the transition to zanubrutinib. At 46.8 %, infections were the most common any-grade TEAEs of interest in the LTE1 study; grade ≥ 3 infections occurred in 6.4 %. Hemorrhages were seen in 12.8 % (grade ≥ 3, 2.1 %) and neutropenia in 10.6 % (grade ≥ 3, 4.3 %).

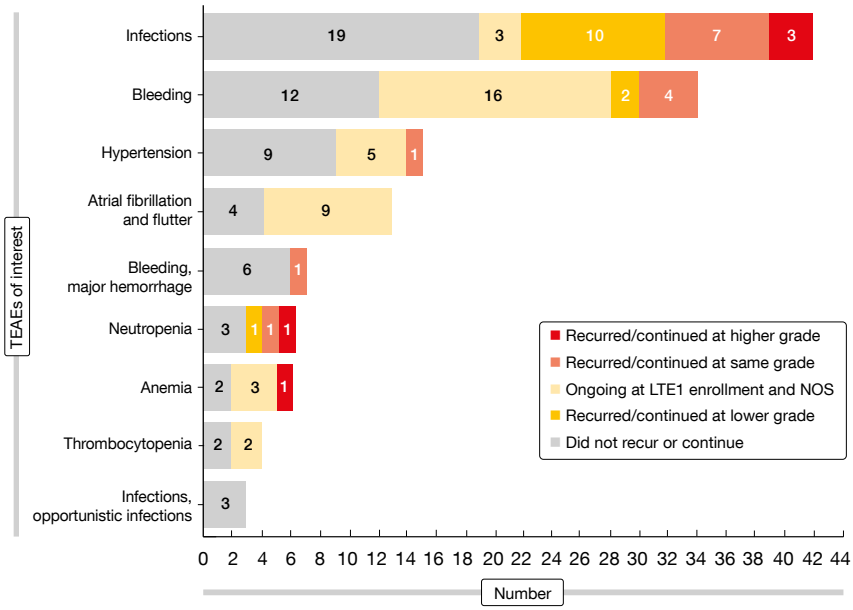


Figure: Recurrence or continuation of ibrutinib-emergent adverse events on zanubrutinib therapy

With respect to efficacy, the best overall response in the LTE1 study was unchanged from the last response in ASPEN in 34 patients (72 %) and improved in 10 (21 %). Overall, disease responses were maintained or improved in 96 % of the efficacy-evaluable population. Complete responses (CRs) and very good partial responses (VGPRs) were noted in 4.3 % and 36.2 %, respectively. IgM values were stable or decreased in the majority of evaluable patients. Although this analysis is limited by sample size and the non-randomized design, it suggests that patients who tolerate ibrutinib might switch to zanubrutinib without compromising safety or efficacy and may even experience improvement of their outcomes.

Frontline bendamustine, rituximab & acalabrutinib

The combination of bendamustine, rituximab and acalabrutinib is being tested in the ongoing BRAWM study as first-line treatment of symptomatic WM with the aim of optimizing CR and VGPR rates. While bendamustine and rituximab are administered for six 28-day cycles, acalabrutinib is taken orally for 1 year. According to interim data reported for 49 patients at ASH 2023, 60 % of participants who reached month 7 achieved CR or VGPR [3]. These rates persisted or improved through month 12 in 80 % and were maintained at month 18 in 89 %. IgM responses occurred already by cycle 3; the results indicated an association of decreases in IgM with increased hemoglobin levels in all study participants. MRD negativity in the peripheral blood was achieved in the total population at cycle 7, and 2.7 to 4.7 log reductions were observed in bone marrow at cycles 7, 12 and month 18. Results in both marrow and blood were sustained throughout the trial.

The most common treatment-related AEs (TRAEs) of the combination included neutropenia, headaches/migraine, fatigue, diarrhea and nausea. Eighteen patients required a total of 31 dose reductions or interruptions during

the combination phase. Two discontinued due to TRAEs. Acalabrutinib monotherapy was well tolerated. After a median follow-up of 6 months, no patient has progressed or died. Overall, fixed-duration combination treatment with bendamustine, rituximab and acalabrutinib was shown to be feasible and safe.

Follow-up after ibrutinib and venetoclax cessation

A multicenter, prospective phase II study was initiated to evaluate daily ibrutinib and venetoclax for a maximum of 24 months in treatment-naïve patients with WM. The study was stopped after four ventricular arrhythmia events that included two grade 5 events. Castillo et al. reported follow-up findings for 45 patients after treatment discontinuation to assess ongoing safety and response durability of this combination [4].

Indeed, the combination of ibrutinib and venetoclax was highly effective, with VGPR and partial response rates of 42 % and 53 %, respectively. In patients with *CXCR4* wildtype and *CXCR4* mutation, VGPR rates were 50 % and 29 %, respectively. The 24-month overall survival and progression-free survival (PFS) rates were 96 % and 76 %, respectively, and the time-to-next-treatment rate at 24 months was 89 %. Additionally, the investigators assessed the outcomes 12 months after the end of treatment. At this time, the analysis showed a PFS rate of 79 %. VGPR attainment appeared to predict longer PFS as the 12-month PFS rate after the end of therapy was 94 % in patients with VGPR but only 69 % in those with < VGPR, although this difference was not significant.

However, the authors noted that they cannot recommend the combination of ibrutinib and venetoclax at the current dose and schedule given that the cause of the unexpected ventricular arrhythmia remains unclear. Nevertheless, the potential for shorter treatment duration or safer combinations offers hope for maintaining efficacy while mitigating adverse effects. ■

REFERENCES

1 Tam C et al., A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood 2020; 136(18): 2038-2050
2 Garcia-Sanz R et al., Clinical outcomes in patients with Waldenström macroglobulinemia receiving ibrutinib on the phase 3 ASPEN study ≥ 1 year after transitioning to zanubrutinib. ASH 2023, abstract 3043
3 Berinstein NL et al., Indolent lymphoma: high CR and VGPR rate with fixed duration bendamustine, rituximab and acalabrutinib in Waldenströms Macroglobulinemia (BRAWM). ASH 2023, abstract 3037
4 Castillo JJ et al., Ibrutinib and venetoclax as primary therapy in symptomatic, treatment-naïve Waldenström macroglobulinemia. ASH 2023, abstract 1661

Improving responses in multiple myeloma

PERSEUS: D-VRd vs. VRd

An established treatment approach for transplant-eligible patients with newly diagnosed multiple myeloma (MM) is induction treatment with bortezomib, lenalidomide and dexamethasone (VRd) followed by autologous stem cell transplantation (ASCT), VRd consolidation, and lenalidomide maintenance. The multinational phase III PERSEUS study compared this schedule to an expanded regimen containing the anti-CD38 antibody daratumumab in addition to induction and consolidation with VRd (D-VRd) as well as lenalidomide maintenance (D-R). While 355 patients were treated with D-VRd, 354 received the standard treatment with VRd followed by lenalidomide maintenance. Induction and consolidation consisted of four and two 28-day cycles, respectively. Daratumumab was administered subcutaneously.

Patients enrolled in the experimental arm were able to eventually discontinue daratumumab if they had achieved at least complete remission (CR) and 12 months of sustained minimal residual disease (MRD) negativity after ≥ 24 months of D-R maintenance. Lenalidomide maintenance was continued in this group. Daratumumab treatment could be restarted upon confirmed loss of CR without disease progression or recurrence of MRD. Progression-free survival (PFS) constituted the primary endpoint. Sonneveld et al. presented the primary analysis of the PERSEUS trial at ASH 2023 [1].

In the D-VRd and VRd groups, 89.5 % and 86.2 % of patients, respectively, completed induction and consolidation, and similar percentages underwent ASCT. Stem cell mobilization and collection were shown to be feasible with D-VRd; the expanded treatment did not impact the patient ability to receive transplant or engraftment. Plerixafor was administered more often in the D-VRd arm, although the number of CD34+ cells collected sufficed for ASCT. Hematopoietic reconstitution resulted in 99.7 % vs. 99.3 %; time to engraftment was 14 days in both arms. In 91.7 % and 86.5 %, respectively, maintenance treatment was initiated. At a median follow-up of 47.5 months, the PFS analysis revealed a 58 % risk reduction in the experimental arm after early separation of the curves, with 48-month PFS rates of 84.3 % vs. 67.7 % (HR, 0.42; p < 0.0001; **Figure 1**). According to the subgroup analysis, the addition of daratumumab improved PFS across clinically relevant subgroups.

Deep and durable MRD negativity

D-VRd significantly improved the depth of response compared to the VRd regimen. The CR and stringent CR (sCR) rate was significantly higher with D-VRd (87.9 % vs. 70.1 %; OR, 3.13; p < 0.0001). sCRs were present in 69.3 % vs. 44.6 %. A subgroup analysis showed consistent improvement of the > CR rate across

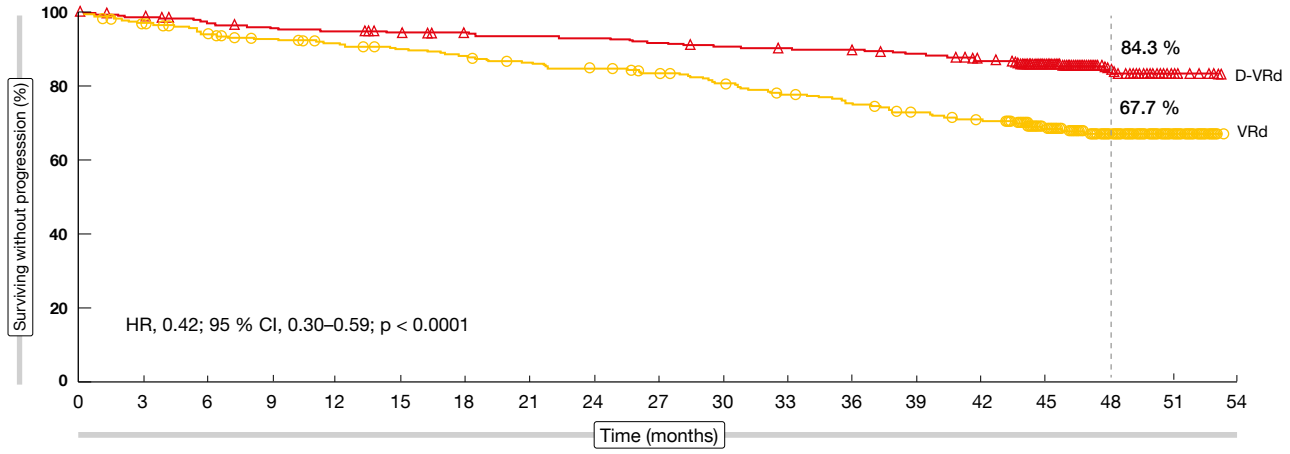


Figure 1: Progression-free survival benefit with D-VRd vs. VRd in transplant-eligible patients

subgroups. The combined approach elicited deep and durable MRD negativity. At a sensitivity threshold of 10^{-5}, MRD negativity resulted in 75.2 % with D-VRd vs. 47.5 % with VRd (OR, 3.40; p < 0.0001); at a level of 10^{-6}, this was 65.1 % vs. 32.2 % (OR, 3.97; p < 0.0001). Sustained MRD negativity (10^{-5}) for ≥ 12 months resulted in 64.8 % vs. 29.7 % (OR, 4.42; p < 0.0001). Sixty-four percent of patients receiving maintenance in the D-VRd group were able to discontinue daratumumab after achieving sustained MRD negativity per protocol. MRD negativity rates increased during maintenance, with the absolute difference between D-VRd and VRd widening over time. This was most evident at the threshold of 10^{-6}; here, MRD negativity rates were 34.4 % vs. 16.1 % after consolidation and 65.1 % vs. 32.2 % overall, which translated into differences across the arms of 18 % and 33 %, respectively.

The observed safety profile of the combination was consistent with the known safety profiles for subcutaneous daratumumab and VRd. In both arms, the most common adverse events (AEs) included infections, neutropenia, diarrhea, peripheral sensory neuropathy and thrombocytopenia. As the PERSEUS trial was partly conducted during the pandemic, the infection rates were comparatively high. In their conclusion, the authors noted that these randomized phase III results support D-VRd followed by D-R maintenance as a new standard of care for transplant-eligible patients with newly diagnosed MM.

Isatuximab in addition to KRd

The randomized phase III IsKia EMN24 trial assessed the addition of the anti-CD38 antibody isatuximab to pre-ASCT induction and post-ASCT consolidation with carfilzomib, lenalidomide and dexamethasone (Isa-KRd) in transplant-eligible patients with newly diagnosed MM. Both induction and consolidation involved four 28-day cycles; this was followed by light consolidation consisting of twelve 28-day cycles using reduced-dose KRd and Isa-KRd. In the experimental arm, 151 patients were treated with Isa-KRd, while 151 patients in the control arm received KRd alone. MRD negativity by NGS after post-ASCT consolidation was defined as the primary endpoint. At 42 sites, patients were enrolled between October 2020 and November 2021.

According to the results reported by Gay et al. at ASH 2023 after a median follow-up of 21 months, Isa-KRd, as compared to KRd, significantly increased post-consolidation MRD negativity at sensitivity levels of 10^{-5} (77 % vs. 67 %; OR, 1.67; p = 0.049) and 10^{-6} (67 % vs. 48 %; OR, 2.29; p < 0.001) [2]. The MRD negativity rates improved over time in both arms, with significantly higher rates in the experimental arm after induction, transplantation, and consolidation; this applied to both sensitivity levels (**Table**). Isa-KRd consistently increased MRD negativity at 10^{-5} and 10^{-6} in all subgroups including patients with high risk whose results were not inferior to those in the group with standard risk. In the cohort harboring ≥ 2 high-risk cytogenetic abnormalities, i.e. in the patients with very high risk, the post-consolidation MRD negativity rates were 77 % vs. 53 % at the 10^{-5} level and 77 % vs. 27 % at the 10^{-6} level.

Isa-KRd proved tolerable, with the toxicity profile being similar to previous observations. Neutropenia occurred as the most common treatment-related adverse event (TRAE) and was more frequent in the experimental arm (41 % vs. 26 %; grade 3/4, 36 % vs. 22 %), although this did not translate into increased in-

TABLE
Improvement of MRD negativity rates over time on Isa-KRd and KRd treatment, with consistent significant benefits for Isa-KRd

MRD negativity rates at certain time points (%)	Sensitivity threshold 10^{-5}			Sensitivity threshold 10^{-6}		
	Isa-KRd (n = 151)	KRd (n = 151)	OR p value	Isa-KRd (n = 151)	KRd (n = 151)	OR p value
Post induction	45	26	2.34 < 0.001	27	14	2.36 0.004
Post ASCT	64	49	1.39 0.006	52	27	3.01 < 0.001
Post consolidation	77	67	1.67 0.049	67	48	2.29 < 0.001

fection rates (infections excluding COVID-19, 36 % vs. 32 %; grade 3/4, 15 % vs. 11 %). COVID-19 infections were observed in 26 % vs. 19 %, with most of them being classified as grade 1 or 2. Peripheral neuropathy occurred in 15 % vs. 17 % and was restricted to grade 1 and 2 events. The isatuximab-based treatment did not increase the rate of cardiac disorders (7 % vs. 13 %; grade 3/4, < 1 % vs. 3 %) and thromboembolism (8 % vs. 11 %; grade 3/4, 3 % vs. 6 %). As the authors pointed out, the 10^{-6} MRD negativity cutoff might be more informative than other response categories in the context of treatment regimens that induce high response rates. With longer follow-up, the IsKia EMN24 trial can offer the opportunity to explore the correlation between the depth of MRD negativity and the survival endpoints PFS and OS.

IFM 2018-04: D-KRd in high-risk patients

Daratumumab was investigated as add-on to KRd induction and consolidation in the single-arm phase II IFM 2018-04 study conducted in high-risk patients with newly diagnosed MM who underwent tandem transplantation. This population showed ≥ 1 of the high-risk cytogenetic features t(4;14), 17p deletion, and t(14;16). Sixty percent of patients presented with ≥ 2 cytogenetic abnormalities. After six D-KRd induction cycles, the first ASCT was performed; this was followed by four D-KRd consolidation cycles and the second ASCT. Finally, the patients received maintenance treatment with daratumumab plus lenalidomide for two years. As eight patients were not able to proceed to tandem transplant due to insufficient stem cell collection, the study protocol was amended to allow for cell collection already after cycle 3 rather than cycle 6. Touzeau et al. reported the findings for 50 patients at ASH 2023 [3].

D-KRd plus double transplant was shown to induce deep responses. CR/sCR was observed in 81 % after the second ASCT. The CR/sCR rate increased in the course of treatment, which also applied to the MRD negativity rate. After the second transplant, 94 % of evaluable patients demonstrated MRD negativity at the 10^{-6} level. In terms of survival endpoints, the analysis showed that at 30 months, 91 % of patients were alive, with 80 % being progression-free.

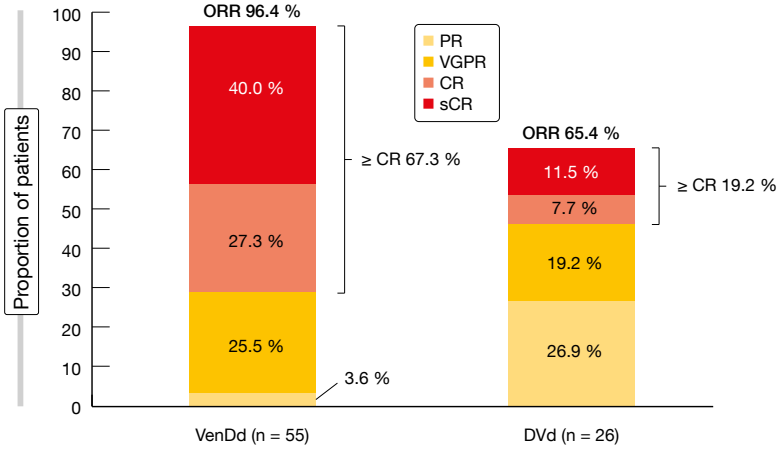


Figure 2: Superiority of VenDd at both doses over DVd regarding response rates

Non-hematologic TRAEs of D-KRd mainly included infections (64 %; grade 3/4, 14 %), gastrointestinal disorders (62 %; 10 %), peripheral neuropathy (20 %; 0 %), and skin rash (18 %; 0 %). The most common grade 3/4 TRAEs were hematologic; grade 3/4 neutropenia, thrombocytopenia and anemia occurred in 44 %, 24 % and 22 %, respectively. In four cases, AEs led to the discontinuation of the study treatment. No new safety signals occurred.

Overall, the IFM 2018-04 study confirmed the efficacy and feasibility of D-KRd induction and consolidation with double transplant in high-risk transplant-eligible patients with newly diagnosed MM. The authors emphasized that stem cell collection should be performed 3–4 cycles in the context of anti-CD38 KRd induction to limit the risk of harvest failure, especially in the setting of tandem transplant.

RRMM with t(11;14) translocation: VenDd …

The t(11;14) translocation is the most frequent translocation in MM. In the phase I setting, the combination of venetoclax, daratumumab and dexamethasone (VenDd) has demonstrated preliminary activity in patients with relapsed/refractory MM harboring t(11;14) [4]. Bahlis et al. reported updated findings from the multicenter phase I/II trial at ASH 2023 [5]. In the experimental group, 55 patients were treated with VenDd containing venetoclax at doses of 400 mg or 800 mg OD. They were compared to 26 patients receiving daratumumab, bortezomib and dexamethasone (DVd). All study participants had previously received ≥ 1 prior line of therapy including a proteasome inhibitor or an immunomodulatory agent.

Responses were more pronounced with the venetoclax-based regimen. The overall response rates were 96.4 % vs. 65.4 % for VenDd and DVd, and patients in the experimental arm derived a considerably higher rate of CR/sCR **(Figure 2)**. Similarly, the MRD negativity rates were higher for either dose of VenDd than for DVd at both the MRD < 10^{-5} cutoff (40 % vs. 8 %) and the 10^{-6} cutoff (24 % vs. 4 %). VenDd induced higher MRD negativity rates than DVd at both MRD thresholds in key patient subgroups including those with ≥ 2 prior lines of therapy, lenalidomide refractoriness, and high-risk cytogenetics. Moreover, rates of sustained MRD negativity were higher in the experimental arm: Seven of 17 VenDd-treated patients undergoing longitudinal MRD assessments remained MRD-negative for > 6 months, while none of the DVd-treated patients did. Two venetoclax-treated patients achieved MRD negativity for > 12 months.

Median PFS was longer with VenDd than with DVd (46.1 vs. 15.5 months), with 33-month PFS rates of 74.3 % vs. 39.7 %. Within the VenDd arm, analyses according to the MRD results showed a trend towards longer OS in MRD-negative patients (< 10^{-5}) compared to the MRD-positive cohort. The safety analysis demonstrated no new signals. VenDd

had a manageable safety profile, with numerically fewer AEs per 100 patient-years compared to DVd (grade 3/4, 134.3 vs. 240.7).

… and sonrotoclax plus dexamethasone

The next-generation Bcl-2 inhibitor sonrotoclax (BGB-11417) has shown more potent and selective Bcl-2 inhibition as well as improved activity against Bcl-2–dependent hematological malignancies than venetoclax *in vitro* [6]. An ongoing phase I/II study is exploring the combination of sonrotoclax and dexamethasone in patients with t(11;14)-positive MM whose disease has relapsed or is refractory to the most recent treatment line. Participants have failed ≥ 3 prior lines including a proteasome inhibitor, an immunomodulator, and an anti-CD38 antibody. At ASH 2023, preliminary data from the dose-escalation cohorts were presented by Quach et al. [7]. Sonrotoclax was evaluated at doses of 80 mg (n = 3), 160 mg (n = 3), 320 mg (n = 3) and 640 mg (n = 10) in addition to dexamethasone. In the total population of 19 individuals, 68 % have been treated with anti-CD38 antibodies, while all patients have previously received immunomodulatory agents and proteasome inhibitors. The median number of prior treatment lines was 4.

In this heavily pretreated patient group, sonrotoclax plus dexamethasone was well tolerated. The most common treatment-emergent AEs included insomnia, fatigue, nausea, arthralgia, COVID-19, alopecia and diarrhea. Most patients experienced grade 1 or 2 AEs. Diarrhea was manageable with dose interruption. The combination did not give rise to any dose-limiting toxicities at any tested dose level. No significant hematologic toxicity has emerged to date; grade 3 events included one case of decreased lymphocyte count and one case of decreased platelet count. All infections were grade 1 or 2 except for one case of COVID-19.

Investigator assessment of treatment response showed the most promising results for the 640 mg dose after a median treatment duration of 5.5 months, with an overall response rate of 70 % and very good partial response, CR and sCR in 40 % of patients. The longest duration of response at data cutoff was 18.9 months. Sonrotoclax 640 mg has been selected as the recommended phase II dose. At present, recruitment is ongoing for the sonrotoclax plus dexamethasone expansion cohort and for the dose-finding arms investigating sonrotoclax plus dexamethasone and carfilzomib. Further combinations will be assessed later on in this study. ■

REFERENCES

1 Sonneveld P et al., Phase 3 randomized study of daratumumab + bortezomib, lenalidomide, and dexamethasone (VRd) versus VRd alone in patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplantation: primary results of the PERSEUS trial. ASH 2023, LBA-1

2 Gay F et al., Results of the phase III randomized IsKia trial: Isatuximab-carfilzomib-lenalidomide-dexamethasone vs. carfilzomib-lenalidomide-dexamethasone and pre-transplant induction and post-transplant consolidation in newly diagnosed multiple myeloma patients. ASH 2023, abstract 4

3 Touzeau C et al., Daratumumab carfilzomib lenalidomide and dexamethasone induction and consolidation with tandem transplant in high-risk newly diagnosed myeloma patients: results of the phase 2 study IFM 2018-04. ASH 2023, abstract 207

4 Bahlis NJ et al., Phase I study of venetoclax plus daratumumab and dexamethasone, with or without bortezomib, in patients with relapsed or refractory multiple myeloma with and without t(11;14). J Clin Oncol 2021; 39(32): 3602-3612

5 Bahlis NJ et al., Venetoclax in combination with daratumumab and dexamethasone elicits deep, durable responses in patients with t(11;14) relapsed/refractory multiple myeloma: Updated analyses of minimal residual disease negativity in phase 1/2 study. ASH 2023, abstract 338

6 Hu N et al., Preclinical characterization of BGB-11417, a potent and selective Bcl-2 inhibitor with superior antitumor activities in haematological tumor models. AACR 2020, abstract 3077

7 Quach H et al., Sonrotoclax (BGB-11417) in combination with dexamethasone for the treatment of relapsed/refractory multiple myeloma with t(11;14): Safety, efficacy, and determination of recommended phase 2 dose. ASH 2023, abstract 1011

Follicular lymphoma: BTK inhibition and bispecific antibodies

Acalabrutinib in addition to lenalidomide/rituximab

With respect to the treatment of newly diagnosed follicular lymphoma (FL), there is room for improvement as many patients relapse after first-line chemoimmunotherapy. The frontline use of lenalidomide and rituximab (R^2) has proven highly active in patients with FL [1, 2]. A single-arm phase II study investigated the addition of the BTK inhibitor acalabrutinib to R^2 in patients with untreated FL based on the hypothesis that this combination will increase efficacy due to beneficial effects on the immune microenvironment. Acalabrutinib 100 mg BID was administered orally for 13 cycles; from cycle 2 onwards, the patients received lenalidomide 20 mg on day 1-21 for 12 cycles plus rituximab 375 mg/m^2 weekly for four doses followed by monthly administration until month 13. Study participants had FL grade 1–3a, stage III/IV, with high tumor burden. Intermediate and high FLIPI scores were present in 46 % and 25 %, respectively. The best complete response (CR) rate constituted the primary endpoint.

According to the analysis presented by Strati et al. at ASH 2023 for 24 patients, the best CR rate was as high as 92 % (**Figure 1**) [3]. Already after 3 cycles, 62.5 % of patients achieved CR. At a median follow-up of 29 months, the 2-year overall survival (OS) and progression-free survival (PFS) rates were 92 % and 79 %, respectively. Acalabrutinib plus R^2 was shown to be a safe regimen. Treatment-emergent adverse events (TEAEs) mainly included anemia, fatigue, thrombocytopenia, headache and diarrhea. Grade 3/4 AEs were mostly seen for neutropenia, transaminase elevations, infection, anemia and skin rash. Lenalidomide and acalabrutinib dose reduction rates were low at 25 % and 8 %, respectively. The authors concluded that the addition of acalabrutinib to R^2 is a safe and effective frontline non-chemotherapy regimen.

Moreover, bulk RNA sequencing with deconvolution performed at baseline and on day 1 of cycles 2 and 6 revealed favorable biological changes in multiple circulating immune cells. Acalabrutinib monotherapy induced significant increases in monocyte-related gene signatures associated with anti-viral activity, monocyte proliferation, monocyte-mediated TNF response, and anti-tumoral activity. The addition of R^2 to acalabrutinib significantly increased the frequency of circulating CD4+ T cells and classical monocytes, and decreased the frequency of circulating regulatory natural killer cells. Meanwhile, the study has been amended to include 26 additional FL patients who will be treated with only 6 cycles of acalabrutinib plus R^2. Analyses of minimal residual disease (MRD) and progression samples are ongoing.

Mosunetuzumab plus lenalidomide

The CD20xCD3 T-cell–engaging bispecific antibody mosunetuzumab is being tested in combination with lenalidomide in an ongoing phase Ib/II study. Previously untreated patients with CD20-positive, grade 1–3a FL are receiving mosunetuzumab subcutaneously Q4W for 12 cycles after step-up in cycle 1. Lenalidomide is being taken orally from cycle 2 to 12. After cycle 12, mosunetuzumab maintenance Q8W for 9 cycles is possible. At ASH 2023, Morschhauser et al. reported preliminary results for 40 patients [4]. Almost 88 % of these had stage III/IV, 42.5 % had FLIPI scores 3–4, and half showed bulky disease.

The combination of mosunetuzumab and lenalidomide demonstrated a manageable safety profile. Injection-site reactions were noted as the most common AE, followed by rash, cytokine release syndrome (CRS) and neutropenia. All of the grade 3/4 AEs reported (55.0 %) were due to neutropenia. No grade 5 events occurred. Dose delays/interruptions of mosunetuzumab and lenalidomide were required in 27.5 % and 42.5 %, respectively. Two AEs (5.0 %) led to treatment discontinuation. Injection-site reactions predominantly emerged in cycles 1 and 2. CRS events occurred in 50 % of patients, were mainly grade 1 and were confined to cycle 1 and early cycle 2. All CRS events resolved, and none necessitated mosunetuzumab discontinuation. Median CRS duration was 2 days.

With an overall response rate (ORR) of 91.9 % and a CR rate of 89.2 %, the combination gave rise to promising anti-lymphoma activity. All responses were still ongoing at the clinical cutoff date. The pharmacokinetic profile of subcutaneous mosunetuzumab following 5/45/45 mg step-up dosing resembled that observed in mosunetuzumab-treated patients with relapsed/refractory FL. In addition, a biomarker analysis was performed that showed early and sustained CD8+ T-cell activation with low PD-1 expression in CD8+ T cells up to cycle 4, although longer follow-up is required.

Taken together, the data support the further development of mosunetuzumab plus lenalidomide as first-line strategy in FL. As the authors noted, this regimen potentially offers outpatient, fixed-duration and chemotherapy-free treatment. The large phase III MorningLyte trial comparing mosunetuzumab plus lenalidomide with chemoimmunotherapy in the first-line setting is being planned.

High-risk disease: EZH2 inhibition

In the setting of high-risk FL, the phase II Epi-RCHOP study was designed to assess the oral EZH2 inhibitor tazemetostat as frontline treatment in addition to chemoimmunotherapy. Patients with FL grade 1–3a, FLIPI scores of 3–5 and high tumor burden were recruited at 23 sites in France and Belgium. They received induction treatment with 6 cycles of R-CHOP and 2 cycles of rituximab monotherapy; tazemetostat 800 mg BID was administered from day 2 of cycle 1. Maintenance consisted of rituximab plus tazemetostat for 3 cycles followed by rituximab alone in cycles 4–12. Thus, tazemetostat was given continuously for one year. The primary endpoint was the complete metabolic response (CMR) rate at the end of induction. *EZH2* mutations were found in 24.2 % of the population according to parallel testing of liquid and tissue biopsy. Bone marrow involvement was present in 68.3 %, and 21 % of patients showed blood dissemination.

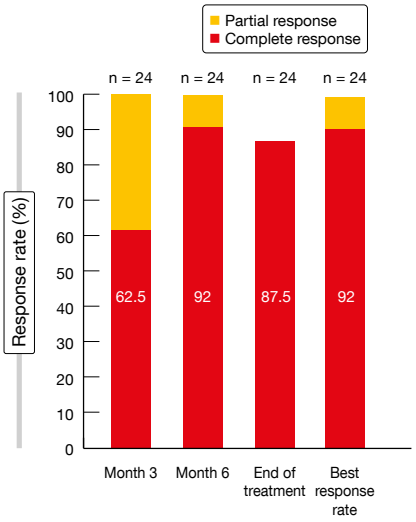


Figure 1: Response rates for first-line acalabrutinib plus lenalidomide/rituximab

The study did not meet its primary objective of improving the CMR rate to ≥ 80 % [5]. In the safety set (n = 62), the CMR rate was only 53.2 % because many patients lacked bone marrow biopsy at the end of induction and were therefore reclassified as partial metabolic responders. A sensitivity analysis assessing bone marrow involvement by central PET review in patients with partial metabolic responses and another sensitivity analysis considering only lymph nodes and organ responses by PET yielded CMRs of 74.2 % and 79 %, respectively, which again stayed below the 80 % threshold (**Table**). However, an encouraging finding is the CMR rate of 73.3 % in patients carrying *EZH2* muta-

TABLE
Overall response rates and metabolic responses achieved with tazemetostat at the end of induction

Analysis sets	Safety set n = 62	Sensitivity set # 1 n = 62	Sensitivity set # 2 n = 62	*EZH2* status mutated vs. wildtype
Overall response rate	59 (95.2 %)	59 (95.2 %)	59 (95.2 %)	100 % vs. 93.6 %
Complete metabolic response	33 (53.2 %)	46 (74.2 %)	49 (79 %)	73.3 % vs. 46.8 %
Partial metabolic response	26 (41.9 %)	13 (21 %)	10 (16.1 %)	Fisher exact p = 0.08

tions (vs. 46.8 % in the group with *EZH2* wildtype). As the authors noted, parallel ctDNA/tissue detection of *EZH2* mutations allowed for better evaluation of the spatial heterogeneity of the mutational burden. This was deemed a promising tool to tailor targeted therapies and to improve results obtained with frontline chemoimmunotherapy.

At 18 months, 89.3 % of patients were progression-free. To date, no impact of the *EZH2* mutation status on PFS has been demonstrated. The hematological safety profile was acceptable for an R-CHOP-based regimen. Dose reductions of vincristine led to improvement of gastrointestinal hypomotility and peripheral neuropathy.

Odronextamab in relapsed/refractory FL

Patients with relapsed/refractory FL often require multiple lines of therapy, with survival decreasing with each line. The CD20xCD3 bispecific antibody odronextamab has shown compelling efficacy and a generally manageable safety profile in heavily pretreated patients with relapsed/refractory FL grade 1–3a in the open-label, multicohort phase II ELM study [6]. Odronextamab 80 mg was administered intravenously on days 1, 8 and 15 of cycles 2–4 after step-up in cycle 1. From cycle 5 onward, odronextamab maintenance consisted of 160 mg Q2W; this was followed by Q4W administration in patients who had achieved CR for ≥ 9 months. The study population was heavily pretreated and highly refractory; they had received ≥ 2 lines of therapy, including an anti-CD20 antibody and an alkylator. Villasboas et al. presented the results of the second prespecified analysis for 128 patients after a median of 19.4 odronextamab treatment cycles [7].

Odrenextamab continued to induce high CR rates. The ORR was 80.5 %, and CR was achieved in 73.4 %. At 12 and 24 months, CR was maintained in 75.8 % and 48.5 %, respectively. Median duration of response and median duration of CR was 22.6 and 23.7 months, respectively. Median OS had not been reached; at 24 months, 69.3 % of patients were alive. In patients with CR, median OS had not been reached at the time of the analysis, while this was 18.4 months in the cohort that obtained partial response (PR). Likewise, median PFS was considerably longer for patients with CR than for those with PR (27.5 vs. 8.0 months). In the total group, median PFS was 20.7 months, with 12-month and 24-month rates of 65.9 % and 45.0 %, respectively.

The safety profile of odronextamab treatment was generally consistent with previous reports. CRS occurred in 56.3 %, neutropenia in 39.8 % and infusion-related reactions in 28.9 %. Median time to CRS onset was 19.7 hours, and CRS events lasted for a median of 2 days. Almost all cases were classified as grade 1 or 2. Treatment-emergent infections of any grade occurred in 79.7 % of patients. COVID-19 infections were reported in 35.9 % and were grade 5 in eight individuals, which is reflective of a study conducted during the pandemic in a population with increased underlying risk for infections. Treatment-related adverse events (TRAEs) led to dose reduction and treatment discontinuation in 9.4 % and 7.8 % of patients, respectively. Patient-reported overall quality-of-life scores were maintained from baseline through week 50. The three randomized phase III trials OLYMPIA-1 (NCT06091254), OLYMPIA-2 (NCT06097364) and OLYMPIA-5 are currently evaluating odronextamab in earlier treatment lines in patients with FL.

First data on epcoritamab

The pivotal EPCORE™ NHL-1 study was designed to explore the efficacy and safety of epcoritamab, a subcutaneously administered CD3 x CD20 bispecific antibody, in patients with relapsed/refractory CD20-positive mature B-cell neoplasms after ≥ 2 prior treatment lines including ≥ 1 anti-CD20 antibody, an alkylating agent or lenalidomide. At ASH 2023, first data after a median follow-up of 17.4 months were reported from the EPCORE™ NHL-1 FL dose-expansion cohort that included 128 patients [8]. One third of them had previously been treated with ≥ 4 lines, and 42 % had developed progression within 24 months of the initiation of first-line chemoimmunotherapy. Seventy percent were double refractory to both anti-CD20 therapy and an alkylating agent. After step-up in cycle 1, epcoritamab 48 mg was administered until disease progression or unacceptable toxicity.

ORRs and CR rates were found to be high regardless of patient subgroup (**Figure 2**). In the full analysis set, 82 % achieved remission, with 63 % experiencing CR. Responses occurred early on and were deep and durable. Median duration of response had not been reached yet, which also applied to median OS and median time to next treatment. MRD negativity by clonoSEQ® was obtained in 67 % of patients. Median PFS was 15.4 months and had not been reached in the groups achieving CR and MRD negativity.

Common TEAEs such as CRS, injection site reactions and fatigue were mostly low-grade. Grade ≥ 3 TEAEs were reported in 38 % of patients. Neutropenia occurred in 29 %, with grade 3/4 events observed in 26 %. TEAEs led to treatment discontinuation in 19 % of patients; half of these were due to COVID-19. The study contained a C1 optimization cohort (n = 50). Compared to the pivotal cohort, this group received an additional dosing step before the first full dose in cycle 1. Optimization was shown to substantially reduce the risk and severity of CRS.

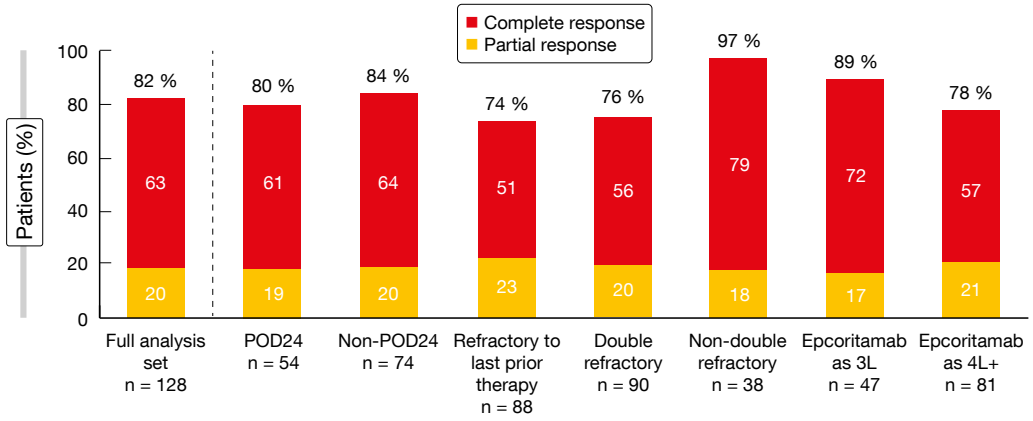


Figure 2: High overall response rates and complete remission rates with epcoritamab regardless of subgroup; POD24: progression within 24 months of first-line chemoimmunotherapy

Promising findings for pirtobrutinib

Results from the phase I/II BRUIN study highlight the potential of the non-covalent BTK inhibitor pirtobrutinib in the setting of relapsed/refractory FL. BRUIN is assessing pirtobrutinib in patients with various B-cell malignancies. At ASH 2023, Shah et al. presented data from the FL cohort of the study (n = 48) [9]. These patients were pretreated with a median of 3 lines, and 46 % had FLIPI scores of 3–5. More than four nodal sites were involved in 40 %.

Pirtobrutinib demonstrated promising efficacy despite massive pretreatment. Half of all patients responded, with 14.6 % and 35.4 % achieving CR and PR, respectively. Four patients had received prior covalent BTK inhibitor therapy: 3 of these obtained PR, and 1 had stable disease. Median duration of response and median PFS was 5.5 and 5.8 months, respectively. Median OS had not been reached yet. At 24 months, 70.2 % of patients were alive, and 24.2 % were progression-free.

TRAEs included fatigue, nausea, neutropenia, diarrhea and arthralgia, with all of these occurring mainly at grades 1 or 2, except for neutropenia (all grades, 10.4; grade ≥ 3, 8.3 %). Among AEs of interest that are typical of covalent BTK inhibitors, grade ≥ 3 TRAEs were observed for rash only (all grades, 8.3 %; grade ≥ 3, 2.1 %). Infections were reported in 8.3 %, while bruising, hemorrhage and atrial fibrillation/flutter occurred in 2.1 % each. No cases of hypertension were noted. TRAEs necessitated pirtobrutinib discontinuations and dose reductions in 2.1 % and 8.3 %, respectively.

Quality of life in the ROSEWOOD trial

The open-label, randomized phase II ROSEWOOD study evaluated the next-generation BTK inhibitor zanubrutinib in addition to obinutuzumab compared to obinutuzumab monotherapy in patients with heavily pretreated relapsed/refractory FL grade 1–3a. Prior to enrolment, the study population had received ≥ 2 systemic therapies including an anti-CD20 antibody and an alkylating agent. Indeed, the combination has shown superior efficacy over obinutuzumab alone, with a manageable safety profile [10].

Health-related quality of life, which was assessed using the EORTC QLQ-C30 and the EQ-5D-5L visual analog scale, constituted a secondary endpoint of the study. According to the results of this analysis reported by Trotman et al. at ASH 2023, the patients treated with zanubrutinib plus obinutuzumab (n = 145) derived larger improvements in role functioning and fatigue **(Figure 3)** through week 48 than those receiving single-agent obinutuzumab (n = 72) [11]. While nausea and vomiting were maintained with the combination, worsening occurred with the monotherapy. No differences resulted regarding physical functioning, pain or diarrhea. Also, the EQ-5D-5L scores did not differ in any meaningful way across the treatment arms.

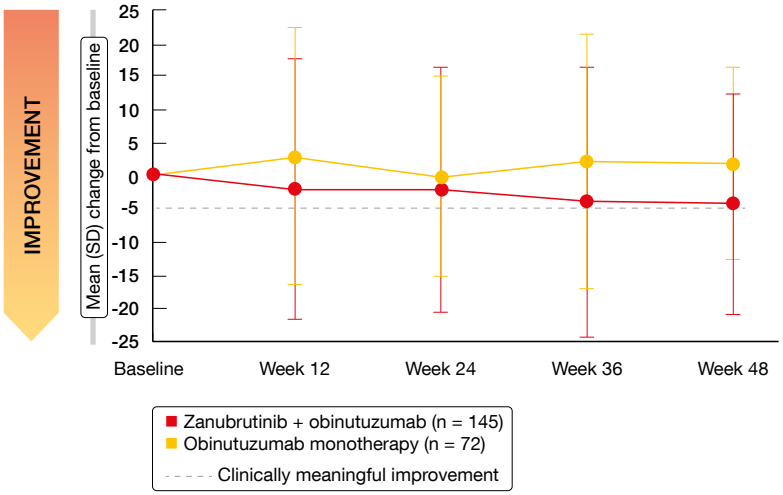


Figure 3: Improvement of fatigue with zanubrutinib plus obinutuzumab vs. single-agent obinutuzumab in the ROSEWOOD trial

A mixed model for repeated measures analysis was used to compare the changes in patient-reported outcome endpoints from baseline to the key clinical cycles. This demonstrated clinically meaningful differences between the arms with respect to global health status/quality of life and fatigue at week 12, as well as role functioning, fatigue and pain at week 24. The authors concluded that these findings, along with the primary clinical outcomes, suggest that zanubrutinib plus obinutuzumab is associated with more pronounced clinical and health-related quality of life benefits than obinutuzumab monotherapy in the setting of relapsed/refractory FL. ■

REFERENCES

1 Morschhauser F et al., Rituximab plus lenalidomide in advanced untreated follicular lymphoma. N Engl J Med 2018; 379(10): 934-947
2 Strati P et al., Long-term follow-up of lenalidomide and rituximab as initial treatment of follicular lymphoma. Blood 2021; 137(8): 1124-1129
3 Strati P et al., Addition of acalabrutinib to lenalidomide and rituximab induces high complete response rates in patients with previously untreated follicular lymphoma: Results of a phase II study. ASH 2023, abstract 983
4 Morschhauser F et al. Preliminary findings of a phase Ib/II trial indicate manageable safety and promising efficacy for mosunetuzumab in combination with lenalidomide in previously untreated follicular lymphoma requiring therapy. ASH 2023, abstract 605
5 Ysebaert L et al., Tazemetostat in combination with R-CHOP in patients with high-risk, frontline follicular lymphoma (Epi-RCHOP): A phase II study from the Lysa. ASH 2023, abstract 297
6 Kim TM et al., Odronextamab in patients with relapsed/refractory follicular lymphoma grade 1-3a: Results from a prespecified analysis of the pivotal phase II study ELM-2. ASH 2022, abstract 949
7 Villasboas JC et al., Results of a second, prespecified analysis of the phase 2 study ELM-2 confirm high rates of durable complete response with odronextamab in patients with relapsed/refractory follicular lymphoma with extended follow-up. ASH 2023, abstract 3041
8 Linton KM et al., Epcoritamab SC monotherapy leads to deep and durable responses in patients with relapsed or refractory follicular lymphoma: First data disclosure from the EPCORE NHL-1 follicular lymphoma dose-expansion cohort. ASH 2023, abstract 1655
9 Shah NN et al., Pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in relapsed/refractory follicular lymphoma: Results from the phase 1/2 BRUIN study. ASH 2023, abstract 3026
10 Zinzani PL et al., ROSEWOOD: A phase II randomized study of zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy in patients with relapsed or refractory follicular lymphoma. J Clin Oncol 2023; 41(33): 5107-5117
11 Trotman J et al., Health-related quality of life in patients with relapsed/refractory follicular lymphoma treated with zanubrutinib + obinutuzumab versus obinutuzumab monotherapy: The ROSEWOOD trial. ASH 2023, abstract 1674

Updated findings in CLL with a focus on BTK- and Bcl-2–targeted therapies

Treatment-naïve disease

Ibrutinib/venetoclax vs. FCR in FLAIR

Personalization of treatment duration of ibrutinib plus venetoclax using measurable residual disease (MRD) was explored in fit patients with previously untreated chronic lymphocytic leukemia (CLL) in the multicenter, randomized, open-label, phase III FLAIR trial. At ASH 2023, Hillmen et al. presented the results for the comparison of ibrutinib plus venetoclax (n = 260) with 6 cycles of fludarabine, cyclophosphamide, and rituximab (FCR; n = 263) [1]. Ibrutinib/venetoclax was administered for 2–6 years depending on the MRD level. Once MRD negativity was achieved, treatment was continued for the same period of time it had taken to obtain undetectable MRD (uMRD). Time to negativity was defined as the first negative result in the peripheral blood that was confirmed by repeated testing after 3 months and then again at 6 months in the peripheral blood and bone marrow. Ibrutinib plus venetoclax was restarted if MRD positivity emerged prior to year 6.

In the arm treated with ibrutinib/venetoclax, as compared to the FCR arm, the rates of complete responses (CRs) and CRs with incomplete count recovery (CRi) were higher at 9 months (59.2 % vs. 49 %) and at any timepoint (92.3 % vs. 71.5 %), as were overall response rates (ORRs) at 9 months (86.5 % vs. 76.4 %) and at any timepoint (95.4 % vs. 83.7 %). uMRD rates in the bone marrow were 61.9 % vs. 40.3 %. The majority of patients treated in the experimental arm eventually met the MRD stopping criteria, with the respective percentages rising from 50 % at 27 months to 72.9 % at 51 months. This differed according to the IGHV mutation status, as a higher proportion of patients with unmutated IGHV stopped treatment at 51 months compared to the mutated group (83.0 % vs. 60.4 %).

Significant OS and PFS benefits

Regarding the primary endpoint, which was progression-free survival (PFS), the analysis yielded an 87 % improvement for ibrutinib/venetoclax vs. FCR after a median follow-up of 43.7 months (**Figure 1**). PFS rates at three years were 97.2 % vs. 76.8 % (HR, 0.13; $p < 0.0001$). In addition, ibrutinib/venetoclax gave rise to a significant overall survival (OS) advantage with a 69 % reduction in mortality risk (HR, 0.31; $p < 0.005$) despite most patients receiving targeted agents as subsequent therapies in the FCR arm. The benefit of the experimen-

tal regimen was most obvious in the group with unmutated IGHV; here, the 3-year PFS rates were 98.3 % vs. 70.9 % (HR, 0.07; p < 0.001), and the 3-year OS rates were 99.2 % vs. 93.9 % (HR, 0.23; p = 0.022). At the same time, no differences resulted regarding PFS or OS in the IGHV-mutated subgroups, although the trends favored MRD-guided ibrutinib/venetoclax. Significant advantages of the MRD-guided targeted approach were observed in patients with ATM (11q) deletion, trisomy 12, 13q deletion and normal karyotype. Notably, no patient with 11q deletion has relapsed or died in the study to date.

Ibrutinib/venetoclax was well tolerated, and no unexpected toxicities occurred. While serious AEs of the blood and lymphatic system were more common with FCR (31 % vs. 5.2 %), serious cardiac AEs occurred more frequently with ibrutinib/venetoclax (10.7 % vs. 0.4 %). The incidence of secondary malignancies was twice as high in the FCR arm as in the ibrutinib/venetoclax arm (5.4 % vs. 2.6 % per 100 person-years). Six deaths in the FCR arm and one death in the ibrutinib/venetoclax arm were attributed to treatment. As the authors noted, the exceptional results seen with ibrutinib/venetoclax support the use of MRD to guide duration of therapy to maximize outcomes.

Venetoclax-based combinations: GAIA/CLL13

Updated findings from the phase III GAIA/CLL13 study that assessed venetoclax combinations in the first-line setting were reported at ASH 2023 [2]. This four-arm study investigated rituximab/venetoclax (RV), obinutuzumab/venetoclax (GV), obinutuzumab/ibrutinib/venetoclax (GIV) and chemoimmunotherapy (CIT) that comprised FCR in patients ≤ 65 years or bendamustine-rituximab (BR) in patients > 65 years. RV and GV were administered for a maximum of 12 months. GIV was given in an MRD-guided manner, with patients not achieving uMRD at 15 months receiving ibrutinib maintenance for up to 36 cycles. The uMRD rate at 15 months and PFS constituted the primary objective of the GAIA/CLL13 trial. Overall, 926 treatment-naïve, fit individuals without *TP53* aberrations were included. Almost all patients treated with RV and GV stopped treatment after 1 year. In the GIV and CIT groups, early discontinuation rates were 13.4 % and 18.5 %, respectively. Only 6.5 % of patients treated with GIV required ibrutinib maintenance due to MRD persistence.

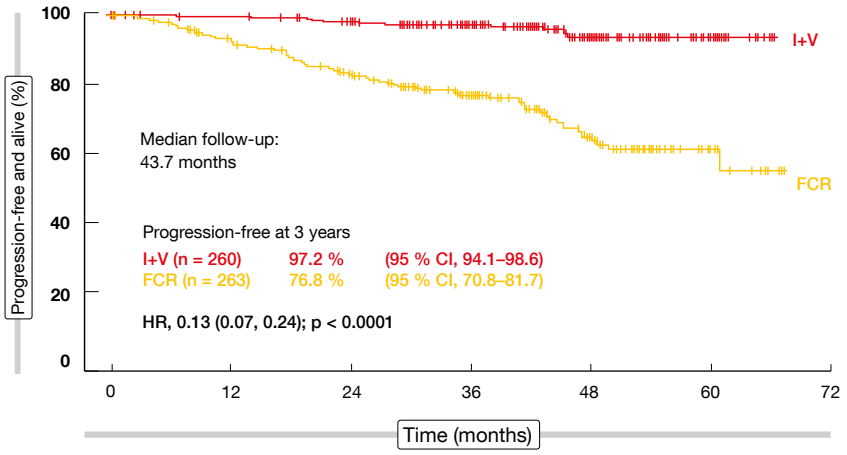
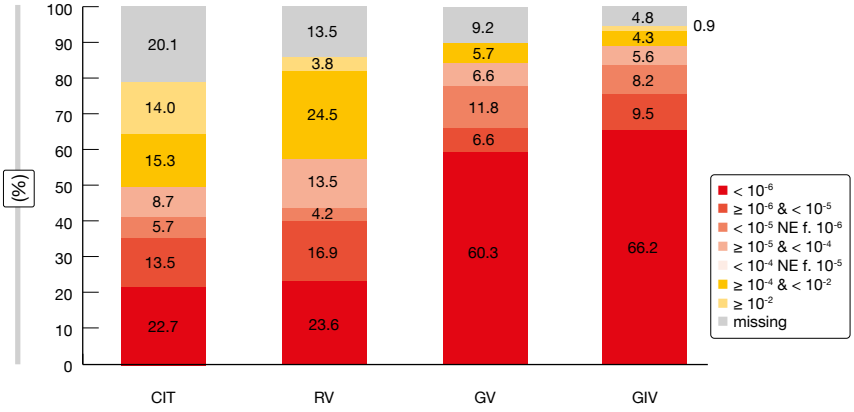


Figure 1: Primary endpoint of the FLAIR study: progression-free survival for ibrutinib/venetoclax vs. FCR

After a median observation time of 50.7 months, GIV showed superior PFS compared to CIT (HR, 0.30; p < 0.001) and RV (HR, 0.38; p < 0.001). Similarly, GV was significantly more effective than CIT (HR, 0.47; p < 0.001) and RV (HR, 0.57; p = 0.001). At 4 years, the PFS rates for GIV, GV, RV and CIT were 85.5 %, 81.8 %, 70.1 % and 62.0 %, respectively. In patients with unmutated IGHV, PFS was longer with GIV than with GV (HR, 0.58; p = 0.025), RV (HR, 0.40; p < 0.001) and CIT (HR, 0.27; p < 0.001). In contrast, no significant differences were observed between GIV and GV in patients with mutated IGHV. OS did not differ across the four treatment arms; the 4-year OS rates ranged from 93.5 % to 96.2 %.

Time to next treatment (TTNT) was significantly prolonged with GIV vs. CIT (HR, 0.17; p < 0.001), GIV vs. RV (HR, 0.27; p < 0.001), GV vs. CIT (HR, 0.34; p < 0.001), and GV vs. RV (HR, 0.54; p = 0.017). The overall rates of patients requiring subsequent therapies were low in the venetoclax-treated arms in spite of the study treatment being limited to one year. Second-line treatments included BTK inhibitors and/or venetoclax in > 90 % of patients. TTNT from the start of second-line therapies was longest in those receiving BTK inhibition plus venetoclax. uMRD at month 15 at the < 10^{-6} threshold according to NGS was most pronounced with GIV (66.2 %) and GV (60.3 %; **Figure 2**). For RV and CIT, this was considerably lower at 23.6 % and 22.7 %, respectively. A landmark analysis assessing the correlation



CIT, chemoimmunotherapy; RV, rituximab/venetoclax;
GV, obinutuzumab/venetoclax; GIV, obinutuzumab/ibrutinib/venetoclax

Figure 2: uMRD rates at month 15 of the GAIA/CLL13 trial with various venetoclax-based combinations and chemoimmunotherapy

between MRD status and PFS in patients treated with GV and GIV showed that patients with uMRD < 10^{-6} had significantly longer PFS than those achieving uMRD levels ≥ 10^{-6} and 10^{-4}. Similar correlations were obtained for the RV- and CIT-treated groups. In patients who obtained uMRD 10^{-6}, PFS did not differ according to the depth of response (i. e., CR vs. PR), which suggests that the clinical response status is of limited prognostic significance in the setting of deep MRD responses.

Adverse events (AEs) and grade 3–5 AEs were most frequent in the CIT group. Among the venetoclax regimens, the triple combination gave rise to the highest rate of infections per 1,000 patient-months, which also applied to cardiac AEs and hypertension, although the absolute numbers were relatively low. The authors concluded that NGS-based MRD detection < 10^{-6} further improves risk stratification and can be used for early identification of patients with very long PFS.

GLOW: update at 57 months

The randomized phase III GLOW study was initiated to evaluate fixed-duration ibrutinib plus venetoclax in untreated patients aged ≥ 65 years or < 65 years with CIRS > 6 or creatinine clearance < 70 mL/min. While 106 patients were treated with ibrutinib/venetoclax for 12 cycles, the control arm comprising 105 individuals received chlorambucil/obinutuzumab for 6 cycles. Updated clinical outcomes were presented at ASH 2023 after a median follow-up of 57.3 months [3].

Ibrutinib/venetoclax PFS continued to improve PFS compared to chlorambucil/obinutuzumab, reducing the risk of progression or death by 74 % (HR, 0.256; p < 0.0001). The estimated 54-month PFS rates were 66.5 % vs. 19.5 %. Patients treated with ibrutinib/venetoclax fared comparatively better regarding PFS irrespective of the IGHV or MRD status at the end of treatment. At 42 months post treatment, the PFS rates in the ibrutinib/venetoclax arm remained high at 78 % and 70 % for patients with and without uMRD, respectively. In the control arm, this was 44 % vs. 6 %. Within the experimental arm, achieving uMRD at the end of treatment appeared to be more critical for long-term PFS in patients with unmutated IGHV than in those with mutated IGHV. In the unmutated group, the 42-month PFS rates were 78 % and 50 % for patients with and without uMRD, respectively, while these rates did not differ in the mutated IGHV group (91 % and 92 %, respectively).

At the end of treatment with ibrutinib/venetoclax, uMRD was present in 54.7 %. Over time, the rates declined, although approximately two thirds of patients retained uMRD over three years. An analysis of uMRD dynamics according to IGHV status showed that the maximum uMRD rate was approximately 40 % in patients with mutated IGHV and remained stable for three years after treatment completion. In those with unmutated IGHV, on the other hand, the uMRD rate was approximately 60 % at the end of treatment but decreased thereafter, with half of patients losing their remission status. TTNT was significantly longer in the experimental arm, resulting in an 82 % reduction in the risk of requiring second-line therapy (HR, 0.185; p < 0.0001). The 54-month TTNT rates were 87.9 % vs. 54.0 %. Likewise, treatment-free survival was significantly prolonged (54-month rates, 75.6 % vs. 34.5 %; HR, 0.303; p < 0.0001).

The ibrutinib-based treatment continued to improve OS at the prolonged follow-up, reducing the risk of death by 55 % compared to chlorambucil/obinutuzumab (HR, 0.453; p = 0.0038). At 54 months, the OS rates were 84.5 % vs. 63.7 %. Nineteen deaths had occurred in the ibrutinib/venetoclax arm vs. 39 in the chlorambucil/obinutuzumab arm after the 57-month follow-up. Three vs. 13 of these were due to post-treatment infections, and 2 vs. 7 were due to second primary malignancies (SPMs). SPMs occurred in 13.2 % vs. 17.1 % and mainly consisted of non-skin cancers (9.4 % vs. 11.4 %). Hematologic malignancies emerged in 3.8 % vs. 1.0 %.

Long-term results from ELEVATE-TN

Previous analyses from the randomized phase III ELEVATE-TN trial at a median follow-up of 28.3, 46.9 and 58.2 months have established the superiority of the combination of acalabrutinib and obinutuzumab over chlorambucil/obinutuzumab in patients with treatment-naïve CLL [4-6]. The study population was aged ≥ 65 years or > 18 to < 65 years with creatinine clearance 30–69 mL/min and CIRS-G score > 6. ELEVATE-TN was designed as a three-arm study; 179

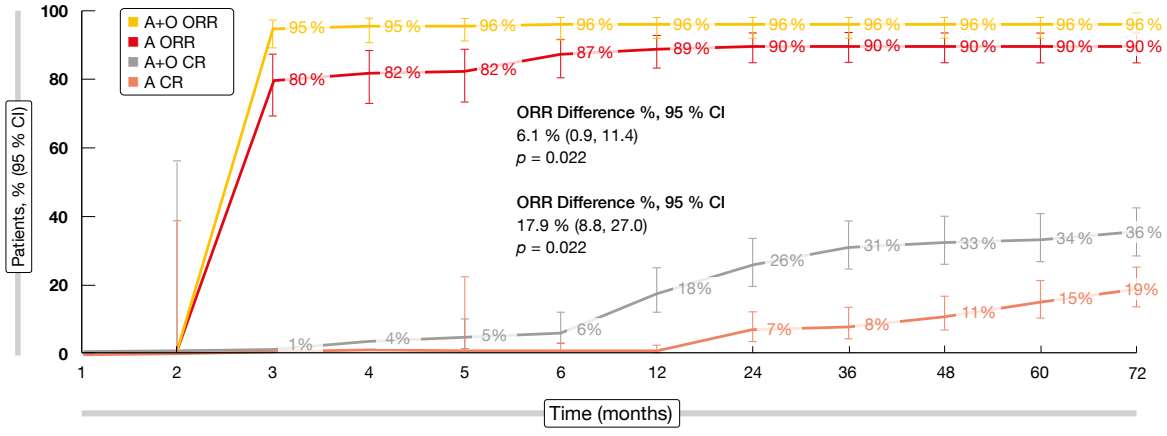


Figure 3: Overall and complete response rates with acalabrutinib/obinutuzumab vs. acalabrutinib alone over time

patients each received either acalabrutinib/obinutuzumab or acalabrutinib monotherapy, while 177 were treated with chlorambucil/obinutuzumab. The primary endpoint was PFS with acalabrutinib/obinutuzumab vs. chlorambucil/obinutuzumab. Sharman et al. presented updated results after a 74.5-month follow-up [7]. At that time, almost half of patients treated with chlorambucil/obinutuzumab had crossed over to single-agent acalabrutinib.

After approximately six years, the efficacy and safety of acalabrutinib/obinutuzumab were maintained. Median PFS was significantly longer for the acalabrutinib-containing arms compared to chlorambucil/obinutuzumab ($p < 0.0001$ each), with 72-month rates of 78 %, 62 % and 17 % for acalabrutinib/obinutuzumab, acalabrutinib monotherapy and chlorambucil/obinutuzumab, respectively. A post-hoc comparison across the acalabrutinib-containing arms showed that acalabrutinib/obinutuzumab induced significantly longer PFS than acalabrutinib monotherapy (HR, 0.58; $p = 0.0229$). Obinutuzumab in addition to acalabrutinib resulted in an early ORR benefit *versus* acalabrutinib alone, although the differences between the acalabrutinib/obinutuzumab and acalabrutinib monotherapy arms narrowed over time (**Figure 3**). The analysis revealed an absolute ORR difference of 6.1 %. For CR/CRi, this difference was larger at 17.9 %. Both ORR and CR/CRi rates were significantly higher with the combination ($p = 0.022$ for both comparisons). Moreover, acalabrutinib-treated patients who achieved CR/CRi had significantly longer PFS than those who did not (HR, 0.23; $p < 0.0001$). Median OS had not been reached in any treatment arm and was significantly longer with acalabrutinib/obinutuzumab vs. chlorambucil/obinutuzumab (HR, 0.62; $p = 0.0349$). At 72 months, the OS rates were 87 %, 79 % and 80 %, respectively. In the crossover population, median time to second progression had not been reached; the 72-month PFS2 rate was 54 %.

Furthermore, the scientists assessed the impact of molecular risk factors on outcomes. Patients with unmutated IGHV fared significantly worse when treated with chlorambucil/obinutuzumab, while those receiving acalabrutinib/obinutuzumab or acalabrutinib monotherapy were not impacted by the IGHV status. PFS did not differ according to the presence of del(17p) and/or *TP53* mutation in patients in the acalabrutinib monotherapy arm; here, the addition of obinutuzumab provided no benefit over single-agent acalabrutinib. The safety of the acalabrutinib-based regimens was consistent with previously reported findings [4-6]. AEs of clinical interest such as cardiac events, bleeding, hypertension and infections were similar for acalabrutinib/obinutuzumab and acalabrutinib monotherapy. After the longer follow-up, the incidence of any-grade atrial fibrillation/flutter and any-grade hypertension remained low in both arms. Neutropenia was more common with acalabrutinib/obinutuzumab than with single-agent acalabrutinib (any grade, 34.3 % vs. 12.8 %), with grade ≥ 3 events noted in 30.9 % vs. 11.7 %.

Biomarker subgroup analysis of the SEQUOIA data

In the phase III SEQUOIA study, treatment with the next-generation BTK inhibitor zanubrutinib, as compared to BR, has shown superior PFS in treatment-naïve patients with CLL or small lymphocytic lymphoma (SLL) without del(17p) [8]. Xu et al. performed a biomarker analysis to determine the association between molecular features and PFS in SEQUOIA [9].

Zanubrutinib significantly improved PFS compared to BR regardless of cytogenetic abnormalities that included del(11q), del(13q), trisomy 12 and complex karyotype ≥ 3 ($p < 0.01$). Within the zanubrutinib-treated arm, comparable PFS benefits were observed for patients with or without most of the prognostic biomarkers analyzed. Median PFS in the zanubrutinib arm did not significantly differ between patients with and without IGHV mutation but was significantly improved over the BR arm regardless of the IGHV mutational status. Patients with gene mutations that are associated with poor prognosis such as *ATM*, *BRAF*, *NOTCH1*, and *SF3B1* had significantly better PFS with zanubrutinib than with BR. Overall, this study provides further evidence in favor of zanubrutinib as a highly effective BTK inhibitor for frontline treatment of patients with CLL/SLL.

Sonrotoclax plus zanubrutinib

The highly selective, oral, second-generation Bcl-2 inhibitor sonrotoclax (BGB-11417) has shown > 10-fold potency compared with venetoclax in the preclinical setting [10]. In the ongoing phase I/II BGB-11417-101 study, sonrotoclax is being evaluated as monotherapy, in combination with zanubrutinib, and in combination with obinutuzumab with or without zanubrutinib in patients with B-cell malignancies. Tam et al. reported preliminary results for sonrotoclax at two doses in addition to zanubrutinib in a treatment-naïve all-comer population with CLL/SLL [11]. Sonrotoclax 160 mg OD plus zanubrutinib was administered in 51 patients and sonrotoclax 320 mg OD plus zanubrutinib in 56 patients, with 8–12 weeks of zanubrutinib monotherapy preceding sonrotoclax dosing that included a daily or weekly ramp-up schedule. Overall, this was a poor-risk study population. Ten percent were aged ≥ 75 years, and 26 % showed del(17p) and/or *TP53* mutation. Approximately one third had increased tumor lysis syndrome (TLS) risk.

Both doses of sonrotoclax in combination with zanubrutinib proved safe and well tolerated. At the time of the analysis, almost all patients remained on treatment. Contusion and neutropenia represented the most common AEs. With the exception of neutropenia and hypertension, AEs were mostly grade 1 and 2. Only one patient required dose reduction due to neutropenia; 17 % received transient treatment with G-CSF. Febrile neutropenia developed in 2 % and resolved without sequelae. Hypertension was not accompanied by any clinical symptoms. No clinical or laboratory TLS occurred with weekly or daily ramp-up. None of the patients developed atrial fibrillation. Diarrhea was mostly grade 1 and did not require any dose reductions. The dose reduction and discontinuation rates of sonrotoclax were low at 5.3 % and 1.1 %, respectively, in the total population.

The analysis revealed promising efficacy of sonrotoclax plus zanubrutinib. All of the patients responded by weeks 24 and 48, with depth of response improving over time (**Figure 4**). At 48 weeks, the CR rates for sonrotoclax 160 mg plus zanubrutinib and sonroto-

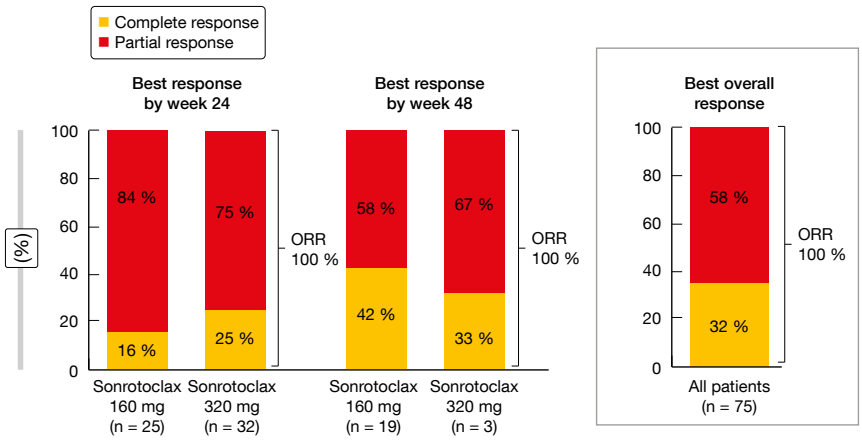


Figure 4: Complete and partial responses observed for sonrotoclax plus zanubrutinib

clax 320 mg plus zanubrutinib were 42 % and 33 %, respectively. High uMRD rates were achieved at both dose levels, although a trend was seen for higher uMRD rates with the 320 mg dose. uMRD4 was achieved in 48 % and 78 % with the 160 mg and 320 mg doses, respectively, at week 24. Again, responses deepened over time. At a median follow-up of 9.7 months, no patient had experienced progression or died at either sonrotoclax dose level. Based on these data, sonrotoclax 320 mg was selected for the phase III study investigating sonrotoclax plus zanubrutinib in patients with treatment-naïve CLL/SLL.

Relapsed/refractory disease

MRD-guided triple combination: CLL2-BAAG

Patients after 1–4 prior treatment lines were included in the phase II CLL2-BAAG study that evaluated an MRD-guided approach for the triple combination of acalabrutinib, venetoclax and obinutuzumab. This was preceded by optional debulking using bendamustine. Obinutuzumab was started in cycle 1, acalabrutinib in cycle 2 and venetoclax in cycle 3 with initial ramp-up. After 6 cycles, the patients entered the maintenance phase that included a reduced obinutuzumab administration schedule, while the other two agents were continued in an unchanged manner. The duration of maintenance therapy was determined by the MRD status, as patients with uMRD at two consecutive measurements could stop treatment.

At the time of the analysis reported at ASH 2023, all patients were off treatment after a median observation time of 34.4 months [12]. The median treatment duration of 14.7 months observed in this study was considerably shorter than the treatment duration with other options usually prescribed in the relapsed/refractory setting, such as continuous BTK inhibition or venetoclax/rituximab. Few patients had to stop treatment early due to AEs (17.8 %); in most cases, discontinuation was prompted by uMRD that was achieved by 76 % of patients. In those who still had detectable MRD after induction, responses deepened with ongoing treatment. This resulted in a best overall uMRD rate of 93.3 %. Patients who were pretreated with BTK inhibitors and/or venetoclax showed a similarly high uMRD rate of 94.4 %. Median time to uMRD in the peripheral blood was 5.4 months. While most patients developed uMRD within the first months of induction treatment, conversion took longer in some cases, which is why the MRD-guided approach was deemed valuable by the scientists as it ensures the suitable amount of treatment in the individual patient. uMRD translated into durable OS and PFS, with 30-month rates of 100 % and 88.2 %, respectively. Despite the shorter duration of treatment, this compared favorably with other options established in the relapsed/refractory setting, all the more since the study population was enriched for patients harboring *TP53* aberrations and those after pretreatment with BTK inhibitors and/or venetoclax.

Moreover, the authors sought to assess whether the addition of circulating tumor DNA (ctDNA)-based MRD measurements to flow cytometry (FCM) contributes to early detection of progression. Overall, 564 paired FCM/ctDNA samples were available. Only five patients have progressed in the study to date. In two of three with CLL-type disease progression, ctDNA was indeed detected before FCM MRD turned positive. In one patient who developed transformation to DLBCL, VDJ ctDNA but not FCM MRD was detected. Taken together, the addition of ctDNA-based analyses to standard FCM MRD assessment appeared to improve the early detection of (molecular) relapses, although the sample sizes were small. ctDNA-based analyses were shown to be particularly beneficial in the setting of more dynamic and advanced disease, as well as in CLL with high-risk genetic features.

ALPINE: 3-year findings

The randomized phase III ALPINE trial was initiated to perform a head-to-head comparison of zanubrutinib 160 mg BID (n = 327) and ibrutinib 420 mg OD (n = 325) in patients with relapsed/refractory CLL/SLL after ≥ 1 systemic treatment. Approximately 23 % in each arm had deletion 17p and/or *TP53* mutation, and bulky disease was present in approximately 45 %. As previously reported, zanubrutinib demonstrated significantly improved PFS compared to ibrutinib, with PFS rates of 78.4 % vs. 65.9 % at 24 months (HR, 0.65; p = 0.0024) [13].

The extended findings presented by Brown et al. at ASH 2023 showed sustained PFS benefit of zanubrutinib [14]. After a median follow-up of 39.0 months, the 36-month PFS rates were 64.9 % vs. 54.8 %, which translated into a 32 % risk reduction (HR, 0.68; p = 0.0011). Zanubrutinib outperformed ibrutinib with respect to PFS across all subgroups including patients with del(17p)/*TP53* mutation; in this population, the 36-month PFS rates were 58.6 % vs. 41.3 % (HR, 0.52; p = 0.0047). Furthermore, the PFS benefit was consistent across multiple sensitivity analyses. Analyses accounting only for events during active treatment and censoring for new CLL/SLL therapies or for death due to COVID-19 yielded significant risk reductions of 31 % to 34 %. This shows that the PFS advantage observed with zanubrutinib was primarily driven by efficacy and not

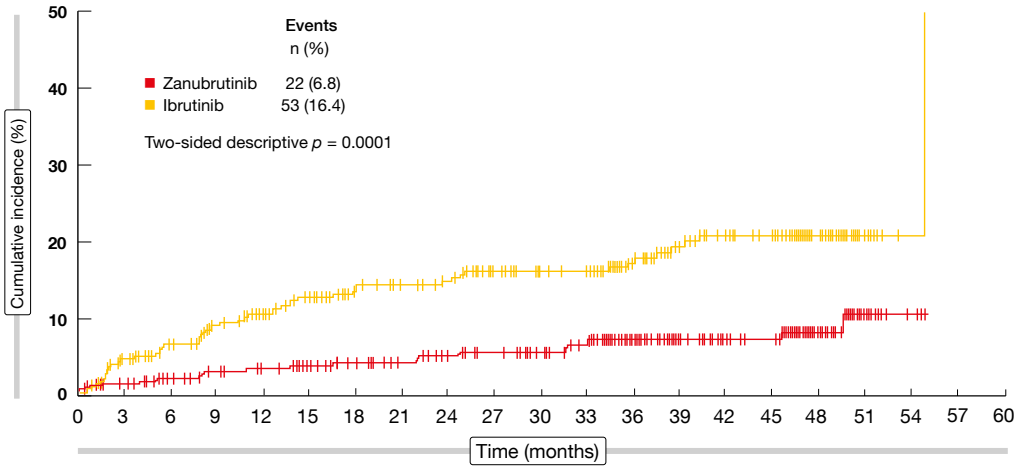


Figure 5: Significantly fewer atrial fibrillation/flutter events with zanubrutinib vs. ibrutinib

by tolerability. Responses including CRs deepened over time in both arms, although comparatively higher proportions of patients treated with zanubrutinib achieved CR/CRi at different timepoints. At 48 months, the ORRs were 90.2 % vs. 82.8 % for zanubrutinib vs. ibrutinib, with CR/CRi rates of 10.4 % vs. 7.1 %. The 36-month OS rates were 82.5 % vs. 79.6 % (HR, 0.75).

The safety profile of zanubrutinib remained favorable compared to that of ibrutinib. Grade 3–5 AE rates were lower (72.5 % vs. 77.5 %), as were those for serious AEs (50.9 % vs. 59.0 %) and AEs leading to dose reduction (14.5 % vs. 18.2 %), treatment discontinuation (19.8 % vs. 26.2 %), and hospitalization (46.3 % vs. 55.6 %). Zanubrutinib gave rise to lower rates of cardiac AEs (24.7 % vs. 34.6 %) and serious cardiac AEs (3.4 % vs. 9.6 %), as well as cardiac AEs leading to treatment discontinuation (0.9 % vs. 4.6 %) and death (0 % vs. 1.9 %). Atrial fibrillation/flutter occurred significantly less frequently with zanubrutinib than with ibrutinib (6.8 % vs. 16.4 %; p = 0.0001; **Figure 5**). Despite similar hypertension rates, the absolute change in systolic blood pressure was lower in the experimental arm. The authors concluded that with more than three years of follow-up, these data reconfirm the improved efficacy of zanubrutinib over ibrutinib and a more favorable safety profile in patients with relapsed/refractory CLL/SLL. To date, ALPINE is the only study to demonstrate PFS superiority in a head-to-head comparison of BTK inhibitors.

Q-TWiST in ALPINE

Using individual patient data from the ALPINE trial, a quality-adjusted time without symptoms of disease and toxicity (Q-TWiST) analysis was conducted to elucidate the benefits and risks of zanubrutinib vs. ibrutinib. The findings reported at ASH 2023 demonstrated an increase in quality-adjusted survival with zanubrutinib compared to ibrutinib in high-risk patients (n = 73 and 71, respectively) [15]. Zanubrutinib treatment brought about a relative Q-TWiST gain of 9.14 %. This difference was statistically significant across the arms (p < 0.001) and exceeded the relative Q-TWiST gain of 3.03 % observed for acalabrutinib vs. ibrutinib in a similar population included in the ELEVATE-RR study [16].

Time before disease progression with toxicity after randomization was slightly longer with zanubrutinib than with ibrutinib (11.54 vs. 11.38 months). As the authors noted, this could be explained in part by better treatment adherence in the experimental arm of the ALPINE study. Overall, these findings that integrate both the length and quality of survival in addition to efficacy and toxicity provide insights that might help to inform clinical decision-making in the treatment of patients with relapsed/refractory CLL.

Performance of ibrutinib in ALPINE vs. ELEVATE-RR

Both zanubrutinib and acalabrutinib were compared to ibrutinib in the randomized, controlled phase III ALPINE and ELEVATE-RR trials. In ALPINE, zanubrutinib demonstrated superior PFS vs. ibrutinib in an all-comer population, whereas in ELEVATE-RR, acalabrutinib showed non-inferior PFS in patients with del(17p) or del(11q) [13, 17]. In the absence of a head-to-head trial, an unanchored matching-adjusted indirect comparison (MAIC) was performed using a comprehensive list of matching variables to compare the performance of the ibrutinib control arms across ALPINE and ELEVATE-RR. To obtain comparable populations, the high-risk subgroup from ALPINE, i.e., 123 patients with del(17p) or del(11q), was matched against aggregated data from 265 patients in the ibrutinib arm of the ELEVATE-RR trial.

After population adjustment, no statistically significant differences were observed between the ibrutinib arms of the two studies in terms of PFS according to independent review (HR, 0.80; p = 0.3485) and PFS according to investigators (HR, 1.18; p = 0.4827) [18]. Moreover, no statistically significant differences were noted regarding OS (HR, 0.91; p = 0.7539). The results were robust across multiple sensitivity analyses. A scenario matching for additional treatment effect modifiers and prognostic factors also generated results consistent with the main analysis.

Richter transformation: tislelizumab/zanubrutinib

Richter transformation, which describes transformation of CLL from an

indolent non-Hodgkin lymphoma into DLBCL or Hodgkin lymphoma, remains a particular unsolved clinical challenge. It occurs in 2–10 % of patients with CLL and involves a median OS of 3–10 months [19-21]. The prospective, multicenter, phase II RT1 trial assessed the combination of continuous zanubrutinib 160 mg BID and the PD-1 inhibitor tislelizumab 200 mg Q3W in patients with Richter transformation. Both induction and consolidation treatment phases comprised six 21-day cycles. Responders were allowed to enter maintenance during which both agents were administered until disease progression. The ORR after induction therapy was defined as the primary endpoint.

At ASH 2023, Al-Sawaf et al. presented the primary analysis of the RT-1 study for 48 patients who constituted the full analysis set [22]. In this group, most had *TP53* alteration and/or unmutated IGHV status and/or complex karyotype. The median number of previous CLL-directed therapies was 3. Prior BTK and/or Bcl-2 inhibition had been administered in the majority of patients. One previous treatment line directed against Richter transformation was allowed; this was the case in 20.8 %. Elevated LDH levels were found in 64.6 %. Almost 96 % of patients had DLBCL transformation. The risk according to CLL-IPI was high or very high in 25.6 % and 38.5 %, respectively.

Feasibility of the combined approach

Combined PD-1 checkpoint inhibition and BTK inhibition using tislelizumab and zanubrutinib was shown to be feasible. Infections, which predominantly included COVID-19, as well as hematological toxicities and gastrointestinal AEs were reported most commonly. The majority of AEs were grade 1 or 2. Apart from three cases of fatal sepsis (5.3 %), no grade 5 AEs occurred. No atrial fibrillation was reported. Hypertension worsened in three patients (grade 1–3), and five cases of hematoma occurred. Potentially immune-related events included two cases of hypothyroidism and five cases of liver enzymes increases.

The primary endpoint of the study was met, with an ORR of 58.3 % (**Figure 6**). Almost 19 % of patients developed CR. At a median observation time of 13.9 months, 19 patients were still on treatment, and most of them had entered the maintenance phase. Median duration of response had not been reached yet, with 70.6 % of patients responding at 6 months. Likewise, median OS had not been reached, while median PFS was 10.0 months. The 12-month OS rate was 74.7 %, and the 12-month PFS rate was 46.9 %.

Subsequent therapies mainly included chemo(immuno)therapy that was administered in 50.0 %. Nineteen percent of patients went on to receive consolidative stem cell transplantation. At present, longer post-transplant follow-up is required to definitely assess long-term outcomes in these patients, although this approach appears feasible. Median TTNT was 12.5 months, with a 12-month TTNT rate of 50.2 %. Furthermore, analyses were conducted to identify predictors of response. Whereas cytogenetic features and patient characteristics were not significantly associated with the ORR, factors associated with PFS included severe constitutional symptoms at presentation, ECOG > 0 and elevated levels of LDH, thymidine kinase and serum β2-microglobulin (> 3.5 mg/L). However, the effect sizes were narrow, and these data are preliminary. A comprehensive workup of all samples is ongoing to enable the identification of patients who might benefit from checkpoint-inhibitor–based treatment. The protocol of the RT1 study has recently been amended to further improve outcomes in an additional cohort treated with tislelizumab plus zanubrutinib and sonrotoclax.

BRUIN study: pirtobrutinib after covalent BTK inhibition

Treatment with covalent BTK inhibitors is eventually discontinued in the vast majority of patients due to progression or intolerance [23, 24]. Limited treatment options in this setting represent a major unmet medical need in the management of patients with CLL/SLL. Venetoclax-based regimens are frequently used after failure of covalent BTK inhibitors, which leads to an increasing number of patients who are refractory both covalent BTK and Bcl-2 inhibition. In light of poor outcomes, additional treatment options are called for [25].

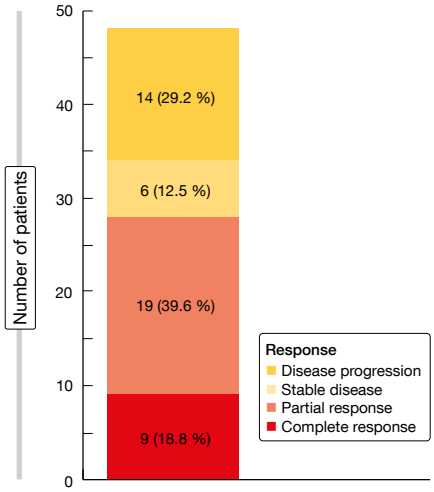


Figure 6: Responses obtained with tislelizumab plus zanubrutinib in the setting of Richter transformation

The phase I/II BRUIN study evaluated the highly selective, non-covalent BTK inhibitor pirtobrutinib in 282 patients pretreated with covalent BTK inhibition. Among these, 154 were Bcl-2-inhibitor–naïve (BCL2i-N), while 128 were Bcl-2-inhibitor–exposed (BCL2i-E). The median number of prior lines of systemic therapy was 3 and 5 for the BCL2i-N and BCL2i-E groups, respectively. Also, greater proportions of the Bcl-2-inhibitor–pretreated patients had undergone CAR-T cell therapy (12 % vs. 1 %) and allogeneic stem cell transplantation (5 % vs. 1 %). After the initial dose escalation evaluating pirtobrutinib doses of 25 to 300 mg OD, the expansion phase of the BRUIN study investigated the recommended phase II dose of 200 mg OD. Woyach et al. reported results after a median follow-up of 30 months [26].

According to this update, pirtobrutinib continued to demonstrate clinically meaningful and durable efficacy. The ORR including partial response with lymphocytosis was 81.6 % in all patients, with CRs resulting in 1.8 %. Almost all patients achieved some decrease in lymph node size. A subgroup of 19 individuals after only one therapy prior to pirtobrutinib showed an ORR of 89.5 %. In the BCL2i-N and BCL2i-E cohorts, the ORRs were similar at 83.1 % and 79.7 %, respectively, although CRs were found in the BCL2i-N cohort only (**Table 1**). Consistent ORR benefits emerged across subgroups in both BCL2i-N and BCL2i-E patients. How-

TABLE 1
Efficacy of pirtobrutinib in BTK-inhibitor–pretreated patients without (left) and with (right) Bcl-2 inhibitor pretreatment

	BCL2i-N (n = 154)	BCL2i-E (n = 128)
Overall response rate including PR-L, %	83.1	79.7
Best response, n (%)		
Complete response	5 (3.2)	0 (0)
Nodular partial response	2 (1.3)	0 (0)
Partial response	108 (70.1)	88 (68.8)
Partial response with lymphocytosis (PR-L)	13 (8.4)	14 (10.9)

ever, within the BCL2i-N cohort, there was a trend toward a lower ORR for patients with *PLCg2* mutation; this also applied to the BCL2i-E group that additionally showed a trend toward a decreased ORR in the presence of IGHV mutation. Responses were increased in the BCL2i-E patients who featured del(17p) and/or *TP53* mutation.

While median OS had not been reached in the total group, median PFS was 19.4 months. At 24 months, 73.2 % of patients were alive, and 38.6 % were progression-free. In the BCL2i-N and BCL2i-E cohorts, median PFS was 23.0 and 15.9 months, respectively, while median OS had not been reached in either cohort and the 24-month OS rates were 83.1 % and 60.6 %, respectively. This indicated the availability of effective subsequent options for the BCL2i-N cohort.

Pirtobrutinib treatment was well tolerated, with relatively low overall rates of significant toxicity. Bruising was the most common treatment-related AE (TRAE) of interest (any grade, 19.1 %; grade 3/4, 0 %), followed by infections (any grade, 12.8 %; grade 3/4, 4.3 %). Atrial fibrillation/flutter occurred in 1.4 % (grade 3/4, 0.7 %). Similar safety profiles were seen across the BCL2i-N and BCL2i-E cohorts. Only four and three individuals in the BCL2i-N and BCL2i-E cohorts, respectively, discontinued treatment due to TRAEs. In nine and two patients, respectively, TRAEs necessitated dose reduction. As the authors concluded, these results suggest that continuation of BTK pathway inhibition is an important sequencing approach in the treatment of patients with CLL/SLL.

Pirtobrutinib plus venetoclax ± rituximab

Another pirtobrutinib-based approach explored in the BRUIN study is 2-year, fixed-duration combination treatment with pirtobrutinib/venetoclax (PV, n = 15) and rituximab/pirtobrutinib/venetoclax (PVR; n = 10). While prior covalent BTK inhibition was permitted, prior venetoclax or other Bcl-2 inhibitors were not. Pirtobrutinib and venetoclax were given for 24 cycles. Rituximab was administered in cycles 1–6.

Findings presented at ASH 2023 showed promising efficacy of pirtobrutinib plus venetoclax ± rituximab [27]. The ORRs for PV and PVR were 93.3 % and 100 %, respectively, with CRs of 46.7 % and 30.0 %, respectively (**Table 2**). Changes in the sum of products of tumor diameters from baseline were similar among BTK-inhibitor–naïve and BTK-inhibitor–pretreated patients. Almost 71 % of patients achieved uMRD at cycle 13, und 87.5 % achieved uMRD at some time during the trial. All but one patient sustained uMRD during subsequent assessments. At 24 months, 79.5 % of the total population were progression-free. Pharmacokinetic analyses demonstrated no apparent drug-drug interactions between pirtobrutinib and venetoclax. Both combination regimens had pharmacokinetic exposures comparable to the monotherapies.

Pirtobrutinib plus venetoclax ± rituximab was well tolerated. No dose-limiting toxicities occurred in either cohort. TRAEs of interest mainly included infections and bruising, and the grade ≥ 3 event rates were very low. Two clinical TLS cases related to venetoclax dose escalation were noted in the PV group, although both patients completed all cycles of combination therapy. The safety profiles were generally similar across the cohorts. At present, the phase III BRUIN CLL-322 trial is comparing PVR with venetoclax/rituximab in previously treated CLL patients (NCT04965493).

TABLE 2
Response rates for pirtobrutinib plus venetoclax ± rituximab

	Pirtobrutinib + venetoclax (n = 15)	Pirtobrutinib + venetoclax + rituximab (n = 10)	Total (n = 25)
Overall response rate, %	93.3	100	96
Best response, n (%)			
Complete response	7 (46.7)	3 (30.0)	10 (40.0)
Partial response	7 (46.7)	7 (70.0)	14 (56.0)
Disease stabilization	1 (6.7)	0	1 (4.0)

Pooled phase Ib/II data on lisaftoclax

The selective Bcl-2 inhibitor lisaftoclax has demonstrated efficacy and tolerability in patients with CLL [28, 29]. Zhou et al. reported updated pooled data for 47 patients with relapsed/refractory CLL who had been treated with lisaftoclax 100 mg, 200 mg, 400 mg, 600 mg and 800 mg OD until disease progression in the phase Ib/II studies APG2575CN001 and APG2575CC101 [30]. A daily ramp-up schedule was used to prevent TLS. Almost half of the population had previously received ≥ 3 treatment lines.

After a follow-up of 14 months, lisaftoclax showed significant efficacy at 400 mg, 600 mg and 800 mg, and potentially at 200 mg. The ORR was 73.3 %, with a CR/CRi rate of 24.4 %. Escalating dose levels were associated with increasing CR/CRi rates; at 400 mg, 600 mg and 800 mg, the rates were 16.7 %, 23.1 % and 33.3 %, respectively. Median OS had not been reached, and the 30-month OS rate was 86.3 %. Median PFS was 18.53 months. Grade 3/4 AEs and serious TRAEs occurred in 68.1 % and 14.9 %, respectively. AEs led to treatment discontinuation in 2.1 %. The analysis identified no significant new or unmanageable safety findings. ■

REFERENCES

1 Hillmen P et al., Ibrutinib plus venetoclax with MRD-directed duration of treatment is superior to FCR and is a new standard of care for previously untreated CLL: Report of the phase III UK NCRI FLAIR study. ASH 2023, abstract 631
2 Fürstenau M et al., First-line venetoclax combinations in fit patients with CLL: 4-year follow-up and NGS-based MRD analysis from the phase 3 GAIA/CLL13 trial. ASH 2023, abstract 635
3 Moreno C et al., First-line fixed-duration ibrutinib plus venetoclax versus chlorambucil plus obinutuzumab: 57-month follow-up from the GLOW study. ASH 2023, abstract 634
4 Sharman JP et al., Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet 2020; 395(10232): 1278-1291
5 Sharman JP et al., Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. Leukemia 2022; 36(4): 1171-1175
6 Sharman JP et al., Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: Five-year follow-up of ELEVATE-TN. J Clin Oncol 2022; 40 (suppl 16; abstr 7539)
7 Sharman JP et al., Acalabrutinib ± obinutuzumab vs obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: 6-year follow-up of ELEVATE-TN. ASH 2023, abstract 636
8 Tam CS et al., Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. Lancet Oncol 2022; 23(8): 1031-1043
9 Xu L et al., Broad superiority of zanubrutinib over bendamustine + rituximab across multiple high-risk factors: Biomarker subgroup analysis in the phase 3 SEQUOIA study in patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma without del(17p). ASH 2023, abstract 1902
10 Hu N et al., Preclinical characterization of BGB-11417, a potent and selective Bcl-2 inhibitor with superior antitumor activities in haematological tumor models. AACR 2020, abstract 3077
11 Tam CS et al., Combination treatment with sonrotoclax (BGB-11417), a second-generation BCL2 inhibitor, and zanubrutinib, a Bruton tyrosine kinase inhibitor, is well tolerated and achieves deep responses in patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma: Data from on ongoing phase 1/2 study. ASH 2023, abstract 327
12 Fürstenau M et al., Long-term remissions with MRD-guided acalabrutinib, venetoclax and obinutuzumab in relapsed/refractory CLL: Follow-up efficacy and ctDNA analysis of the CLL2-BAAG trial. ASH 2023, abstract 203
13 Brown JR et al., Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med 2023; 388(4): 319-332
14 Brown JR et al., Extended follow-up of ALPINE randomized phase 3 study confirms sustained superior progression-free survival of zanubrutinib versus ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma. ASH 2023, abstract 202
15 Levy V et al., Toxicity, progression-free survival, and quality of life of patients treated with zanubrutinib versus ibrutinib: A Q-TWiST analysis from the ALPINE study in relapsed or refractory chronic lymphcytic leukemia. ASH 2023, abstract 1909
16 Seymour JF et al., A quality-adjusted survival (Q-TWiST) analysis to assess benefit-risk of acalabrutinib versus idelalisib/bendamustine plus rituximab or ibrutinib among relapsed/refractory chronic lymphocytic leukemia patients. Blood 2021; 138(suppl. 1): 3722-3724
17 Byrd JC et al., Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: Results of the first randomized phase III trial. J Clin Oncol 2021; 39(31): 3441-3452
18 Shadman M et al., Similar efficacy of ibrutinib arms across ALPINE and ELEVATE-RR in relapsed/refractory chronic lymphocytic leukemia: A matching-adjusted indirect comparison. ASH 2023, abstract 4655
19 Al-Sawaf O et al., Richter transformation in chronic lymphocytic leukemia (CLL)-a pooled analysis of German CLL Study Group (GCLLSG) front line treatment trials. Leukemia 2021; 35(1): 169-176
20 Davids et al., Richter's syndrome in patients with chronic lymphocytic leukemia on novel agent therapy. J Clin Oncol 2017; 35(15 suppl): 7505
21 Moulin et al., Clinical and biological characteristics and outcomes of Richter transformation : A French multicenter study from the Filo Group. Blood 2019; 134 (Supplement_1): 4112
22 Al-Sawaf O et al., Tislelizumab plus zanubrutinib in patients with Richter transformation: primary endpoint analysis of the prospective, multicenter, phase II RT1 trial of the German CLL Study Group. ASH 2023, abstract 204
23 Woyach et al., BTKC481S-mediated resistance to ibrutinib in chronic lymphocytic leukemia. J Clin Oncol 2017; 35(13): 1437-1443
24 Barr PM et al., Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. Blood Adv 2022; 6(11): 3440-3450
25 Mato et al. Outcomes for patients with chronic lymphocytic leukemia (CLL) previously treated with both a covalent BTK and BCL2 inhibitor in the United States: A real-world database study. Clin Lymphoma Myeloma Leuk 2023; 23(1): 57-67
26 Woyach JA et al., Pirtobrutinib in post-cBTKi CLL/SLL: ~ 30 months follow-up and subgroup analysis with/without prior BCL2i from the phase 1/2 BRUIN study. ASH 2023, abstract 325
27 Roeker LE et al., Fixed-duration pirtobrutinib combined with venetoclax ± rituximab in relapsed/refractory chronic lymphocytic leukemia: Updated results, including MRD data, from the BRUIN phase 1b study. ASH 2023, abstract 3269
28 Davids MS et al., Lisaftoclax (APG-2575) safety and activity as monotherapy or combined with acalabrutinib or rituximab in patients with treatment-naïve, relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: initial data from a phase 2 global study. Blood 2022; 140(suppl 1): 2326-2328
29 Ailawadhi S et al., Novel BCL-2 inhibitor lisaftoclax in relapsed or refractory chronic lymphocytic leukemia and other hematologic malignancies: First-in-human open-label trial. Clin Cancer Res 2023; 29(13): 2385-2393
30 Zhou K et al., Updated efficacy and safety results of lisaftoclax (APG-2575) in patients with heavily pretreated chronic lymphocytic leukemia: Pooled analyses of two clinical trials. ASH 2023, abstract 1900

Exploring chemotherapy-free approaches in the treatment of DLBCL

Smart Stop: quadruplet therapy

For decades, the CHOP regimen has been the first-line standard of care for patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL). Significant improvement was achieved through the addition of rituximab (R-CHOP). Ever since, however, multiple clinical trials investigating expanded or alternative treatment regimens have not succeeded in further improving patient outcomes. The Smart Start study assessing rituximab, lenalidomide and ibrutinib was the first study to address newly diagnosed DLBCL with a targeted combination before chemotherapy [1]. This regimen gave rise to an overall response rate (ORR) of 86 %, a complete remission (CR) rate of 36 % and durable responses, thus establishing the potential for the development of biologically driven and non-cytotoxic first-line therapies in the setting of DLBCL.

In order to improve upon Smart Start, the single-center, open-label phase II Smart Stop study was conducted using the LTRA combination, i.e., lenalidomide, the CD19-directed antibody tafasitamab, rituximab, and the second-generation BTK inhibitor acalabrutinib instead of ibrutinib. At

ASH 2023, Westin et al. reported the results for Cohort 1 (n = 30) [2]. After 4 cycles of LTRA, patients who showed CR according to PET/CT received 6 cycles of LTRA, with CHOP being administered for the first 2 cycles only. Those who had partial response (PR), stable disease (SD) or disease progression after the initial 4 cycles were treated with 6 cycles of LTRA plus CHOP. The ORR after 4 cycles of LTRA and the CR rate at the end of therapy constituted the primary endpoints.

This comparison was based on the hypothesis that LTRA for 4 cycles will improve upon the 36 % CR observed in Smart Start, thus enabling the use of less or no chemotherapy. Patients with any subtype of large B-cell lymphoma were eligible. Twenty-five (83 %) had a non-germinal center B-cell (GCB) subtype, while 5 (17 %) had a GCB subtype.

Deep responses despite reduced CHOP

After 4 cycles of LTRA, the CR rate was 63.3 %, which included four of the five GCB patients (**Table 1**). All patients responded to the treatment. Nineteen patients achieved CR and were allocated to 2 cycles of CHOP plus 6 cycles of LTRA, while 11 concurrently received LTRA and CHOP for 6 cycles after failing to achieve CR. The CR of the total group after 6 cycles of LTRA and 2 cycles of CHOP was 93.3 % (**Table 1**). At the time of the analysis, 22 individuals had completed the entire treatment; all of them achieved CR. Seven of the first 10 patients received only 2 cycles of CHOP and remained in ongoing remission at > 9 months. To date, no patient has progressed or died.

The depth of response was assessed using circulating tumor DNA (ctDNA) in 15 patients. Among these, 12 (80 %) achieved CR according to imaging. Five patients (33 %) had undetectable disease burden after 4 cycles of LTRA. In 87 %, a > 2 log-fold reduction was observed. Toxicities of interest reported with LTRA and CHOP included neutropenia (87 %), fatigue (73 %), rash (43 %) and infections (30 %). Rash was manageable with dose reductions and interruptions. Neutropenia was the most common toxicity with the combined regimen (any grade, 80 %) but did not lead to dropouts due to infections.

TABLE 1
Responses to treatment with lenalidomide, tafasitamab, rituximab and acalabrutinib (LTRA) in Smart Stop

Response rate, n (%)	After 4 cycles of LTRA		After 6 cycles of LTRA and 2 cycles of CHOP
	All (n = 30)	GCB (n = 5)	All (n = 30)
Complete response	19 (63.3)	4 (80)	28 (93.3)
Partial response	11 (36.7)	1 (20)	2 (6.7)
Stable disease	0	0	0
Progressive disease	0	0	0
Overall response rate	30 (100)		30 (100)

In their summary, the authors noted that targeted therapies alone are safe and effective as initial first-line treatment in patients with DLBCL, with less than 6 cycles of CHOP appearing feasible in case of response to LTRA with short follow-up. Basically, the Smart Stop study established the feasibility of targeted therapy with reduced chemotherapy and of response-adapted trials evaluating novel combinations. The next stage of the Smart Stop study will assess the efficacy of a completely chemotherapy-free approach involving 6 further cycles of LTRA in patients who have achieved CR after the first 4 cycles.

Mosunetuzumab/polatuzumab vedotin for the unfit

In elderly, unfit or frail patients, first-line standard treatment with R-CHOP is frequently administered at reduced doses such as R-miniCHOP [3], although attenuated regimens are associated with inferior outcomes [4]. This raises the need for approaches that are both less toxic and more efficacious. At ASH 2023, Olszewski et al. presented initial safety and efficacy data from an ongoing phase I/II study evaluating the combination of the CD20xCD3 bispecific antibody mosunetuzumab and the CD79b-directed antibody-drug conjugate polatuzumab vedotin as first-line therapy for elderly and unfit patients (i.e., aged ≥ 80 years or 65–79 years and considered ineligible for chemoimmunotherapy) [5]. Step-up dosing of subcutaneously administered mosunetuzumab in cycle 1 was followed by mosunetuzumab 45 mg on day 1 of cycles 2–8. Patients who achieved PR or SD at the end of this treatment period were allowed to continue for up to 9 additional cycles. Polatuzumab vedotin was administered intravenously on day 1 of cycles 1–6.

The ORR at the time of the primary response assessment after cycle 8 was defined as the primary efficacy endpoint. Other cytokine release syndrome (CRS) mitigation strategies in addition to step-up dosing of mosunetuzumab included pre-medication with dexamethasone, acetaminophen and diphenhydramine. According to the simplified geriatric assessment, only one out of 108 patients (0.9 %) was considered fit; 59.3 % and 39.8 % were classified as unfit and frail, respectively. Multiple comorbidities and polypharmacy were present. The safety and efficacy cohorts comprised 108 and 101 patients, respectively.

Mosunetuzumab/polatuzumab vedotin was shown to induce encouraging response rates and durable CRs. At the

TABLE 2
Response rates observed with mosunetuzumab plus polatuzumab

Response rate, n (%)	End of treatment (n = 101)	Best overall response (n = 101)
Overall response rate	65 (64.4)	81 (80.2)
Complete response	57 (56.4)	66 (65.3)
Partial response	8 (7.9)	15 (14.9)
Stable disease	4 (4.0)	4 (4.0)
Progressive disease	10 (9.9)	4 (4.0)
Not done or missing	22 (21.8)	12 (11.9)

end of treatment, the ORR was 64.4 %, and 56.4 % of patients experienced CR (**Table 2**). The best ORR was 80.2 %, with CRs resulting in 65.3 %. The difference between these two analyses is attributed to 22 patients who were not evaluable at the end of treatment due to adverse events (AEs), death, and subject withdrawal after attaining response. This again reflects the frailty and high comorbidity burden of this study population. Six of 8 patients with PR at the end of treatment continued mosunetuzumab therapy beyond cycle 8, and three of them succeeded in converting to CR. Median duration of CR had not been reached, and 71.4 % remained in remission at 9 months. Similar observations were made with respect to progression-free survival (PFS). Median PFS was 11.9 months; at 12 months, 49.7 % of patients were progression-free. Overall, 63.4 % of patients remained in follow-up without any evidence of progression.

Fatal COVID-19 infections mainly in frail patients

Immunohistochemistry and immunofluorescence analyses based on pretreatment biopsies found no association between the tumor immune cell composition and the treatment response, as the latter was independent of the baseline levels of B cells, cytotoxic T cells, and activated lymphocytes. This suggests that combining a bispecific antibody with an antibody-drug conjugate contributes to mitigating the dependence of responses on these features.

Overall, the safety profile of the combination was consistent with that of the individual drugs. Among mosunetuzumab-related AEs, neutropenia (any grade, 36.1 %) and CRS (any grade, 29.6 %) prevailed. CRS events were mostly grade 1 and 2 and were well managed, with no treatment discontinuations reported due to this AE. Grade 3/4 neutropenia occurred in 30.6 %, although no febrile neutropenia was observed. Serious infections were noted in 25.0 % (grade ≥ 3, 23.1 %). Thirteen of 18 fatal AEs were infections, and 10 (77 %) of these were COVID-19 infections that mostly affected patients who were frail per simplified geriatric assessment. Eighty percent of fatal COVID-19 events occurred during the Omicron waves in 2022. All patients had received at least one dose of COVID-19 vaccine, and seven had undergone COVID-19–specific antiviral treatments.

The authors noted that the number of fatal AEs other than COVID-19 was comparable with those observed in similar patient populations with DLBCL. They concluded that elderly unfit or frail patients with previously untreated DLBCL may be at increased risk of severe complications of COVID-19 infections. At the same time, regimens such as mosunetuzumab/polatuzumab vedotin might help to improve the future treatment landscape for this understudied population. Incorporation of simplified geriatric assessments in clinical trials of elderly unfit or frail patients appeared feasible and beneficial to identify a population for treatment approaches that minimize or eliminate cytotoxic chemotherapy.

Zanubrutinib, rituximab & polatuzumab vedotin

A Chinese study investigated the combination of polatuzumab vedotin, zanubrutinib and rituximab in previously untreated frail and elderly patients (aged > 70 years or 60–69 plus ECOG 2–4) with DLBCL. After 3 cycles of triplet therapy, patients who had CR or PR continued treatment for another 3 cycles, while those with SD or disease progression received second-line agents. The second response assessment at cycle 6 was followed by zanubrutinib monotherapy in case of CR, whereas patients with PR, SD or progressive disease went on to second-line treatment. Polatuzumab vedotin and rituximab were administered intravenously on day 1 of each cycle, while zanubrutinib 160 mg BID was taken on days 1-21 of the 21-day cycles. The ORR after 6 cycles constituted the primary endpoint. At ASH 2023, Ren et al. reported findings for 19 patients, most of whom were aged ≥ 70 years, had IPI scores of 3–5, and Ann Arbor disease stage III-IV [6].

All of the 12 patients who underwent the interim efficacy assessment after 3 cycles responded, with 8 and 4 obtaining CR and PR, respectively. Three patients were evaluable for the primary endpoint; in this group, too, all patients were responders, and all of them achieved CR. After a median follow-up of 114 days, no progression or relapse had occurred. The most common any-grade AEs were decreased neutrophil count (15.8 %) and upper respiratory infection (10.5 %). Lung infections represented the most common grade 3/4 AE. All patients recovered from AEs under best supportive care. The zanubrutinib dose was decreased to 80 mg BID in one individual due to transaminase elevation.

In their summary, the authors noted that the triple combination of polatuzumab vedotin, rituximab and zanubrutinib showed promising efficacy with rapid and deep responses in previously untreated frail and elderly patients with DLBCL. A prospective phase IIb trial is ongoing to further evaluate the triplet regimen as first-line treatment for this population (NCT05940064).

ELM-2: odronextamab

Patient outcomes in the relapsed/refractory DLBCL setting are still poor, and there is an unmet need for novel therapies that provide rapid disease control while improving long-term outcomes. The CD20xCD30 bispecific antibody odronextamab has shown encouraging efficacy and generally manageable safety in heavily pretreated patients with relapsed/refractory DLBCL in the phase I ELM-1 study [7] and the open-label, multicohort, multicenter phase II ELM-2 trial. At the time of the interim analysis of ELM-2, the ORR was 49.2 %, with a CR rate of 30.8 % and median duration of response of 10.2 months [8]. Ayyapan et al. presented the final analysis of the relapsed/refractory DLBCL cohort from the ELM-2 study at ASH 2023 [9].

Patients in this cohort (n = 127) were refractory to or had relapsed after ≥ 2 prior lines of therapy, which included an anti-CD20 antibody and an alkylator. Overall, this was a heavily pretreated, highly refractory population. Fifty-five percent had primary refractory disease, and 86.6 % were refractory to the last line of therapy. Cycle 1 included the step-up to odronextamab 20 mg, while odronextamab 160 mg was administered on days 1, 8 and 15 of cycles 2–4. Finally, maintenance treatment consisted of 320 mg Q2W from cycle 5. Patients who achieved CR for ≥ 9 months in the maintenance phase could transition from biweekly to four-weekly inter-

vals. ORR by independent review was defined as the primary endpoint.

Encouraging efficacy in high-risk individuals

After a median follow-up of 29.9 months, 52.0 % of patients responded, and 31.5 % achieved CR. The median duration of response and CR was 10.2 and 17.9 months, respectively. At 12 and 24 months, CRs persisted in 61.5 % and 47.2 % of patients, respectively. Odronextamab gave rise to encouraging ORRs across high-risk subgroups such as elderly patients and those with transformed and double-hit disease. In the total study group, median PFS was 4.4 months, with 12-month and 24-month PFS rates of 29.6 % and 21.1 %, respectively. Patients who obtained CR fared considerably better with respect to median PFS than those achieving PR (20.4 and 5.8 months, respectively). At 24 months, 47.5 % vs. 18.9 % of complete and partial responders, respectively, were progression-free. Likewise, median OS had not been reached in patients with CR and was 17.0 months in those with PR. In the overall population, median OS was 9.2 months.

Exploratory biomarker analyses demonstrated that PFS was better in patients with undetectable minimal residual disease (MRD) than in those with ctDNA that persisted at day 15 of cycle 4 (HR, 0.27). Even in the absence of CR, there was a marked difference between the cohorts with detectable and cleared ctDNA (**Figure 1**). Moreover, the assessment of PFS by the LymphGen classification indicated that the EZB subtype conferred longer PFS than the other subtypes.

The safety profile of odronextamab therapy was consistent with previous reports. CRS was observed in 55.1 %, although most events were grade 1 (40 %) or 2 (11.7 %) and confined to cycle 1. With supportive measures, they resolved within a median of 2 days. No immune effector cell-associated neurotoxicity syndrome (ICANS) events were reported. Pyrexia occurred in 22.8 % and neutropenia in 20.5 %. Treatment-related AEs led to dose reduction and discontinuation in 3.1 % and 9.4 %, respectively. Any-grade infections emerged in 64.6 %, with COVID-19 observed in 18.1 % that was fatal in 5 patients (3.9 %). Other infection events included pneumonia (14.2 %), upper respiratory tract infection (8.7 %), urinary tract infection (8.7 %), and *Pneumocystic jirovecii* pneumonia (6.3 %). Treatment-related infections prompted permanent discontinuation of odronextamab in 4.7 %. Patient-reported outcomes were collected using the EORTC QLQ-C30 and other instruments throughout the study. According to this analysis, the scores for pain and emotional functioning were maintained or improved from baseline through week 42.

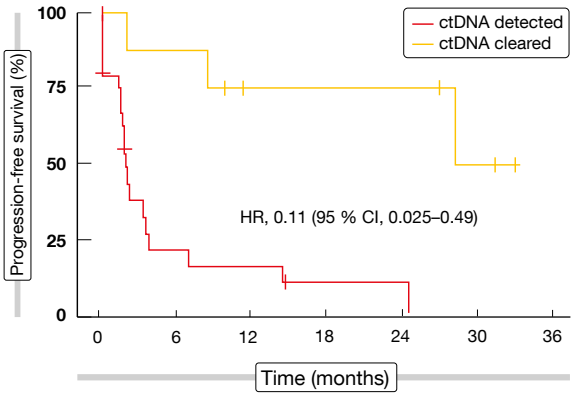


Figure 1: Progression-free survival by ctDNA MRD response in patients without complete remission at day 15 of cycle 4 of odronextamab therapy

Taken together, the final results from the pivotal phase II ELM-2 study confirm highly encouraging clinical activity of odronextamab in patients with heavily pretreated relapsed/refractory DLBCL. Based on these findings, the randomized phase III trials OLYMPIA-3 and OLYMPIA-4 are evaluating odronextamab in patients with previously untreated and relapsed/refractory DLBCL, respectively.

Epcoritamab plus lenalidomide

Avivi et al. reported the first results for the combination of the subcutaneously administered CD3xCD20 bispecific antibody epcoritamab and lenalidomide in patients with CD20-positive, relapsed/refractory DLBCL who were treated in arm 1 of the EPCORE NHL-5 study (n = 35) [10]. They had previously received ≥ 1 anti-CD20 antibody-containing systemic therapy and were ineligible for autologous stem cell transplantation or had failed prior stem cell transplantation; prior CAR T-cell therapy was allowed. This was a high-risk population, as 51 % had R-IPI scores of 3–5 and primary refractory disease was present in 43 %. Prior CAR T-cell therapy had been administered in 23 %. The experimental treatment in arm 1 of the EPCORE NHL-5 trial included twelve 28-day cycles of the combination. Epcoritamab was administered at its full dose of 48 mg on days 15 and 22 of cycle 1 after initial step-up, as well as on days 1, 8, 15 and 22 of cycles 2–3 and on day 1 of cycles 4–12. Lenalidomide 25 mg OD was taken on days 1–21 of all 12 cycles. CRS prophylaxis using diphenhydramine, acetaminophen and corticosteroids was mandatory with the first four epcoritamab doses.

Epcoritamab in combination with lenalidomide induced deep and durable responses. The ORR was 71.9 %, with CR resulting in 53.1 %. ORR and CR rates were fairly consistent across the prespecified high-risk subgroups including patients with advanced age and prior CAR T-cell therapy. Median duration of CR had not been reached at the time of the analysis. MRD negativity was achieved early on, with 83 % of patients showing MRD-negative CR after 2 cycles, and was sustained throughout treatment.

Epcoritamab plus lenalidomide demonstrated a manageable safety profile that was consistent with the established profiles. Grade 3/4 epcoritamab-related treatment-emergent AEs (TEAEs) were observed in 66 %. TEAE-induced delay or interruption of epcoritamab was observed in 80 %, while only 3 % of patients discontinued epcoritamab due to TEAEs that were related to this drug. No grade 5 TEAEs related to epcoritamab occurred. The most common grade ≥ 3 TEAE was neutropenia (51 %), although no neu-

tropenic events led to the discontinuation of epcoritamab. At 69 %, CRS was the most common TEAE; these events were primarily low-grade, and all resolved with tocilizumab and/or corticosteroid treatment. The CRS onset showed predictable timing, with most events occurring after the first full dose.

According to a biomarker analysis, the incidence and severity of CRS were reflected by the cytokine levels, as IL-6 peaked on day 16 of cycle 1, i.e., immediately after the first full dose (**Figure 2**). The analysis revealed similar findings for IL-2 and IFN-γ. One patient developed grade 3 ICANS that resolved after two days. The authors pointed out that these data are the first results of a bispecific antibody in combination with lenalidomide for relapsed/refractory DLBCL and support further exploration of epcoritamab plus lenalidomide in these patients. ■

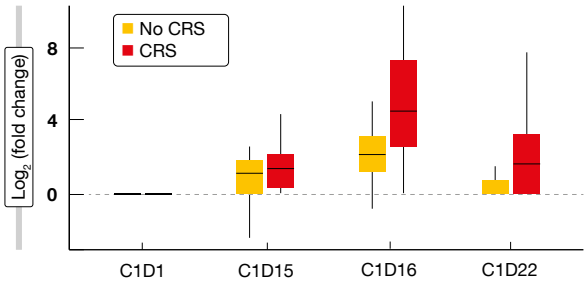


Figure 2: Treatment with epcoritamab plus lenalidomide: peak of the IL-6 levels at day 16 of cycle 1

REFERENCES

1 Westin et al., Smart Start: Rituximab, lenalidomide, and ibrutinib in patients with newly diagnosed large B-cell lymphoma. J Clin Oncol 2023; 41(4): 745-755
2 Westin J et al., Smart Stop: Lenalidomide, tafasitamab, rituximab, and acalabrutinib alone and with combination chemotherapy for the treatment of newly diagnosed diffuse large B-cell lymphoma. ASH 2023, abstract 856
3 Tilly H et al., Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26 Suppl 5: v116-125
4 Al-Sarayfi D et al., R-miniCHOP versus R-CHOP in elderly patients with diffuse large B-cell lymphoma: A propensity matched population-based study. Am J Hematol 2024; 99(2): 216-222
5 Olszewski AJ et al., Mosunetuzumab and polatuzumab vedotin demonstrates preliminary efficacy in elderly unfit or frail patients with previously untreated diffuse large B-cell lymphoma. ASH 2023, abstract 855
6 Ren Y et al., Polatuzumab vedotin, zanubrutinib and rituximab achieved rapid and deep response in previously untreated frail and elderly diffuse large B-cell lymphoma patients. ASH 2023, abstract 1747
7 Bannerji R et al., Odronextamab, a human CD20×CD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial. Lancet Haematol 2022; 9(5): e327-339
8 Kim WS et al., Odronextamab in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL): Results from a prespecified analysis of the pivotal phase II study ELM-2. ASH 2022, abstract 444
9 Ayyapan S et al., Final analysis of the phase 2 ELM-2 study: Odronextamab in patients with relapsed/refractory diffuse large B-cell lymphoma. ASH 2023, abstract 436
10 Avivi I et al., Subcutaneous epcoritamab plus lenalidomide in patients with relapsed/refractory diffuse large B-cell lymphoma from EPCORE NHL-5. ASH 2023, abstract 438

Innovative agents in marginal zone lymphoma and other B-cell malignancies

Relapsed/refractory MZL: sonrotoclax

Relapses are common in patients with marginal zone lymphoma (MZL), and sequential therapy is often necessary. At ASH 2023, Tedeschi et al. reported findings for 22 patients with relapsed/refractory MZL who received the oral second-generation Bcl-2 inhibitor sonrotoclax at different dose levels (i.e., 40 mg, 160 mg, 320 mg, 640 mg OD) in the first-in-human, phase I, multicenter BGB-11417-101 study [1]. Dose expansion started with the 640 mg dose; the 320 mg dose was expanded later to include 10 additional patients.

Ten participants received sonrotoclax 640 mg. Even at this dose level, the maximum tolerated dose was not reached, although pyrexia was more common with the 640 mg dose than with all other doses (40 % vs. 25 %). This also applied to constipation (30 % vs. 17 %), diarrhea (30 % vs. 8 %), and headache (30 % vs. 8 %). No clinical tumor lysis syndrome (TLS) occurred, while two transitory cases of laboratory TLS emerged in patients with high baseline levels of circulating cells, including a patient with a very large spleen that significantly decreased in size with the first dose. Dose interruptions were called for in three patients due to adverse events (AEs), and one patient had to discontinue treatment.

In the efficacy-evaluable cohort, 70 % responded to sonrotoclax 640 mg, with 40 % achieving complete response (CR). Responses proved durable in the 640 mg group; at a median follow-up of 8.7 months, 6 of 10 patients were continuing on treatment. Taken together, sonrotoclax demonstrated promising single-agent activity in the setting of relapsed/refractory MZL.

TABLE
Outcomes observed for pirtobrutinib in heavily pretreated patients with relapsed/refractory MZL

Endpoint	All MZL patients (n = 36)	Prior cBTKi treatment (n = 26)	No prior cBTKi treatment (n = 10)
Overall response rate, %	50.0	46.2	60.0
Complete response, n (%)	1 (2.8)	0 (0.0)	1 (10.0)
Partial response, n (%)	17 (47.2)	12 (46.2)	5 (50.0)
Median duration of response, months	12.7	7.4	Not estimable
Median progression-free survival, months	16.5	9.2	Not estimable
Median overall survival, months	Not estimable	Not estimable	Not estimable

Non-covalent BTK inhibition with pirtobrutinib

Another option under investigation in relapsed/refractory MZL is the non-covalent BTK inhibitor pirtobrutinib. The phase I/II BRUIN study evaluated pirtobrutinib in 36 patients with MZL after a median of three prior systemic treatment lines. Covalent BTK inhibition (cBTKi) had been administered in 72 % of patients, and all of them had received anti-CD20 antibodies. Progression had been the reason for discontinuation of cBTKi therapy in 77 %.

In this heavily pretreated cohort, pirtobrutinib showed encouraging efficacy with an overall response rate (ORR) of 50.0 % in the total cohort; in patients with and without previous cBTKi therapy, the ORRs were 46.2 % and 60.0 %, respectively (**Table**) [2]. Responses lasted for a median of 12.7 months, and median progression-free survival was 16.5 months. For both of these endpoints, the results were improved in cBTKi-naïve patients compared to the cBTKi-pretreated group. Median overall survival had not been reached in any of these cohorts. At 18 months, 81.8 % of all patients were alive, and 46.6 % were progression-free.

Pirtobrutinib was well tolerated. Treatment-related adverse events (TRAEs) required discontinuation and dose reduction in 5.6 % and 11.1 %, respectively. Among TRAEs of interest, bruising and rash were most common (any grade, 25.0 % and 19.4 %, respectively). No grade 3/4 TRAEs occurred with the exception of hypertension (2.8 %). The authors concluded that pirtobrutinib might be a promising chemotherapy-free option after cBTKi pretreatment in patients with relapsed/refractory MZL.

BTK degrader BGB-16673

Disease progression in BTK-inhibitor–treated patients with B-cell malignancies can be due to resistance mutations within BTK that arise on both covalent and non-covalent agents [3, 4]. Consequently, there is a need for new approaches to address the shortcomings of existing BTK inhibitors. The BTK degrader BGB-16673 has been shown to degrade both wild-type BTK and covalent as well as non-covalent BTK-inhibitor–resistant mutant proteins such as V416L, M437R, T474I, C481S, thus inducing tumor suppression [5, 6].

Seymour et al. presented preliminary safety and efficacy results for 50 patients enrolled in the ongoing BGB-16673-101 study that is testing BGB-16673 in patients with relapsed or refractory B-cell malignancies including MZL, follicular lymphoma (FL), mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia (WM), diffuse large B-cell lymphoma (DLBCL), and Richter transformation [7]. Prior to inclusion, patients had been treated with ≥ 2 therapies and had received a covalent BTK inhibitor if this was locally approved for their disease. BGB-16673 was administered at five dose levels ranging from 50 mg to 500 mg.

The agent resulted in meaningful responses, with an ORR of 57 % at all doses and a median time to first response of 2.76 months. The disease control rate was 75 %. Seven out of 10 patients with CLL/SLL, all of whom were pretreated with covalent BTK inhibitors, responded to the treatment. The disease control rate in this group was 90 %. Patients with MCL, MZL or WM achieved responses and disease control in 56 % and 75 %, respectively. Furthermore, substantial reductions in BTK protein levels were observed in the peripheral blood and tumor tissue, which is a proof of concept of a strong on-target effect.

The safety profile of BGB-16673 appeared tolerable. Grade 3 rash was reported as the only dose-limiting toxicity, occurring in a single patient. Two patients discontinued BGB-16673 due to treatment-emergent AEs (TEAEs). No atrial fibrillation or hypertension had occurred at the time of data cutoff. Phase II dose expansions within the BGB-16673-101 study are planned for patients with CLL/SLL and MCL.

NX-2127: immunomodulation plus BTK degradation

Preclinical and clinical evidence suggests that modulation of cereblon to degrade Ikaros family proteins might synergize with BTK inhibition in non-Hodgkin lymphoma (NHL) [8]. NX-2127 is an oral, first-in-class small molecule that combines BTK degradation with the immunomodulatory activity of a degrader for the transcription factor Ikaros [9]. Compared with classical BTK inhibitors, NX-2127 is expected to exert superior efficacy by overcoming BTK-mutation–driven resistance. The first-in-human, phase Ia/Ib NX-2127-001 study is currently assessing NX-2127 in patients with advanced B-cell malignancies. Updated safety and efficacy data were reported for a total of 54 patients with relapsed/refractory DLBCL, MCL, MZL, WM, FL and CLL/SLL at ASH 2023 [10]. In the overall population, the median number of prior treatment lines was 4. Patients were predominantly elderly, had received multiple lines of targeted agents and showed acquired mutations associated with drug resistance.

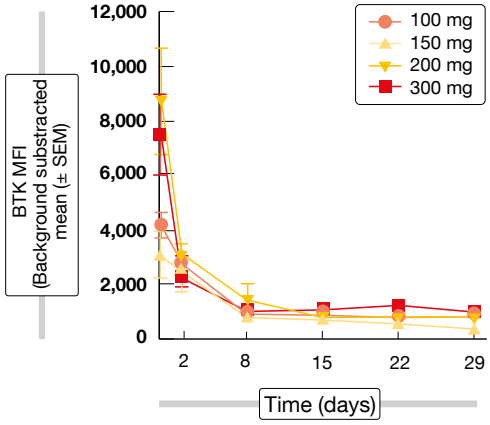


Figure: BTK degradation with NX-2127 at dose levels of 100-300 mg

NX-2127 demonstrated a manageable safety profile that was consistent with previous reports for BTK-targeted and immunomodulatory compounds. The most common TEAEs included neutropenia (any grade, 46.3 %; grade ≥ 3, 42.6 %), fatigue (46.3 %; no grade ≥ 3 events), and hypertension (33.3 %; 14.8 %). Atrial fibrillation was observed in 11.1 % of patients, with 5.6 % experiencing grade ≥ 3 events. Two patients developed dose-limiting toxicities at the 300 mg dose level, and NX-2127 had to be discontinued due to TEAEs in 13 patients.

The treatment gave rise to rapid, robust and sustained degradation of BTK (**Figure**) in all patients regardless of their absolute BTK starting level, tumor type, or NX-2127 dose level. Consistent with the immunomodulatory activity of NX-2127, biologically relevant degradation of Ikaros was observed. In the group with NHL and WM (n = 17), two individuals each showed complete and partial responses. Among 27 patients with CLL/SLL, 11 (40.7 %) developed partial responses with and without lymphocytosis. Twelve patients (44.4 %) had stable disease at the time of data cutoff. Responses were seen in double- and triple-exposed individuals. Eight patients had been on treatment for > 12 months at the time of the analysis, and treatment was ongoing in 13 individuals. Dose-expansion cohorts of patients with NHL have been initiated at the 300 mg dose level. ■

REFERENCES

1 Tedeschi A et al., Monotherapy with second-generation BCL2 inhibitor sonrotoclax (BGB-11417) is well tolerated with high response rates in patients with relapsed/refractory marginal zone lymphoma: Data from an ongoing phase 1 study. ASH 2023, abstract 3032

2 Patel K et al., Pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in relapsed/refractory marginal zone lymphoma: results from phase 1/2 BRUIN study. ASH 2023, abstract 1660

3 Woyach JA et al., Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. N Engl J Med 2014; 370(24): 2286-2294

4 Wang E et al., Mechanisms of resistance to noncovalent Bruton's tyrosine kinase inhibitors. N Engl J Med 2022; 386(8): 735-743

5 Feng X et al., Bruton tyrosine kinase protein degrader BGB-16673 is less apt to cause, and able to overcome variable BTK resistance mutations compared to other BTK inhibitors. EHA 2023, abstract P1239

6 Wang H et al., BGB-16673, a BTK degrader, overcomes on-target resistance from BTK inhibitors and presents sustainable long-term tumor regression in lymphoma xenograft models. EHA 2023, abstract P1219

7 Seymour JF et al., First results from a phase 1, first-in-human study of the Bruton Tyrosine kinase degrader BGB-16673 in patients with relapsed or refractory B-cell malignancies. ASH 2023, abstract 4401

8 Montoya S et al., Efficacy of pirtobrutinib in covalent BTK-inhibitor pre-treated relapsed/refractory CLL/SLL: additional patients and extended follow-up from the phase 1/2 BRUIN study. Blood 2022; 140(Suppl 1): 1811-1813

9 Noviski M et al., Concurrent degradation of BTK and IMiD neosubstrates by NX-2127 enhances multiple mechanisms of tumor killing. Cancer Res 2022; 82 (Suppl 12): 1128

10 Danilov A et al., A first-in-human phase 1 trial of NX-2127, a first-in-class Bruton's tyrosine kinase dual-targeted protein degrader with immunomodulatory activity, in patients with relapsed/refractory B-cell malignancies. ASH 2023, abstract 4463

ASH 2023

The ASH 2023 slide deck is now available! It contains summaries of selected posters and presentations from last years' congress focusing on emergent therapeutic options for B-cell malignancies, in particular the use of Bcl-2 and BTK inhibitors in CLL.
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Ramón García-Sanz gives insights into the assessment of residual disease in multiple myeloma and explains future clinical implications of these data. Moreover, he discusses in which ways the evaluation of minimal residual disease might improve the management of patients with Waldenström macroglobulinemia and shares his personal highlight from the ASH 2023 congress.

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Barbara F. Eichhorst describes possible approaches to improve the early detection of molecular CLL relapses, discusses venetoclax-based first-line combinations in CLL, and rates the relative efficacy and safety of different BTK inhibitors in relapsed/refractory CLL while finally sharing her personal highlights from the ASH 2023 congress.

Stephan Stilgenbauer discusses the current evidence regarding the treatment of Richter transformation with modern agents and reviews the findings of the RT1 trial presented at the ASH 2023 meeting. Finally, he highlights future combinations of novel agents like adding the next-generation BCL-2 inhibitor sonrotoclax to tislelizumab plus zanubrutinib which will be investigated in the amendment of the RT1 trial or the use of the non-covalent BTK inhibitor pirtobrutinib combined with epcoritamab, a bispecific antibody, that will be in the focus of the international RT2 trial.

This special issue will be offering a synopsis from the ASCO and EHA 2024 meeting that will be held in May/June 2024. The report promises to make for stimulating reading, as both congresses draw on the input from a number of partner organizations, representing a multidiscplinary approach to cancer treatment and care. Stay tuned for the latest news in hematologic diseases and its subspecialties.

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