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Congress Report EHA 2024

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

Report from the European Hematology Association (EHA) 2024 Congress (hybrid), 13th – 16th June 2024

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Preface

Dear Colleagues,
At the European Hematology Association (EHA) congress held in Madrid, Spain, and virtually from 13th–16th June 2024, world-leading experts from 150 countries presented cutting-edge research and clinical trials.

This year, we witnessed significant advancements in the treatment of chronic lymphocytic leukemia (CLL). In the treatment-naïve CLL section of this report, you will discover results for innovative therapies such as zanubrutinib combined with venetoclax, the triplet regimen of pirtobrutinib, venetoclax, and obinutuzumab, and the comparative efficacy of ibrutinib and venetoclax against standard treatments. Data from the CAPTIVATE study shed light on retreatment outcomes in high-risk patients. In the relapsed/refractory setting, studies have explored promising strategies such as prolonged induction with ibrutinib and venetoclax, pirtobrutinib monotherapy, and obinutuzumab in addition to ibrutinib and venetoclax. Analyses have investigated the relative efficacy and safety of BTK inhibitors, with real-world data confirming these observations.
The second chapter deals with unmet needs in mantle cell lymphoma (MCL), where the ECHO study investigating acalabrutinib plus chemoimmunotherapy as well as the phase II trial evaluating the BOVen triplet regimen are pointing towards alternative treatment approaches in older MCL patients. In the relapsed/refractory setting, high response rates and durable remissions have been reported for glofitamab, and real-world data have shown favorable results for zanubrutinib compared to other BTK inhibitors with respect to survival outcomes and treatment adherence.
The emerging class of BTK degraders that includes agents such as NX-5948 and BGB-16673 addresses resistance patterns in B-cell malignancies that limit the utility of BTK and BCL2 inhibitors. Phase I/II data have demonstrated promising efficacy even in hard-to-treat populations with relapsed/refractory disease.
The BCL2 inhibitor sonrotoclax has shown impressive results across CLL, MCL, Waldenström macroglobulinemia, multiple myeloma and AML. Studies have revealed high uMRD rates and a favorable safety profile, while the clinical development is ongoing.
Bispecific antibodies like odronextamab and mosunetuzumab have proven effective in relapsed/refractory follicular lymphoma across patients with and without poor-prognosis factors such as progression of disease within 24 months of initiation of first-line treatment. For epcoritamab, cycle 1 optimization has been successfully explored regarding reductions in typical adverse events.
Last but not least, the matching-adjusted indirect comparison (MAIC) technique is highlighted as it enables the assessment of new treatments versus alternatives where direct comparisons through randomized controlled trials are not available, aiding decision-making in oncology and hematology by addressing uncertainties related to disease severity and treatment costs.
We hope that you enjoy reading about the groundbreaking findings from EHA 2024 in the field of hematology. Together, let us continue advancing research for the benefit of our patients.

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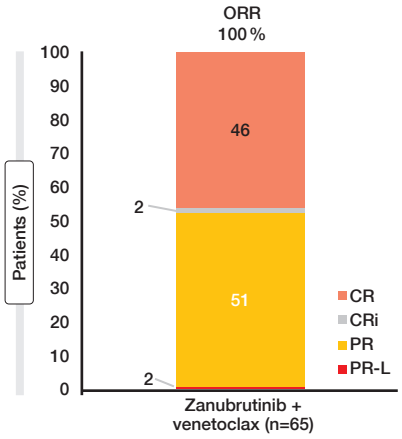
Reducing risks further in chronic lymphocytic leukemia

Treatment-naïve CLL

SEQUOIA arm D: zanubrutinib in addition to venetoclax

The second-generation BTK inhibitor zanubrutinib is being tested in the phase III SEQUOIA trial in the setting of untreated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with and without del(17p). Zanubrutinib monotherapy has shown high tolerability and efficacy in arm C of the study that included patients with del(17p) [1]. At EHA 2024, Ma et al. reported preliminary results for 66 individuals harboring del(17p) and/or *TP53* mutation who received zanubrutinib plus venetoclax in arm D [2]. The combination was started in cycle 4 following a zanubrutinib lead-in and was continued for 12-24 cycles.

Venetoclax and zanubrutinib could be discontinued early after ≥12 and ≥ 27 cycles, respectively, if complete response (CR) or CR with incomplete hematological recovery (CRi) confirmed by bone marrow biopsy was achieved together with undetectable minimal residual disease (uMRD) at a sensitivity level of 10^{-4} (MRD4). uMRD had to be demonstrated in two consecutive peripheral blood or bone marrow aspirate tests conducted ≥ 12 weeks apart. In patients who did not meet these criteria, zanubrutinib was continued as monotherapy beyond cycle 28 until confirmed uMRD. In addition to del(17p) and/or *TP53* mutation, 85 % of patients had unmutated IGHV, and a complex karyotype with ≥ 3 or ≥ 5 abnormalities was present in 50 % and 36 % of cases, respectively. To date, only small per-



CR, complete response; CRi, complete response with incomplete hematological recovery; PR, partial response; PR, partial response with lymphocytosis

Figure 1: Response rates obtained with zanubrutinib plus venetoclax

centages of patients have met the early stopping criteria due to short follow-up.

Zanubrutinib plus venetoclax showed favorable safety and tolerability. COVID-19 was the most common treatment-emergent adverse event (TEAE; any grade, 55 %), followed by diarrhea (39 %), nausea (30 %), contusion (29 %), fatigue (23 %), neutropenia (22 %) and arthralgia (15 %). Grade ≥ 3 TEAEs included neutropenia (17 %), diarrhea (9 %) and COVID-19 (3 %). Among TEAEs of special interest, infections ranked first due to the high COVID-19 rate (any grade, 71 %; grade ≥ 3, 15 %), while hemorrhage ranked second (any grade, 54 %; grade ≥ 3, 2 %) and neutropenia third (any grade, 22 %; grade ≥ 3, 17 %). Second primary malignancies occurred in 13 % (grade ≥ 3, 8 %). Low rates were reported regarding hypertension (any grade, 10 %; grade ≥ 3, 8 %) and atrial fibrillation/flutter (2 %). The zanubrutinib lead-in gave rise to a 91 % reduction in the proportion of patients at high risk of tumor lysis syndrome (TLS).

Zanubrutinib plus venetoclax induced deep and durable remissions after a median follow-up of 31.6 months. All of the 65 response-evaluable patients responded, with 48 % achieving CR/CRi (**Figure 1**). The rates of uMRD in the peripheral blood increased with longer treatment duration. At the time of this interim analysis, best uMRD rates were 59 % in ≥ 1 peripheral blood sample and 37 % in ≥ 1 bone marrow sample. Median progression-free survival (PFS) had not been reached; at 12 and 24 months, 95 % and 94 % of patients, respectively, were alive and progression-free. Results in patients who meet the MRD-guided early stopping rules will be reported as data mature. The ongoing phase III CELESTIAL-TNCLL trial is evaluating fixed-duration therapy with zanubrutinib and the next-generation BCL2 inhibitor sonrotoclax in patients with treatment-naïve CLL [3].

Pirtobrutinib plus venetoclax/obinutuzumab

Venetoclax plus obinutuzumab in addition to the non-covalent BTK inhibitor pirtobrutinib is currently being investigated as a limited-duration triplet combination in a phase II study containing untreated patients with CLL/SLL. While pirtobrutinib is taken orally through 13 cycles, obinutuzumab is administered in cycles 1-6 and venetoclax in cycles 2-13 with ramp-up in cycle 2. Patients with detectable MRD at ≥ 10^{-5} in either peripheral blood or bone marrow at the end of cycle 13 can continue pirtobrutinib plus venetoclax for an additional 12 cycles. The uMRD4 rate in the bone marrow after cycle 7 is defined as the primary endpoint of the study. Jain et al. presented the first results for 40 patients after a median follow-up of 11.7 months [4]. At that time, 20 individuals had completed cycle 13.

One cycle of pirtobrutinib and obinutuzumab prior to the initiation of venetoclax enabled downgrading of the TLS risk to the medium- or low-risk categories in most patients with high or medium risk. The triple combination induced very high uMRD rates at a sensitivity level of 10^{-6} (**Figure 2**). At the end of cycle 7, 79 % and 64 % of patients had obtained uMRD in the peripheral blood and bone marrow, respectively. These rates increased further to 90 % and 85 %, respectively, at the end of cycle 13. They are numerically higher than those achieved with ibrutinib and venetoclax in the blood marrow after 6 and 12 months (33 % and 52 %, respectively) [5]. At the time of the analysis, no patient had progressed or died.

Pirtobrutinib and venetoclax dose reductions were necessary in 30 % each, with neutropenia being the most common reason. Grade 3-4 neutropenia and thrombocytopenia occurred in 60 % and 18 %, respectively. Fifty-five percent of patients required G-CSF prophylaxis. One patient developed atrial fibrillation, which was grade 2. The trial is currently enrolling into a 40-patient expansion cohort.

MRD findings for ibrutinib/venetoclax

The phase II ERADIC trial is comparing the standard fludarabine, cyclophosphamide and rituximab (FCR) regimen to an MRD-guided approach using the combination of ibrutinib and venetoclax in patients with intermediate risk in whom FCR is less effective. The intermediate-risk cohort is defined by either unmutated IGHV status, 11q deletion or complex karyotype in the absence of *TP53* alteration. While arm 1 received 6 cycles of FCR Q4W, arm 2 was treated with ibrutinib for 3 cycles followed by the combination including an initial venetoclax ramp-up. After 9 months, pa-

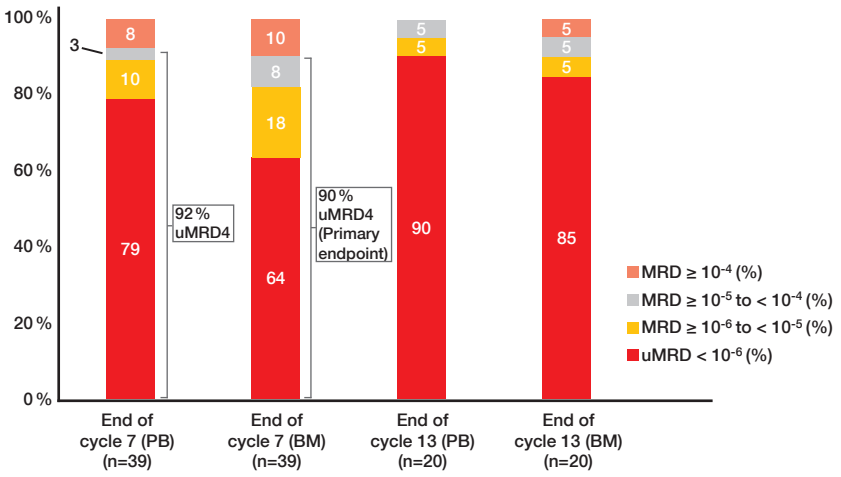


Figure 2: Pirtobrutinib plus venetoclax and obinutuzumab: MRD results at serial time points

tients with MRD < 0.01 % in the bone marrow continue ibrutinib plus venetoclax for another 6 months and stop at month 15. Those with MRD ≥ 0.01 % at month 9 continue ibrutinib and venetoclax for 18 months and stop at month 27 irrespective of their clinical response or MRD status. The primary endpoint is the percentage of patients with MRD < 0.01 % in the bone marrow at month 27. Each study arm contains 60 individuals. Interim results of MRD kinetics after a median follow-up of 29.7 months were presented at EHA 2024 [6].

The MRD analysis revealed a clear increase in the uMRD rates on ibrutinib plus venetoclax therapy between months 9 and 21, suggesting that a 9-month treatment course is too short to achieve a very good MRD < 10^{-4} response. At 9 months, the uMRD rates in the bone marrow were 38 % vs. 69 % for ibrutinib plus venetoclax vs. FCR. In the peripheral blood, this was 57 % vs. 78 %; at month 15, the uMRD rates were equal (78 % vs. 77 %), and at 21 months, the rate for ibrutinib plus venetoclax exceeded that for FCR (82 % vs. 66 %). Sixteen out of 20 patients with uMRD in the peripheral blood at 9 months discontinued treatment at 15 months according to the trial design. Two more discontinuations took place at month 21, and treatment was continued in two patients with partial response based on investigator's choice. Only two conversions to detectable MRD were identified at month 27. In the group that had not achieved uMRD in the peripheral blood at month 9, 21 patients continued treatment. Eight of these converted to uMRD at month 15, with only one showing a detectable MRD result again at month 21. Clinically, CR/CRi was present in 66 % with ibrutinib plus venetoclax vs. 56 % with FCR at 9 months. Overall, these results support the use of MRD kinetics for treatment decision-making.

However, toxicity remained an important factor in both arms. Grade ≥ 3 serious AEs included TLS (n = 5 vs. 3 with ibrutinib plus venetoclax vs. FCR), COVID 19 (4 each), febrile neutropenia (0 vs. 5) and atrial fibrillation (2 vs. 0), among others. Infections were generally more common with FCR, whereas cardiovascular disorders emerged more frequently with the targeted approach. One case each of colorectal cancer and basal cell carcinoma was reported as grade ≥ 3 secondary malignancies in the experimental arm. In the control arm, one patient developed MDS and another AML which led to death in both cases. Another patient treated with FCR died of septic shock. Three deaths occurred in the group that received ibrutinib and venetoclax (2 sudden deaths, 1 COVID-19–related death).

The authors noted that toxicity should be taken into account when determining whether treatment should be continued because of detectable MRD in the bone marrow at month 9. Upcoming data of the primary endpoint analysis of the study at month 27 will be highly relevant with a view to determining the best strategy.

CAPTIVATE: results in high-risk subgroups

First-line treatment with ibrutinib plus venetoclax was evaluated in the phase II CAPTIVATE study in two cohorts. The fixed-duration (FD) cohort was treated with 12 cycles of the combination after 3 cycles of ibrutinib lead-in. In the MRD-guided cohort, patients with uMRD after the regimen described for the FD cohort were randomized to either placebo or ibrutinib. Upon disease progression, ibrutinib-based treatment could be reinitiated in both cohorts. At EHA 2024, Jacobs et al. reported outcomes in patients from the FD cohort who had high-risk genomic features [7]. Also, retreatment outcomes were presented for the FD cohort and the placebo arm of the MRD-guided cohort.

A total of 159 patients received the combination in the FD cohort. Median PFS had still not been reached in this group after a follow-up of 5.5 years, and the 5-year PFS rate was 67 %. In patients with del(17p), mutant *TP53*, or complex karyotype (n = 51), the 5-year PFS rate was 54 %, and in those without these genomic high-risk features (n = 85), 77 %. Irrespective of other risk factors, the group with unmutated IGHV was shown to have a lower 5-year PFS rate than that with mutated IGHV (56 % vs. 80 %). After exclusion of patients with del(17p), *TP53* mutation or complex karyotype, the respective rates were 68 % and 85 %, which demonstrated the impact of these risk features on PFS. Moreover, 5-year PFS was improved in patients who achieved uMRD4 in the peripheral blood or bone marrow. In the high-risk genomic subgroups, the 5-year PFS rates were consistently higher in those with uMRD4 at 3 months after the end of treatment than in those without MRD4. For overall survival (OS), the analysis yielded 5-year rates ≥ 90 % regardless of genomic risk features (**Figure 3**). The authors noted that fixed-duration ibrutinib plus venetoclax confers meaningful survival benefits in patients with high-risk genomics.

Among 61 patients with disease progression after completion of fixed-duration ibrutinib plus venetoclax, 32 initiated retreatment with single-agent ibrutinib (n = 25) or ibrutinib plus venetoclax (n = 7). Unmutated IGHV and del(17p)/mutant *TP53* were present in these groups in 78 % and 31 %, respectively. Thirty-four percent had a complex karyotype and bulky lymph node disease ≥ 5 cm. In spite of this high-risk setup, retreated patients showed promising responses with overall response rates (ORRs) of 86 % and 71 % in the

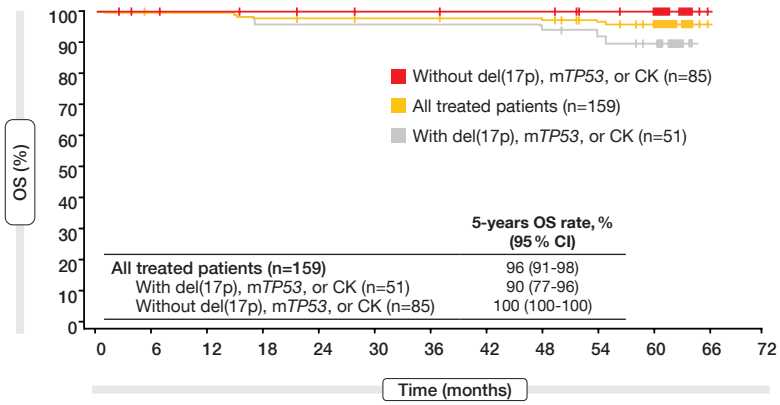


Figure 3: High 5-year overall survival rates observed for ibrutinib plus venetoclax irrespective of genomic risk features irrespective of the genomic risk features del(17p), *TP53* mutation and complex karyotype (CK)

groups receiving single-agent ibrutinib (22 evaluable patients) and ibrutinib plus venetoclax, respectively. CRs were observed in 5 % and 14 %, respectively. The AEs reported with ibrutinib-based retreatment were consistent with the known safety profiles of ibrutinib monotherapy and the combination. As the authors concluded, based on the safety profiles of fixed-duration ibrutinib plus venetoclax and ibrutinib-based retreatment, this approach appears to offer a favorable benefit-risk ratio.

Zanubrutinib vs. ibrutinib/venetoclax

In the absence of head-to-head clinical studies comparing zanubrutinib with venetoclax plus ibrutinib in the setting of treatment-naïve CLL, Munir et al. conducted a matching-adjusted indirect comparison (MAIC) using individual patient-level data from the SEQUOIA study that were matched against aggregate data from the GLOW and CAPTIVATE trials [8]. Due to the lack of common control arms linking SEQUOIA with GLOW or CAPTIVATE, two unanchored MAICs were performed. The zanubrutinib population from Cohort 1 of the SEQUOIA study (arm A) was reweighted to match the key characteristics of the ibrutinib plus venetoclax population in GLOW. At the same time, the pooled zanubrutinib population from Cohort 1 and 2 of SEQUOIA (arms A and C) was reweighted to match the key characteristics of the ibrutinib plus venetoclax population in CAPTIVATE.

While no statistically significant difference in investigator-assessed PFS was demonstrated for zanubrutinib vs. ibrutinib plus venetoclax, the population-adjusted estimate revealed a potential trend in favor of zanubrutinib (HR, 0.78). Also, the safety profile of zanubrutinib was significantly better than that of the combination despite longer treatment exposure (median, 43-44 months vs. 13.8 months). Multiple AEs showed significantly lower incidence with zanubrutinib, in particular diarrhea, neutropenia, nausea, anemia, atrial fibrillation, decreased appetite, and arthralgia. These differences might be considered at the time of treatment decision-making.

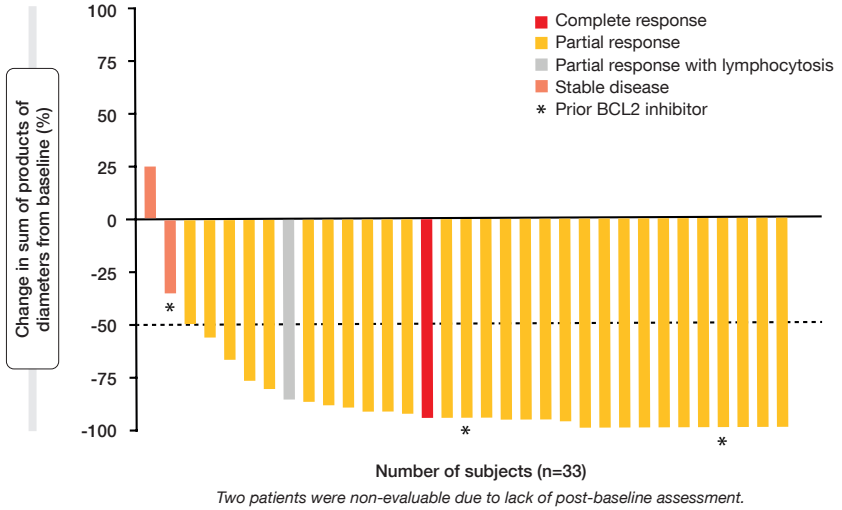
Relapsed/refractory CLL

Prolonged venetoclax/ibrutinib induction: SAKK 34/17

Studies exploring ibrutinib plus venetoclax typically incorporate a brief initial ibrutinib treatment phase to mitigate the TLS risk, with treatment discontinuation after 12 months. However, uMRD rates obtained in these trials have often fallen short of expectations [9-11]. The SAKK 34/17 trial was conducted to evaluate the efficacy of a prolonged 24-month induction phase with ibrutinib plus venetoclax to maximize the uMRD and CR/CRi rates. Furthermore, the scientists chose a longer ibrutinib lead-in period of 6 cycles. In cycle 7, the venetoclax dose was stepped up, and ibrutinib plus venetoclax was administered from cycle 8 to 31. Finally, this study assessed whether circulating tumor DNA (ctDNA) captures the genetics and residual disease from tissue-restricted CLL clones, and whether ctDNA can identify resistance mutations early on during the treatment period. uMRD with CR/CRi at the end of cycle 30 was defined as the primary endpoint. Patients who were MRD-negative and had achieved CR/CRi at that time were observed for up to 5 years. On the other hand, if MRD persisted, ibrutinib plus venetoclax was continued for up to 5 years until MRD negativity, CR/CRi, progression, or intolerance.

According to the findings reported for 30 patients at EHA 2024, the study met its primary endpoint. Forty percent of patients showed uMRD with CR/CRi at cycle 30 [12]. This rate exceeded the rates obtained in trials with 1 year of ibrutinib plus venetoclax exposure [9, 10]. However, a higher discontinuation rate of 37 % indicates a trade-off. After 6 cycles of ibrutinib lead-in, the percentage of patients at low TLS risk shifted from 33 % to 50 %. One TLS event occurred (3.3 %) that was grade 3. The PFS rate at cycle 31 was 85.5 % after a median follow-up of 42 months, with median PFS not having been reached.

The analysis of cell-free DNA did not enable early detection of resistance mutations, and the measurements did not add any information to immunoglobulin high-throughput sequencing. Moreover, no clinical mutations beyond those detected in CLL cells from the peripheral blood were revealed by the ctDNA assessments.



Two patients were non-evaluable due to lack of post-baseline assessment.

Figure 4: Reductions in tumor burden with pirtobrutinib monotherapy

Pirtobrutinib in BTKi-naïve patients

Reversible BTK inhibition with pirtobrutinib monotherapy is being assessed in various B-cell malignancies in the phase I/II BRUIN study. Results for 35 BTK-inhibitor–naïve patients with relapsed/refractory CLL/SLL were presented at EHA 2024 by Eyre et al. [13]. The median number of prior lines of systemic therapy in this cohort was 2. Almost half had bulky lymphadenopathy ≥ 5 cm and complex karyotype. Eighty percent showed unmutated IGHV, and *TP53* mutations and/or del(17p) were present in 37 %.

The ORR achieved with pirtobrutinib monotherapy was as high as 91.4 % and 94.3 % according to the independent re-

view committee (IRC) and the investigators, respectively. Almost all patients experienced substantial reductions in tumor burden (**Figure 4**). One patient developed CR (2.9 %). ORRs for the population with genomic high-risk features were favorable, ranging from 85.7 % to 100 %. Neither median PFS nor median OS had been reached after a median follow-up of approximately 30 months. At 24 months, 88.0 % of patients were alive, and 74.7 % were progression-free according to IRC.

The safety profile of pirtobrutinib in BTK-inhibitor–naïve patients resembled that observed in the overall BRUIN cohort. Treatment-related AEs (TRAEs) mainly comprised neutropenia (40.0 %), diarrhea (20.0 %), contusion (14.3 %), and anemia (11.4 %). Among TRAEs of interest, infections were most common (any grade, 25.7 %; grade ≥ 3, 2.9 %), followed by rash (17.1 %) and bruising (14.3 %). Except for infections, no TRAEs of interest were graded as ≥ 3. The analysis revealed low rates of dose reduction and discontinuation due to TRAEs (11.4 % and 5.7 %, respectively). Phase III trials are currently evaluating pirtobrutinib monotherapy in treatment-naïve patients with CLL/SLL (BRUIN CLL-313; NCT05023980) and patients who are treatment-naïve or pretreated with non-BTK inhibitor therapy (BRUIN CLL-314; NCT05254743).

ALPINE: PRO-based prediction of progression

The randomized phase III ALPINE study has demonstrated significantly increased PFS for zanubrutinib compared to ibrutinib in patients with relapsed/refractory CLL [14]. Zanubrutinib is the only BTK inhibitor to date that has shown PFS superiority vs. ibrutinib in this setting. Serrano et al. conducted analyses based on patient-reported outcomes (PRO) from 601 patients in ALPINE with the aim of developing a joint model to examine the association between the time to recurrent PRO-based deterioration and disease progression [15]. Investigator-assessed PFS was analyzed as the terminal event measure.

After predicting PFS from the risk of recurrent symptomatic deterioration events and using a joint model to adjust for baseline stratification factors and change from baseline in corresponding symptoms, zanubrutinib remained superior to ibrutinib regarding disease progression in the ALPINE trial. The analysis demonstrated that leading predictors for the risk of disease progression included recurrent symptomatic deterioration in appetite, diarrhea, and dyspnea. Accordingly, patient reporting of deterioration in these symptoms might indicate a need for increased clinical monitoring.

Statistical comparisons in the relapsed setting

Multilevel network meta-regression is a newly developed method that facilitates the estimation of relative treatment effects between interventions for different target populations based on networks of any size. Shadman et al. used this method to estimate the treatment effect of zanubrutinib relative to acalabrutinib and ibrutinib in patients with relapsed/refractory CLL based on the ALPINE and ELEVATE-RR trials [16]. ELEVATE-RR has established the non-inferiority of acalabrutinib compared to ibrutinib in relapsed/refractory CLL, with lower rates of atrial fibrillation, hypertension and bleeding [17].

The results indicated that zanubrutinib conferred significantly longer PFS compared to acalabrutinib and ibrutinib in a population akin to that of the ALPINE trial as well as ELEVATE-RR patients who were characterized by high-risk cytogenetics. Zanubrutinib also demonstrated potential improvement in OS *versus* both ibrutinib and acalabrutinib, although these results were not statistically significant, possibly due to the limitations in the number of studies available and their sample sizes.

Another group of investigators used MAIC to evaluate the relative efficacy of zanubrutinib and acalabrutinib in the relapsed/refractory CLL setting [18]. Individual patient-level data from ALPINE were matched against aggregate data from the ASCEND trial that has revealed PFS improvement with acalabrutinib vs. rituximab plus idelalisib/bendamustine [19, 20]. Due to the lack of a common comparator arm, an unanchored MAIC was used.

After matching, investigator-assessed PFS was significantly improved for zanubrutinib vs. acalabrutinib (HR, 0.68; p = 0.0448), while OS was potentially improved (HR, 0.60; p = 0.0575). The CR rates favored zanubrutinib in both unadjusted (OR, 2.88; p = 0.0198) and base case-adjusted (OR, 2.90; p = 0.0270) populations. These results were robust across multiple sensitivity analy-

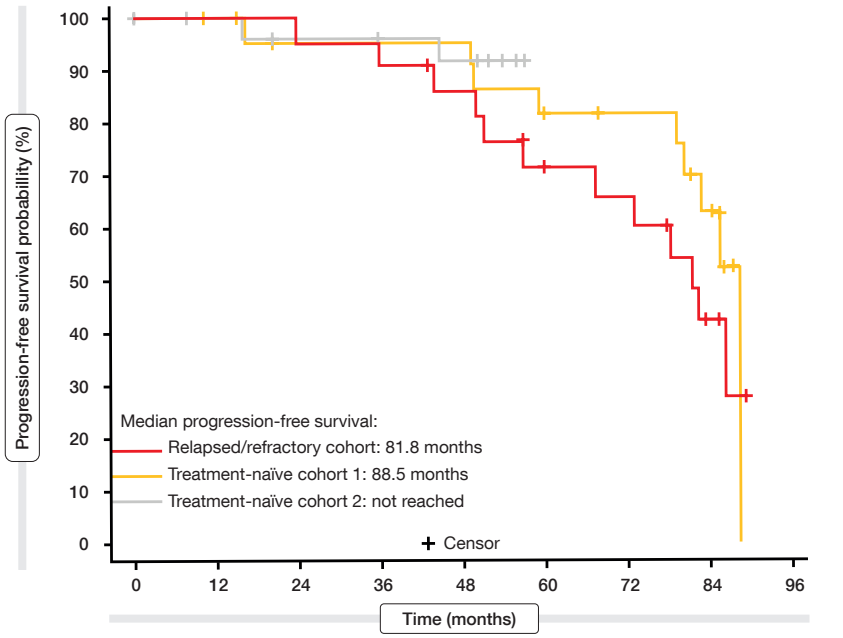


Figure 5: Ibrutinib plus venetoclax and obinutuzumab: 7-year progression-free survival

ses. However, as the authors pointed out, randomized controlled trials remain the gold standard for evaluating evidence of relative efficacy.

7-year update for obinutuzumab/ibrutinib/venetoclax

Longer-term outcomes are still being assessed for combination regimens containing a BTK inhibitor and BCL2 inhibitor with or without an anti-CD20 antibody. Rogers et al. presented the 7-year follow-up for a phase II study exploring ibrutinib plus venetoclax and obinutuzumab in treatment-naïve (TN) and relapsed/refractory (RR) CLL/SLL [21]. The patients had been accrued in one RR cohort and two TN cohorts (n = 25 each). While the RR cohort completed accrual in 2017 and had a median follow-up of 83.0 months, TN1 and TN2 completed accrual in 2016 and 2019, respectively, and had median follow-up times of 85.6 and 51.7 months, respectively. Treatment consisted of 8 cycles of obinutuzumab, ibrutinib from cycle 2, and venetoclax from cycle 3 including initial ramp-up. After 14 cycles, the treatment was stopped. Response assessment occurred 2 months after completion of cycle 14 (end of treatment, EOT).

At EOT, the ORR was 88 % for the RR cohort and 90 % for the TN cohorts. In the RR group, 44 % had achieved uMRD; for TN1 and TN2, this was 56 % and 60 %, respectively. Median PFS had been reached for the RR and TN1 cohorts (81.8 and 88.5 months, respectively; **Figure 5**). In the TN2 group, 91 % of patients were alive and progression-free at 48 months. Unexpectedly, PFS after treatment did not differ according to the MRD status at EOT. Median OS had not been reached in any cohort. The 60-month OS rates were 95.0 % and 90.9 % in the RR and TN1 groups, respectively.

Characteristics associated with lower PFS and decreased probability of achieving uMRD were non-specific markers of more aggressive CLL biology such as increases in beta-2-microglobulin and lactate dehydrogenase. No mutations showing associations with either PFS or uMRD status were identified. After treatment, 10.7 % of patients developed grade ≥ 3 infections. COVID-19 of any grade occurred in 29.3 % (grade ≥ 3, 4 %). Second neoplasms were observed in 25.3 %; among these, 71 % were non-melanoma skin cancers. Notably, no second myeloid malignancies emerged. Infections constituted the most common cause of death. Overall, nine patients died, with all of the fatalities occurring after completion of active treatment. Additional studies are required to determine the benefit of 3-drug regimens vs. 2-drug regimens, mechanisms of resistance and sensitivity, and the optimal sequence of treatments over the lifespan of CLL patients.

ASSURE: safety of acalabrutinib

The ongoing global, open-label phase IIIB safety study ASSURE is examining acalabrutinib monotherapy in patients with CLL in a real-world setting. ASSURE contains three cohorts including TN patients, those with RR disease, and ibrutinib-intolerant individuals who had previously discontinued ibrutinib therapy for any reason apart from disease progression. Acalabrutinib is being administered for 48 cycles and beyond in patients still benefiting from it. Opat et al. reported interim safety results for 310 and 202 patients in the TN and RR groups, respectively, and for 40 ibrutinib-intolerant patients [22].

At 30 months, the proportions of those who were still receiving treatment in these three groups were 71 %, 62 % and 45 %, respectively. The safety profile of acalabrutinib was in keeping with the observations from previous clinical studies. Rates of cardiac events were low. Among events of clinical interest, atrial fibrillation/flutter occurred in 4.7 % (grade ≥ 3, 1.6 %) in the total group, while hemorrhage was observed in 48.9 % (grade ≥ 3, 3.8 %) and hypertension in 7.8 % (grade ≥ 3, 3.3 %). Substantial proportions of patients with atrial fibrillation or hypertension had a prior history of these conditions.

Grade ≥ 3 TEAEs were reported in 57 % of patients overall (TN, 54 %; RR, 63 %; ibrutinib-intolerant, 45 %). TEAEs led to treatment discontinuation in 19 % (TN, 15 %; RR, 26 %; ibrutinib-intolerant, 18 %). Seventy-five percent of patients had infections including COVID-19 (grade ≥ 3, 29.9 %). Deaths due to TEAEs occurred in 56 patients, with the majority dying from COVID-19 and related complications. Second primary malignancies excluding non-melanoma skin cancer were reported in 8.9 % (grade ≥ 3, 4.5 %).

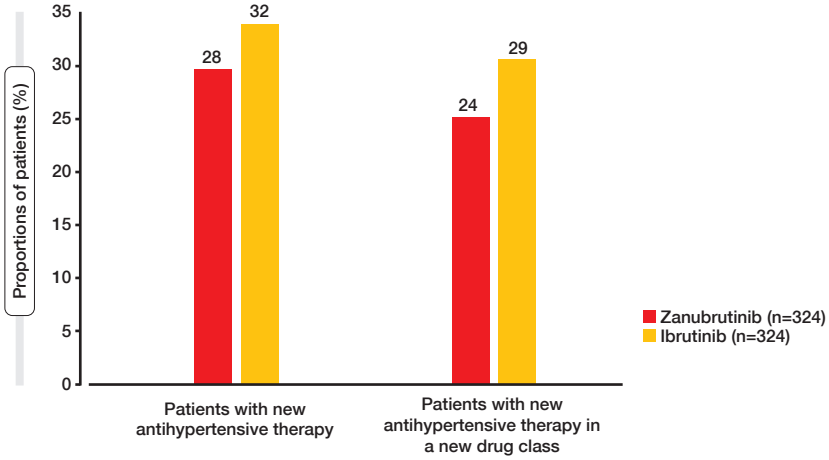


Figure 6: Proportions of patients who required new antihypertensive medication in the ALPINE study

Hypertension on BTK inhibitor treatment

As is known, BTK inhibitor therapy can elicit cardiovascular AEs such as hypertension. A retrospective cohort study based on the Symphony Health Solutions Database sought to describe the risk of new-onset and worsening hypertension in 30,559 patients with newly diagnosed CLL who received treatment with (n = 2,392) or without (n = 28,167) BTK inhibitors [23]. The baseline prevalence of hypertension was 73 % and 72 % in the BTK inhibitor and non-BTK inhibitor cohorts, respectively.

Patients in the BTK inhibitor cohort,

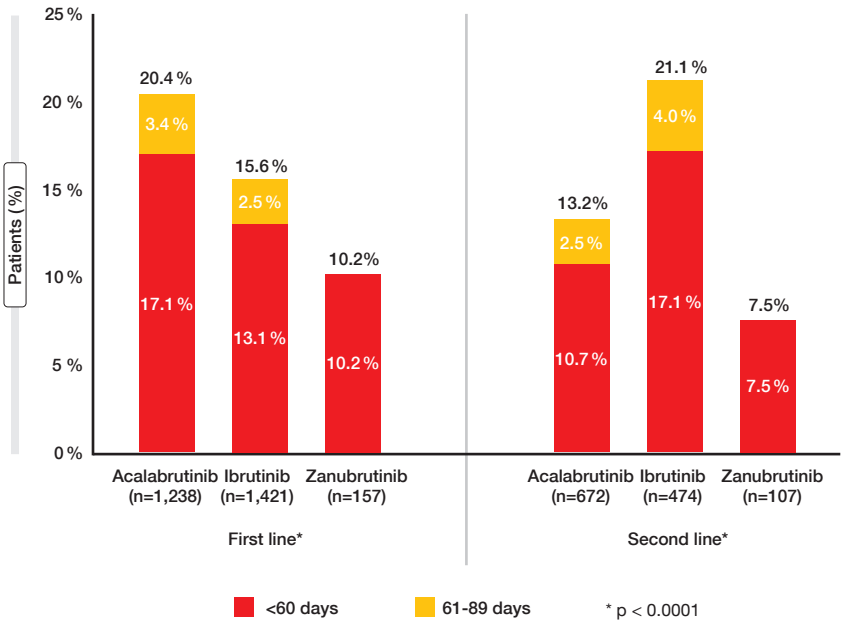


Figure 7: Switching rates within 90 days for acalabrutinib, ibrutinib and zanubrutinib in clinical practice

as compared to the non-BTK inhibitor cohort, had a higher rate of new-onset hypertension (inverse probability treatment weighting [IPTW] HR, 1.50) or worsening hypertension (IPTW HR, 1.16) within 1 year of treatment initiation. Comparatively more patients in the BTK inhibitor cohort increased their number of antihypertensive drug classes (19.5-24.8 %) than patients in the non-BTK inhibitor cohort (14.2-17.5 %). These data suggest that development of hypertension is an important consideration in the long-term management of patients with CLL undergoing BTK inhibition.

In the ALPINE trial, treatment-emergent hypertension rates were similar across the zanubrutinib and ibrutinib arms, which is not consistent with other clinical studies that have demonstrated lower hypertension rates with zanubrutinib [14, 24, 25]. Therefore, a post-hoc analysis evaluated the risk of developing hypertension with zanubrutinib vs. ibrutinib in ALPINE based on the initiation of antihypertensive therapy reported in this study. According to the results, smaller proportions of zanubrutinib-treated patients started new antihypertensive drugs or new classes of antihypertensives compared to those treated with ibrutinib (**Figure 6**) [26]. Time to initiation of the first antihypertensive drug in a new class was significantly longer with zanubrutinib (HR; 0.72; $p < 0.05$), and for the time to initiation of the first new antihypertensive drug, the analysis showed a trend favoring zanubrutinib (HR, 0.77; $p = 0.071$). As the authors noted, these findings should be considered when starting BTK inhibitor therapy in patients with CLL/SLL who have an elevated cardiovascular risk.

BTKi use in US community oncology practices

Real-word results in a total of 6,875 CLL/SLL patients who initiated BTK inhibitor treatment in the USA between January 2020 and July 2023 were analyzed by Hou et al. with the aim of describing treatment patterns and AEs [27]. The investigators used the Integra Connect database of electronic health records, practice management, and claims data from 55 practices and > 1,600 providers from the community oncology setting. While 2,815 patients started BTK inhibitor treatment in the first line, 249 did so in later lines. In the first-line setting, ibrutinib was most commonly used (49.3 %), followed by acalabrutinib (43.4 %) and zanubrutinib (7.2 %). In later lines, acalabrutinib ranked first (43.4 %), followed by ibrutinib (39.8 %) and zanubrutinib (16.9 %).

Safety and efficacy outcomes were better for acalabrutinib and zanubrutinib than for ibrutinib. Significantly more patients experienced cardiovascular AEs in the first-line setting with ibrutinib vs. acalabrutinib and zanubrutinib at month 6 (12.1 % vs. 7.6 % and 7.3 %, respectively; $p < 0.05$) as well as month 9 (14.6 % vs. 9.4 % and 8.5 %, respectively; $p < 0.05$). Median time to treatment discontinuation or death in the first line was shortest with ibrutinib (13.7 vs. 19.2 and 19.3 months, respectively). Zanubrutinib showed improved time to next treatment (TTNT) in the first line compared to ibrutinib and acalabrutinib (median TTNT, not reached vs. 30.2 and 35.8 months, respectively). Additional research is required to explain and validate the observed differences favoring zanubrutinib over acalabrutinib.

A retrospective study assessed real-world switching and sequencing to the next line of treatment in US-based patients initiating BTK inhibition as their first-line or second-line CLL/SLL therapy [28]. Information on 2,816 and 1,253 individuals starting their first- and second-line treatment, respectively, was obtained from the Integra Connect database. Ibrutinib was the most commonly used first-line agent (50.5 % vs. 44.0 % and 5.6 % for acalabrutinib and zanubrutinib, respectively), whereas acalabrutinib therapy prevailed in the second line (53.6 % vs. 37.8 % and 8.54 % for ibrutinib and zanubrutinib, respectively). Compared to the groups treated with the other BTK inhibitors, the zanubrutinib cohort had the highest mean age in the second line ($p = 0.0037$) and the highest percentages of patients with SLL across the lines ($p < 0.0001$).

Regardless of the line of therapy, the switching rates at ≤ 60 days and 61-89 days were significantly lower for zanubrutinib than for ibrutinib and acalabrutinib ($p < 0.0001$, **Figure 7**). This resulted in significantly lower proportions of patients receiving their next line of treatment at 180 days in the first-line setting (13.9 % for zanubrutinib vs. 21.1 % and 24.5 % for ibrutinib and acalabrutinib, respectively; $p < 0.0001$) and in the second-line setting (9.1 % vs. 29.2 % and 18.6 %; $p < 0.0001$). The authors emphasized that longer follow-up and larger zanubrutinib sample size are required for a comprehensive assessment of outcomes associated with the use of BTK inhibitors in CLL/SLL. ■

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Meeting unmet needs in mantle cell lymphoma

In older or unfit patients with mantle cell lymphoma (MCL), bendamustine plus rituximab (BR) is the most common first-line therapy, while intensive regimens are usually unsuitable in this population even though they provide durable responses [1, 2]. The addition of the first-in-class BTK inhibitor ibrutinib to first-line BR has been shown to prolong progression-free survival (PFS) in the SHINE trial [3]. However, there was no improvement in overall survival (OS), which was probably due to unexplained deaths in the experimental arm which suggests excess toxicity with the addition of ibrutinib.

First-line setting: acalabrutinib plus chemoimmunotherapy

The double-blind, placebo-controlled, phase III ECHO trial was designed to evaluate the second-generation BTK inhibitor acalabrutinib 100 mg BID until progression in addition to 6 cycles of BR in patients with untreated MCL aged ≥ 65 years who had an ECOG performance status of ≤ 2. Those who achieved at least partial response (PR) after 6 cycles of BR received maintenance treatment with rituximab for 2 years. In the control arm, placebo was administered in addition to 6 cycles of BR and maintenance rituximab in the group with ≥ PR. Crossover to acalabrutinib or other BTK inhibitors was permitted after disease progression. The experimental and control arms each contained 299 patients who were enrolled at 195 sites in 26 countries across the world. PFS constituted the primary endpoint of the ECHO trial.

Acalabrutinib plus BR led to PFS improvement by approximately 17 months, with a 27 % in the risk of disease progression or death (median PFS, 66.4 vs. 49.6 months; HR; 0.73; p = 0.0160) [4], although this benefit is less than what was noted in the SHINE trial [3]. Whereas the overall response rates (ORR) were similar across the arms (91.0 % vs. 88.0 %), the proportion of patients who obtained complete response (CR) was higher with the combination than with BR alone (66.6 % vs. 53.5 %). For OS, the data demonstrated a trend in favor of the acalabrutinib-based regimen (HR, 0.86; p = 0.2743). This was sustained even with most patients in the control arm receiving BTK inhibition as salvage therapy after progression (69 %), although receipt of acalabrutinib was delayed due to logistical hurdles. As the trial had taken place during the pandemic, prespecified PFS and OS analyses censored for COVID-19 deaths were performed. According to these, PFS was improved by 36 % with the addition of acalabrutinib (HR, 0.64; p = 0.0017; **Figure 1**), and OS

was improved by 25 % (HR, 0.75; p = 0.0797).

The safety profile of acalabrutinib plus BR was consistent with that of the individual drugs. Any-grade atrial fibrillation occurred in 6.1 % vs. 4.4 % with acalabrutinib plus BR vs. placebo plus BR (grade ≥ 3, 3.7 % vs. 1.7 %). For hypertension, the rates were lower in the experimental arm (any grade, 12.1 % vs. 15.8 %; grade ≥ 3, 5.4 % vs. 8.4 %), which also applied to major bleeding (any grade, 2.4 % vs. 5.4 %; grade ≥ 3, 2.0 % vs. 3.4 %). Infections were reported in 78.1 % vs. 71.0 % (grade ≥ 3, 41.1 % vs. 34.0 %). Treatment-emergent adverse events (TEAEs) led to discontinuation of acalabrutinib in 42.8 % (vs. 31.0 % for placebo). Median treatment exposure was longer in the experimental arm than in the control arm (29 vs. 25 months).

In their conclusion, the authors pointed out that the ECHO study provided first evidence of a positive trend in OS when adding a BTK inhibitor to frontline standard chemoimmunotherapy for older patients with MCL. These data suggest that acalabrutinib in combination with BR may represent an alternative treatment approach in older MCL patients as compared to the traditional sequential use of BR followed by a BTK inhibitor.

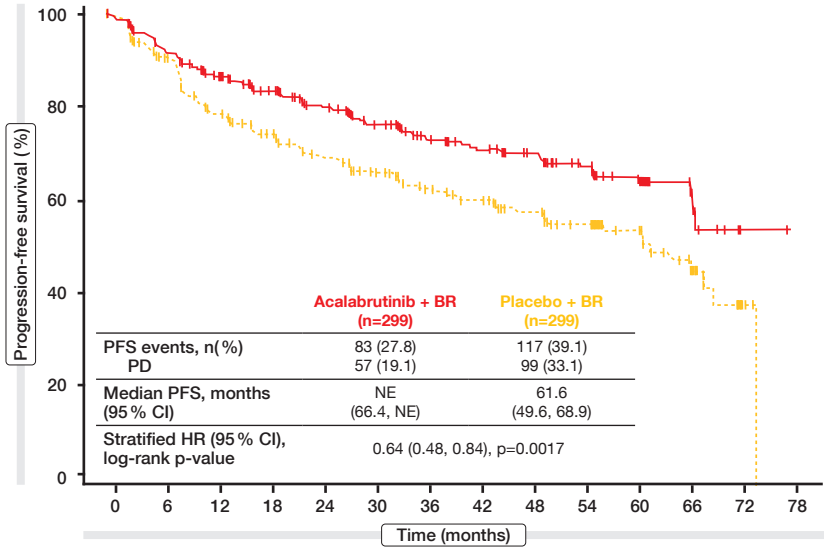

Figure 1: Progression-free survival censored for COVID-19 deaths: acalabrutinib plus BR vs. BR alone

BOVen in older patients

Another option for untreated older patients is the BOVen triplet including the second-generation BTK inhibitor zanubrutinib, obinutuzumab and venetoclax, which has the advantage of being devoid of cytotoxic chemotherapy agents. BOVen has demonstrated promising efficacy and safety in 25 patients with untreated *TP53*-mutant MCL [5]. A multicenter phase II trial is being conducted to characterize the triplet as a first-line approach in patients who are ≥ 65 years of age or have comorbidities precluding autologous stem cell transplantation. While zanubrutinib is being taken continuously from cycle 1, 10 doses of obinutuzumab are administered through cycle 8. The venetoclax therapy starts with a 5-week ramp-up from cycle 3 and is continued until the end of treatment (EOT). At 24 cycles, the investigators will use an MRD-driven approach to limit treatment duration in selected patients: Those with CR and undetectable MRD (uMRD) will discontinue their medication, while those with < CR and/or detectable MRD will continue zanubrutinib and venetoclax. At EHA 2024, Kumar et al. reported preliminary results for 46 patients with a median age of 71 years [6].

BOVen appeared to be safe and well tolerated in untreated older MCL patients. No new safety signals emerged. The most common AEs included bruising (any grade, 39 %), diarrhea (39 %), neutropenia (26 %), and thrombocytopenia (24 %). With the exception of neutropenia, AEs were mostly grade 1 and 2. No grade 5 events occurred. The efficacy analysis revealed an ORR of 98 %, with CR obtained in 79 %. At cycle 3, uMRD5 and uMRD6 were achieved in 50 % and 26 % of patients, respectively. These percentages rose to 100 % and 87 %, respectively, at cycle 13. Almost all patients remained on treatment at the time of data cut-off.

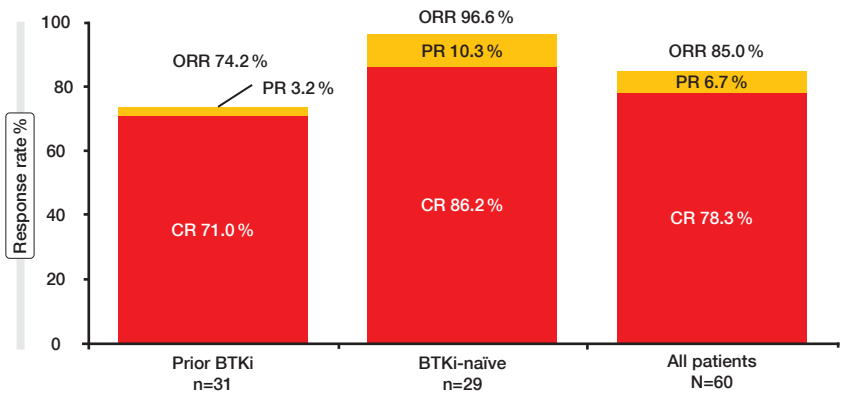

Figure 2: Responses to glofitamab monotherapy in BTKi-pretreated and BTKi-naïve patients

Relapsed/refractory MCL: fixed-duration glofitamab

In the relapsed/refractory setting, there is an unmet medical need as response duration decreases after each relapse. New treatment options are called for, particularly in light of the growing importance of first-line BTK-inhibitor (BTKi)-based regimens. One of these options might be the CD20 x CD3 bispecific antibody glofitamab that has already shown high CR rates and durable responses as monotherapy in patients with heavily pretreated relapsed/refractory MCL in the multicenter, phase I/II NP30179 study [7]. In this study, glofitamab 30 mg is administered in 21-day cycles for a maximum of 12 cycles. Measures for the mitigation of cytokine release syndrome (CRS) include obinutuzumab pretreatment with either 1,000 mg or 2,000 mg in addition to step-up dosing of glofitamab from 2.5 mg to 10 mg

during the first cycle. Phillips et al. presented updated findings after a median follow-up of 19.6 months [8]. Among 60 patients, 31 had previously received BTK inhibitor treatment, while 29 were BTKi-naïve. Refractoriness to the last prior therapy was present in 87.1 % and 58.6 %, respectively, in these two groups. Their median number of prior lines was 3.0 and 2.0, respectively.

High overall response and CR rates were observed in both BTKi-pretreated and BTKi-naïve patients (**Figure 2**). Responses also proved durable as they lasted for a median of 16.2 and 12.6 months in the overall population and the BTKi-pretreated cohort, respectively. Median duration of CR was 15.4 and 12.6 months, respectively. Almost 60 % of CRs were still ongoing at data cut-off in the total group. Moreover, the analysis revealed clinically significant PFS and OS results. In all patients, the 15-month PFS and OS rates were 54.0 % and 71.4 %, respectively, and in the BTKi-pretreated cohort, 33.0 % and 55.0 %, respectively. According to landmark analyses performed by response, the majority of patients who had achieved CR at EOT remained alive and progression-free at 15 months after EOT, with PFS and OS rates of 59.2 % and 72.7 %, respectively.

The incidence and severity of AEs were consistent with the known safety profile of glofitamab. CRS, which occurred as the most frequent AE, was less common with the higher obinutuzumab dose (87.5 % and 63.6 % with 1,000 mg and 2,000 mg, respectively); also, events took longer to occur and resolved sooner with obinutuzumab 2,000 mg pretreatment. The CRS rates were higher than those observed with glofitamab in the setting of relapsed/refractory diffuse large B-cell lymphoma [9]. Other common AEs included neutropenia, COVID-19, pyrexia, and anemia. Glofitamab-related grade 3/4 AEs emerged in 58.3 %. No patient died due to the study medication. The majority of CRS events were grade 1 or 2 and predominantly occurred in cycle 1. Median duration of CRS was shorter in patients in the 2,000 mg obinutuzumab cohort than in the 1,000 mg cohort.

Any-grade infections were reported in 73.3 % in the overall group; 31.7 % of patients developed COVID-19/COVID-19 pneumonia, with 8.3 % dying due to the infection. All patients who died due to COVID-19 had achieved a CR, with six of the seven still in remission at the time of death. Immune effector cell-associated neurotoxicity syndrome (ICANS) was observed in only 5.0 %. All ICANS events were restricted to grade 1 and 2 and resolved. The 2,000 mg obinutuzumab pretreatment regimen is being used in the ongoing phase III GLOBRYTE study that is comparing glofitamab monotherapy with treatment according to investigators' choice in patients with relapsed/refractory MCL (NCT06084936).

Indirect comparison of zanubrutinib and acalabrutinib

The second-generation BTK inhibitors zanubrutinib and acalabrutinib have demonstrated clinical benefits in separate single-arm trials elucidating their activity in patients with relapsed/refractory MCL [10-14]. In the absence of head-to-head clinical trials, Shah et al. evaluated the comparative efficacy of the two agents using population-adjusted indirect treatment comparison via a simulated treatment comparison approach [15]. The analysis was based on the pooled individual patient-level data from the BGB-3111-206 and BGB-3111-AU-003 trials assessing zanubrutinib, as well as on the published aggregated data of the ACE-LY-004 study that investigated acalabrutinib [10-14]. A key difference among these was that BGB-3111-206 had a Chinese population, whereas BGB-3111-AU-003 included Western patients and ACE-LY-004 was a global trial. Overall, the zanubrutinib and acalabrutinib populations included 123 and 124 individuals with relapsed/refractory MCL, respectively.

According to the simulated treatment comparison, zanubrutinib therapy was associated with advantages regarding several efficacy endpoints. PFS was statistically significantly longer compared to acalabrutinib (HR, 0.57; p = 0.0272), as was OS (HR, 0.43; p = 0.0105). For ORR, the difference did not reach statistical significance, although the odds of responding were higher in the zanubrutinib-treated group (OR, 2.05; p = 0.1798). The proportion of patients with high LDH levels and > 2 prior treatment lines was found to be significantly predictive of survival outcomes in the regression models. Overall, these data provide some evidence to support the superiority of zanubrutinib over acalabrutinib in relapsed/refractory MCL. Limitations arise from differences in designs, treatment regimens and populations across the studies (i.e., Chinese vs. Western and other ethnicities) that potentially affect the validity of indirect comparisons.

Real-world data on covalent BTK inhibitors

A retrospective observational cohort study compared the covalent BKI inhibitors zanubrutinib, acalabrutinib and ibrutinib as second- or third-line single-agent treatment of US-based patients with relapsed/refractory MCL [16]. Overall, the investigators identified 602 individuals from the Flatiron Health database. Zanubrutinib, acalabrutinib and ibrutinib had been administered in 107, 301 and 194 patients, respectively. Most received the BTK inhibitor as their second-line treatment.

Unadjusted median time to next treatment (TTNT) was 16.8 months for zanubrutinib, 11.5 months for acalabrutinib, and 8.6 months for ibrutinib. Median OS had not been reached for zanubrutinib, while the unadjusted median OS for acala-

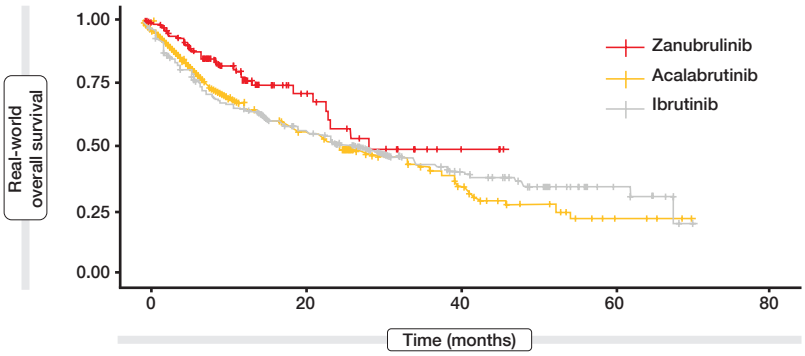

Figure 3: Real-world overall survival for zanubrutinib, acalabrutinib and ibrutinib as second- or third-line treatment of relapsed/refractory MCL

brutinib and ibrutinib was 27.4 and 29.3 months, respectively (**Figure 3**). The fully adjusted inverse probability of treatment weighting model took the following factors into account: age, sex, time from first to second line, time from second to third line, ECOG stage at initial diagnosis, LDH status, bulky disease status, and Ki67 status. According to this, zanubrutinib performed significantly better than ibrutinib regarding both TTNT (HR, 0.64; p = 0.02) and OS (HR, 0.56; p = 0.02), with the caveat that with retrospective studies, certain nuances such as discontinuation or medical non-compliance are hard to truly take into account. The respective differences between zanubrutinib and acalabrutinib showed trends favoring zanubrutinib (TTNT: HR, 0.84 and p = 0.30; OS: HR, 0.74 and p = 0.20), although the number of patients on acalabrutinib was much higher in this dataset. Future research is warranted to identify factors influencing the utilization of covalent BTK inhibitors and reasons for differences in real-world TTNT and OS.

Adherence and resource utilization

Data from the Symphony Integrated Dataverse database were used to examine treatment adherence and healthcare resource utilization of patients with MCL undergoing BTK inhibitor treatment in the USA [17]. The scientists identified two cohorts: One included patients receiving their first BTK inhibitor (zanubrutinib, acalabrutinib, or ibrutinib) during the index period, while the other contained patients who received ibrutinib as their first BTK inhibitor and initiated acalabrutinib or zanubrutinib thereafter during the index period. Compliance was calculated as the proportion of days covered using 30-day intervals from initiation of treatment to 1 year. Persistence, on the other hand, was measured as the proportion of patients who remained on treatment within the cohort that had sufficient follow-up.

Among the first-ever BTK inhibition patients (n = 2,122), 519, 878 and 725 initiated zanubrutinib, acalabrutinib and ibrutinib, respectively. Compliance at 1 year was numerically highest for zanubrutinib (16.73 %) followed by acalabrutinib (16.45 %) and ibrutinib (11.80 %). Likewise, treatment persistence at 1 and 2 years was numerically highest for zanubrutinib (33.1 %; 18.6 %) compared to acalabrutinib (32.8 %; 16.3 %) and ibrutinib (30.6 %; 15.7 %).

A total of 228 patients switched from ibrutinib to acalabrutinib (n = 140) or zanubrutinib (n = 88). In this group, the analysis showed numerically improved 1-year compliance for zanubrutinib compared to acalabrutinib (p = 0.2176), as well as numerically better treatment persistence at 1 and 2 years (p = 0.2687 and p = 0.6270; **Figure 4**).

In similar vein, healthcare resource utilization favored zanubrutinib. In patients who switched from ibrutinib to zanubrutinib, the mean number of outpatient visits was lower than in those who switched from ibrutinib to acalabrutinib (1.12 vs. 1.62; p = 0.1755). This observation also applied to inpatient services (0.22 vs. 0.68; p = 0.1693). Taken together, zanubrutinib, when used as the first BTK inhibitor and after prior ibrutinib, was associated with a trend toward improved compliance, persistence, and health care resource utilization compared to acalabrutinib.

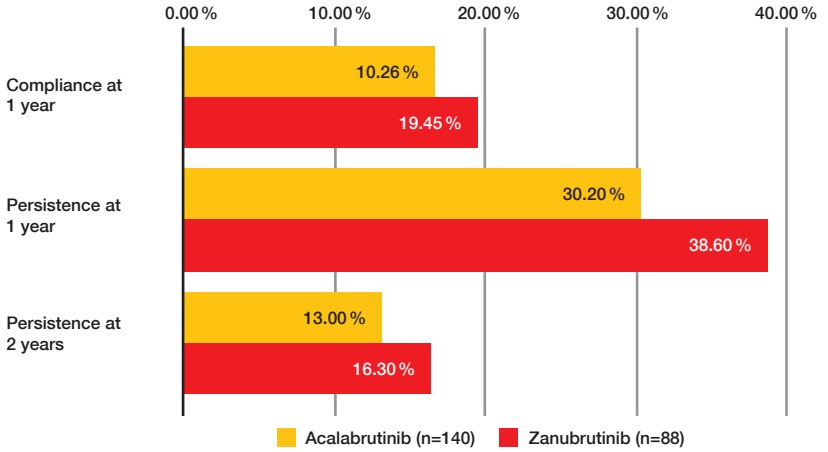

Figure 4: Treatment compliance and persistence with acalabrutinib und zanubrutinib after switching from ibrutinib

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BTK degraders: emerging activity in various B-cell malignancies

The new class of BTK degraders is being developed in response to emerging patterns of resistance that limit the utility of BTK and BCL2 inhibitors. On one hand, *BTK* mutations decrease the efficacy of both covalent and non-covalent BTK inhibitors; on the other hand, some mutations lead to "kinase dead" or "kinase bypassing" *BTK* mutants with intact B-cell receptor signaling through a scaffolding function of BTK [1, 2].
This raises the need for a new treatment modality that targets both emerging resistance mutations and the BTK scaffolding activity. These two mechanisms are potentially addressed by BTK degraders such as NX-5948, which is a chimeric targeting molecule that works by catalyzing ubiquitylation and proteasomal degradation of BTK [3].

Responses to NX-5948 despite poor-prognosis mutations

NX-5948 is being evaluated in an ongoing phase IA/IB trial conducted in adults with relapsed/refractory B-cell malignancies. At EHA 2024, Linton et al. presented the latest results for 31 patients with chronic lymphocytic leukemia (CLL) and 48 patients with mantle cell lymphoma, marginal zone lymphoma (MZL), follicular lymphoma (FL), diffuse large B-cell lymphoma, primary CNS lymphoma, and Waldenström macroglobulinemia (WM) [4]. All of them had relapsed/refractory disease and were pretreated with ≥ 2 lines of therapy (≥ 1 for CNS lymphoma). The average age in the total population was 67.0 years. A median of 4.0 prior lines had been administered before study entry, with BTK and BCL2 inhibitors having been used in 74.7 % and 44.3 %, respectively. Forty-three percent of patients had received both drug classes. Almost 50 % of the CLL cohort were carriers of *TP53* mutations, and 43.3 % showed *BTK* mutations. These alterations indicate a hard-to-treat and genetically diverse population.

According to the safety analysis across the CLL and non-Hodgkin lymphoma (NHL) groups, NX-5948 was well tolerated in this elderly and heavily pretreated patient group. Common treatment-emergent adverse events (TEAEs) included purpura/contusion (35.4 %), thrombocytopenia (26.6 %), neutropenia (20.3 %), fatigue (17.7 %), anemia (16.5 %), petechiae (16.5 %), rash (16.5 %), and headache (15.2 %). Neutropenia constituted the most frequent grade 3 TEAE (15.2 %). One dose-limiting toxicity occurred, and two TEAEs resulted in drug discontinuation in the NHL cohort. No additional safety signals were observed at higher doses. In particular, the treatment did not give rise to cardiac TEAEs.

The efficacy findings reported at EHA focused on the CLL cohort. In response-evaluable patients (n = 26), NX-5948 induced a high ORR of 69.2 %, with all of the responses being partial remissions (PR) and PR with lymphocytosis. Responses occurred across the entire dose range; they were already evident at the time of the first scan after 8 weeks in most responders and were ongoing in all of them at data cut-off. No significant pattern of response was observed in patients with treatment-resistance and poor-prognosis mutations, which implies that the poor prognosis associated with these mutations may be overcome by the treatment. The analysis revealed no distinct genotypic profile linked to intrinsic NX-5948 resistance. In 30 individuals with CLL, NX-5948 caused rapid and robust degradation of wild-type and mutant BTK (**Figure**).

These results support the continued development of NX-5948 in the setting of CLL, where phase IB dose expansion is planned. The dose escalation part of the study is still ongoing. According to the authors, BTK degraders have the potential to replace BTK inhibitors, particularly in patients with many mutations.

Promising efficacy of BGB-16673

The chimeric degradation activating compound BGB-16673 has been designed to induce BTK degradation via polyubiquitination [5]. In the first-in-human phase I/II CaDAnCe-101 study, BGB-16673 is being assessed in adults with relapsed/refractory B-cell malignancies after ≥ 2 prior therapies including covalent BTK inhibition, if approved for the respective disease. Preliminary data have shown a tolerable safety profile of BGB-16673 and clinical responses even in the presence of resistance to covalent and non-covalent BTK inhibitor therapy, along with substantial reductions in BTK protein levels in peripheral blood and tumor tissue [6]. Parrondo et al. presented updated safety and efficacy results for patients with relapsed/refractory CLL and small lymphocytic lymphoma (SLL) [7]. Forty-nine individuals were included in

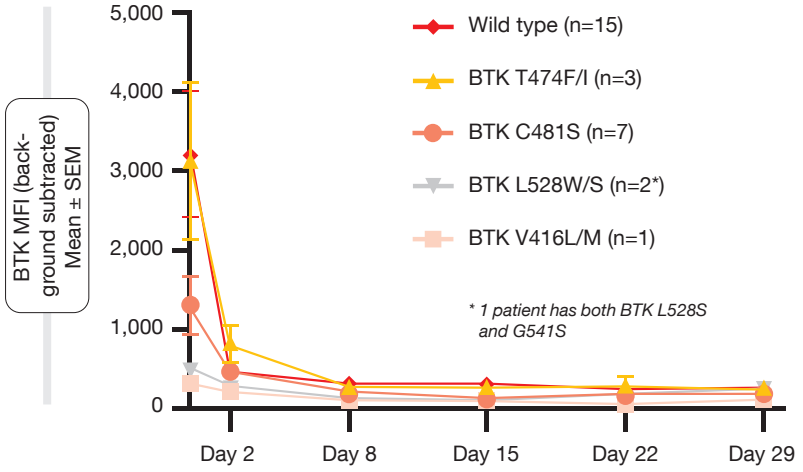

Figure: Rapid and robust degradation of wild-type and mutant BTK with NX-5948

TABLE
CaDAnCe-101 study: responses achieved with BGB-16673 in CLL patients

Outcome	50 mg (n = 1)	100 mg (n = 5)	200 mg (n = 16)	350 mg (n = 14)	500 mg (n = 7)	Total (n = 43)
Best overall response, n (%)						
Complete response	0	0	2 (13)	0	0	2 (5)
Partial response	1 (100)	4 (80)	10 (63)	6 (43)	1 (14)	22 (51)
Partial response with lymphocytosis	0	0	2 (13)	2 (14)	3 (43)	7 (16)
Stable disease	0	1 (20)	1 (6)	2 (14)	3 (43)	7 (16)
Progressive disease	0	0	1 (6)	1 (7)	0	2 (5)
Discontinued prior to first assessment	0	0	0	3 (21)	0	3 (7)
Overall response rate, n (%)	1 (100)	4 (80)	14 (88)	8 (57)	4 (57)	31 (72)
Disease control rate, n (%)	1 (100)	5 (100)	15 (94)	10 (71)	7 (100)	38 (88)
Time to first response, months	2.9	4.2	2.8	2.8	2.8	2.8

the analysis with a median follow-up of 4.6 months. They had received a median of 4 prior lines of treatment, with 89 % having discontinued BTK inhibitor treatment due to disease progression. Many showed high-risk features such as unmutated IGHV status (82 %), del(17p) or *TP53* mutation (60 %), or complex karyotype (47 %). BGB-16673 is being tested within a dose range from 50 mg to 500 mg/d.

Among any-grade AEs, the most common were fatigue (33 %), contusion (29 %), anemia (22 %), diarrhea (22 %) and neutropenia/decreased neutrophil count (22 %). Grade ≥ 3 neutropenia occurred in 20 %. The maximum tolerated dose had not been reached at the time of the analysis. One dose-limiting toxicity was noted at the 200 mg dose, which was grade 3 maculopapular rash that resolved after a 5-day dose hold and did not reappear on resumed treatment. To date, no cases of atrial fibrillation or grade ≥ 3 hypertension have been observed, and no treatment-related fatal AEs were reported. Dose interruptions and reductions were called for in 37 % and 6 %, respectively.

BGB-16673 demonstrated promising anti-tumor activity, including in patients with covalent and non-covalent BTK-inhibitor–resistant mutations and those previously exposed to BCL2 and BTK inhibitors. Overall, 72 % of 43 response-evaluable patients responded (**Table**). The ORR for the 200 mg group was 88 %, with two individuals obtaining complete remission. After data cut-off, an additional patient in the 200 mg dose cohort experienced deepening of response from stable disease to PR, which increased the ORR in this cohort to 94 %. Also, in patients after prior covalent BTK and BCL2 inhibitor treatment, the ORR was as high as 70 %; patients with del(17p) or *TP53* mutation responded in 68 % and those with complex karyotype in 67 %. Responses were observed irrespective of the presence of *PLCG2* mutations and C481S, T474I and/or L528S *BTK* mutations. A phase II cohort of patients with CLL/SLL exposed to both covalent BTK and BCL2 inhibition is currently enrolling.

Findings for BGB-16673 in indolent NHL

Another analysis from the CaDAnCe-101 study reported at EHA 2024 relates to updated findings in the setting of FL, MZL and WM [8]. Twenty-five patients included in the data set were treated with BGB-16673 100 mg, 200 mg, or 350 mg/d. Sixty-four percent of them remained on treatment at a median follow-up of 5.85 months. They were heavily pretreated, with a median of 4 prior lines of therapy.

BGB-16673 appeared to be safe and tolerable, with no dose-limiting toxicities seen to date. The most common TEAEs across dose groups were contusion (32 %) followed by fatigue, neutropenia/decreased neutrophil count, asymptomatic transient elevation of amylase levels, and upper respiratory tract infection (each 24 %). Grade ≥ 3 TEAEs mainly included neutropenia/decreased neutrophil count (20 %) and anemia (8 %). None of the BGB-16673–related TEAEs led to death or treatment discontinuation. The ORRs were 57 % in patients with FL, 60 % in those with MZL, and 92 % in the group with WM. Disease control resulted in 86 %, 80 % and 100 %, respectively. All patients with WM showed numerical reductions in IgM levels from baseline. Ongoing anti-tumor activity with a short time to response was noted, which also applied to patients who had BTK-inhibitor–resistant disease.

Overall, these data support further investigation of the clinical activity of BGB-16673 in patients with NHL. Dose finding and additional safety expansion are ongoing, and enrollment is continuing in the CaDAnCe-101 study. ■

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Innovative BCL2 inhibition: indications fanning out across B-cell malignancies

Sonrotoclax in patients with CLL

The combination of the first-generation BCL2 inhibitor venetoclax and the first-in-class BTK inhibitor ibrutinib has demonstrated efficacy in patients with chronic lymphocytic leukemia (CLL) [1], although tolerability of this regimen is limited. Next-generation agents can be expected to provide optimized toxicity profiles. The second-generation BCL2 inhibitor sonrotoclax inhibits BCL2 in a more selective and pharmacologically potent manner than venetoclax, with a shorter half-life preventing drug accumulation that might contribute to toxicity [2]. Likewise, the second-generation BTK inhibitor zanubrutinib has shown superior safety and tolerability compared with ibrutinib, including fewer cardiac events, in patients with relapsed/refractory CLL [3].

BGB-11417-101, an ongoing global, phase I/IB study, is evaluating sonrotoclax as monotherapy or in combination with zanubrutinib, obinutuzumab, or both, in the setting of B-cell malignancies. At EHA 2024, Opat et al. presented updated findings for patients with relapsed/refractory CLL who received sonrotoclax plus zanubrutinib in BGB-11417-101 [4]. Treatment consisted of 8–12 weeks of zanubrutinib lead-in (320 mg QD or 160 mg BID) followed by the combination with sonrotoclax (with weekly or daily ramp-up to the target dose) until disease progression. Overall, 47 patients were treated with sonrotoclax 40 mg, 80 mg, 160 mg, 320 mg, or 640 mg. The cohorts included considerable percentages of patients with high-risk cytogenetics including del(17p), *TP53* mutation and unmutated IGHV.

Deep responses at all dose levels

No dose-limiting toxicities occurred, and the maximum tolerated dose (MTD) was not reached. The sonrotoclax 320 mg dose was selected for dose expansion. Sonrotoclax plus zanubrutinib displayed a tolerable safety profile at all dose levels. At a median follow-up of 19.3 months, 46 of 47 patients remained on treatment. The analyses yielded no cardiac toxicity, including atrial fibrillation, and no tumor lysis syndrome (TLS). Adverse events (AEs) mostly comprised contusion, neutropenia, COVID-19, diarrhea, fatigue, nausea and upper respiratory tract infections, with the majority being grade 1 or 2. In the cohort receiving the recommended phase II sonrotoclax dose of 320 mg plus zanubrutinib (n = 22), neutropenia was observed in 41 %, with 36 % of patients experiencing grade ≥ 3 events. Despite the high proportion of severe neutropenia, no febrile neutropenia occurred on the study, and no deaths were reported overall. Treatment-emergent AEs (TEAEs) led to sonrotoclax discontinuation in one individual treated with the 640 mg dose. None of the patients experienced TEAEs prompting sonrotoclax dose reductions. Zanubrutinib discontinuations and dose reductions due to TEAEs were necessary in 4 % and 2 %, respectively.

Sonrotoclax plus zanubrutinib showed promising efficacy. Deep responses were obtained across all dose levels, with an overall response rate (ORR) of 97 % and a 57 % rate of complete responses (CR) plus CR with incomplete hematologic recovery (CRi) across all doses. Five of six evaluable patients with prior BTK inhibitor therapy responded to treatment. In the sonrotoclax 320 mg cohort, all patients experienced responses, and the CR/CRi rate was 73 %. Eighty-five percent of 33 minimal residual disease(MRD)-evaluable patients had undetectable MRD (uMRD) at the time of data cut-off (**Figure 1**). Responses deepened over time. All patients in the 160 mg, 320 mg and 640 mg cohorts who reached week 48 achieved uMRD. Only one progression-free survival event had occurred at the time of the analysis. Follow-up of this phase I/IB study is ongoing.

In addition, sonrotoclax plus zanubrutinib is currently being investigated in treatment-naïve patients with CLL. The randomized, open-label, phase III CELESTIAL-TNCLL trial is comparing the combination to the standard regimen of venetoclax plus obinutuzumab [5]. PFS has been selected as the primary endpoint.

Findings obtained for mantle cell lymphoma

Moreover, the BGB-11417-101 study contains a cohort of patients with relapsed/refractory mantle cell lymphoma (MCL). As for CLL, the combination of venetoclax and ibrutinib has proven efficacious in this setting, although the rates of toxicity were high, demonstrating a need for safer regimens [6]. Tam et al. reported results for 40 patients with relapsed/refractory MCL who received

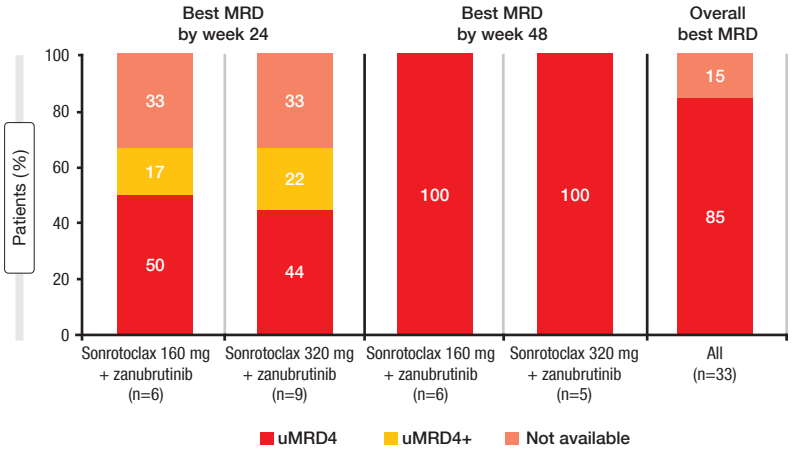

Figure 1: Undetectable minimal residual disease in the peripheral blood of relapsed/refractory CLL patients treated with sonrotoclax plus zanubrutinib

sonrotoclax 80 mg, 160 mg, 320 mg or 640 mg in addition to zanubrutinib in the BGB-11417-101 study [7]. The 160 mg and 320 mg dose levels were chosen for the expansion cohorts.

Sonrotoclax plus zanubrutinib was generally well tolerated. Dose escalation was completed without MTD being reached. No atrial fibrillation and no clinical or laboratory TLS events were observed regardless of target dose. The most common any-grade TEAEs were contusion (30 %), neutropenia (28 %), and diarrhea (28 %). Neutropenia once again constituted the most common grade ≥ 3 TEAE (18 %) but proved manageable, with no dose reductions and only one dose hold due to a concurrent COVID-19 infection. G-CSF was prescribed in 6 patients for a median treatment duration of 3.5 days. Thrombocytopenia occurred in 23 %, with 13 % of cases graded as ≥ 3. TEAEs led to sonrotoclax discontinuation in 13 %, while no dose reductions were required. For zanubrutinib, the discontinuation and dose reduction rates were 15 % and 5 %, respectively.

The combination gave rise to deep responses with ORRs of 73 % and 92 % in the 160 mg and 320 mg cohorts, respectively, and CR rates of 46 % and 83 %, respectively. Two of three response-evaluable patients with prior BTK inhibitor treatment responded, with one of them achieving CR. The 320 mg dose was selected as the recommended phase II dose for further development in future pivotal studies.

Relapsed/refractory WM: encouraging activity

Another analysis presented at EHA 2024 that is based on the BGB-11417-101 study assessed sonrotoclax monotherapy in the cohort with relapsed/refractory Waldenström macroglobulinemia (WM) [8]. Twenty individuals with a median number of prior therapies of 2.5 were treated with sonrotoclax 80 mg, 160 mg, 320 mg, or 640 mg. Twelve of them had undergone prior BTK inhibitor therapy, with 9 receiving it as their last prior systemic treatment.

The most common any-grade TEAEs across the dose cohorts included anemia (35 %), COVID-19 (30 %), and pyrexia (25 %). Anemia was the most common grade ≥ 3 event (20 %). Neutropenia and thrombocytopenia were reported in 20 % (grade ≥ 3, 5 %) and 15 % (grade ≥ 3, 10 %), respectively. One patient in the 160-mg dose cohort experienced a dose-limiting toxicity of grade 3 febrile neutropenia that resolved after 2 days without dose reduction. No laboratory or clinical TLS was observed irrespective of target dose. TEAEs led to sonrotoclax discontinuation and dose interruption in 10 % and 25 %, respectively. Dose escalation is ongoing at 640 mg, after the MTD has not been reached at data cut-off. The preliminary antitumor activity of sonrotoclax monotherapy was encouraging in this heavily pretreated population, with high and durable responses across the tested dose levels. Overall, the ORR was 79 % (**Figure 2**).

Sonrotoclax monotherapy is being further evaluated in patients with relapsed/refractory WM in the pivotal, phase II BGB-11417-203 study that is currently recruiting [9]. BGB-11417-203 contains three cohorts that are refractory to different drug classes. The major response rate has been defined as the primary endpoint. Patient recruitment is ongoing in Australia, the USA, China, and Europe.

BGB-11417-105: multiple myeloma

Sonrotoclax is also being investigated in the setting of multiple myeloma (MM). Here, no BCL2-targeted therapies have been approved to date although BCL2 is an attractive target in MM with t(11;14) and responses have been obtained with venetoclax [10]. The open-label, phase IB/II BGB-11417-105 study is testing sonrotoclax as the backbone for different combination regimens including dexamethasone, dexamethasone plus carfilzomib, daratumumab, or pomalidomide. Patients with relapsed/refractory MM harboring t(11;14) are participating in the study. Dhakal et al. presented results for 32 individuals treated with sonrotoclax 640 mg once daily, which is the recommended dose for expansion [11]. In addition, dexamethasone 40 mg was administered weekly. This group had received a median number of prior treatment lines of 3. All patients had prior proteasome inhibitor and immunomodulatory drug exposure, and most had previously received anti-CD38 antibody therapy (72 %). Many were refractory to these three drug classes. Sixty-three percent had undergone autologous stem cell transplantation.

According to the findings reported at EHA 2024, sonrotoclax plus dexamethasone was well tolerated in this heavily pretreated population. No dose-limiting toxicities occurred during dose escalation. During dose expansion, low rates of hematologic toxicities (any hematologic TEAEs, 12.5 %) and infections (21.9 %) were observed. The most common TEAEs

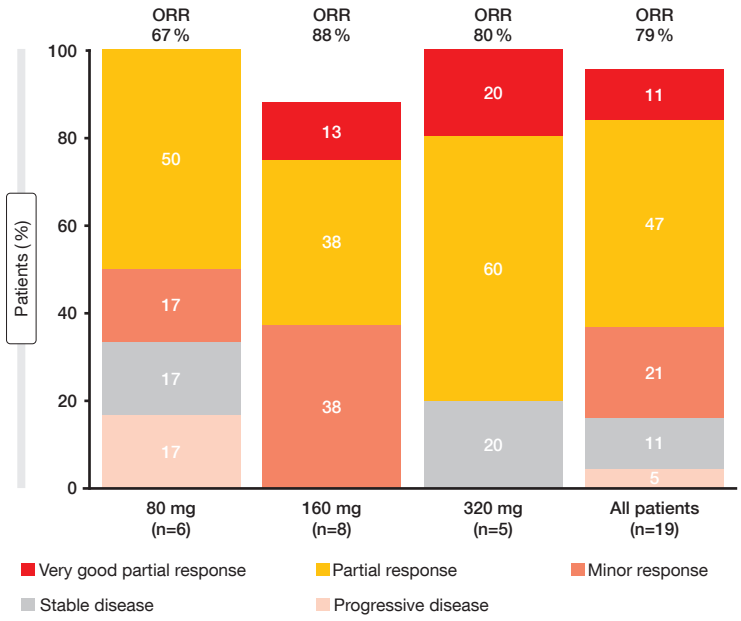

Figure 2: Responses observed for sonrotoclax monotherapy in relapsed/refractory Waldenström macroglobulinemia

TABLE
Sonrotoclax plus azacitidine in treatment-naïve AML: disease responses

Response	All patients (n = 46)
CR, n (%)	24 (54)
Median time to CR, months	1.8
Median duration of CR, months	15.1
CR/CRh, n (%)	29 (63)
Median time to CR/CRh, months	1.3
Median duration of CR/CRh, months	16.9
CR/CRi, n (%)	32 (70)
Median time to CR/CRi, months	1.3
Median duration of CR/CRi, months	16.9

CRh, complete response with partial hematologic recovery
CRi, complete response with incomplete hematologic recovery

were fatigue and insomnia (each 28 %), diarrhea (22 %), as well as constipation and nausea (each 16 %). TEAEs gave rise to dose interruptions of sonrotoclax in 18.8 %, while no dose reductions were necessary.

The combination provided deep and durable responses. Overall, 75 % of patients responded, with 16.7 % and 4.2 % experiencing CR and stringent CR, respectively. Very good partial responses and partial responses resulted in 29.2 % and 25.0 %, respectively. The longest duration of response was 18 months, and two patients remained on treatment for more than one year.

Tackling AML with sonrotoclax-based treatment

Venetoclax combined with the hypomethylating agent azacitidine, as compared to azacitidine alone, has improved outcomes in treatment-naïve patients with acute myeloid leukemia (AML) who were unfit for intensive chemotherapy [12]. However, there is still an unmet need as relapses are common. BGB-11417-103, an ongoing, global, phase IB/II study, is assessing sonrotoclax 40 mg, 80 mg, 160 mg, and 320 mg with or without azacitidine in patients with AML and myelodysplastic syndromes/myeloproliferative neoplasms. Preliminary safety and efficacy were reported at EHA 2024 for sonrotoclax plus azacitidine in 48 treatment-naïve patients with unfit AML [13].

The most common any-grade TEAEs were neutropenia (79 %), thrombocytopenia (68 %), constipation (52 %), and nausea (52 %). Grade ≥ 3 neutropenia and thrombocytopenia were observed in 77 % and 60 %, respectively, and grade ≥ 3 anemia and febrile neutropenia occurred in 38 % and 42 %, respectively. Half of patients experienced grade ≥ 3 infections and infestations. TEAEs leading to death in five patients (10 %) included pneumonia, neutropenic sepsis, bronchopulmonary aspergillosis, pulmonary sepsis and metastatic squamous cell carcinoma, although none of these were considered related to the study treatment. Three dose-limiting toxicities (i.e., grade 4 neutropenia and thrombocytopenia) were reported in two patients treated with azacitidine plus sonrotoclax 80 mg. Laboratory TLS occurred in one patient receiving azacitidine plus sonrotoclax 160 mg and resolved in 4 days without concomitant allopurinol.

Regarding antileukemic activity, the analysis revealed an ORR of 78 % and a CR rate of 54 % in the efficacy-evaluable population (n = 46; **Table**). CR plus CR with partial hematologic recovery was achieved in 63 % of patients, while CR plus CRi resulted in 70 %. After a median follow-up of 19.8 months, median duration of CR was 15.1 months. Thirty-seven percent of all efficacy-evaluable patients obtained MRD negativity. At the time of the analysis, the study stopping criteria had not been met in any of the dose cohorts. The safety expansion is ongoing in the 80 mg, 160 mg, and 320 mg cohorts to determine the recommended phase II dose. ■

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Follicular lymphoma: news on bispecific antibody treatment

Primary analysis of the ELM-2 study

In the setting of relapsed/refractory follicular lymphoma (FL), progression-free survival (PFS) deteriorates with successive relapses, which implies a high unmet need for therapies that can improve disease control and extend survival after relapse [1]. The Fc-silenced CD20 x CD3 bispecific antibody odronextamab is being investigated in patients with relapsed/refractory B-cell malignancies in the multicohort, multicenter, phase II ELM-2 study. At EHA 2024, Taszner et al. presented the primary analysis for the FL cohort (n = 128) [2].

These patients had FL grade 1-3a and were refractory to, or had relapsed after, ≥ 2 lines of treatment that included an anti-CD20 antibody and an alkylator. Their median number of prior lines was 3 (range, 2–13). Seventy-two percent were refractory to the last line of therapy. Double refractoriness to anti-CD20 antibody therapy and an alkylator was present in 41 %. In 49 % of patients, progression of disease had occurred within 24 months of the initiation of first-line treatment (POD24).

Odronextamab was stepped up in cycle 1 to mitigate the risk of cytokine release syndrome (CRS). During the induction phase in cycles 2–4, treatment consisted of odronextamab 80 mg on days 1, 8 and 15 intravenously. This was followed by the maintenance period with 160 mg administered Q2W. The two-weekly intervals could be changed to four-weekly intervals in patients who had achieved complete response (CR) for ≥ 9 months. Anti-infection prophylaxis included immunoglobulin supplementation in patients with severe hypogammaglobulinemia (i.e., < 400 mg/dL) or recurrent episodes of infection with immunoglobulin levels of 400–600 mg/dL, as well as antivirals and *Pneumocystis jirovecii* pneumonia prophylaxis.

Durable responses in a heavily pretreated population

Among 128 individuals included in the FL cohort of the ELM-2 study, 85 % completed ≥4 cycles of treatment. The objective response rate (ORR), which was defined as the primary endpoint, was 80 % after a median follow-up of 20 months. CR was obtained in 73 %. Median duration of objective response and CR was 23 and 25 months, respectively. Subgroup analyses yielded consistent efficacy regarding ORR across most prespecified high-risk subgroups including those with POD24, refractoriness to the last line of treatment, and double refractoriness.

Median PFS was 21 months in all patients and was longer in those with CR compared to those with partial response (PR; 28 vs. 11 months). At 12 months, 79 % vs. 50 % of patients with CR and PR, respectively, were alive and progression-free. Median OS had not been reached in the total population, with 12-month and 24-month OS rates of 86 % and 70 %, respectively. While median OS had not been reached in the group that achieved CR, this was 18 months in the partial responders. At 24 months, the OS rates were 81 % vs. 19 % for patients with CR vs. PR.

PFS was also assessed by MRD status in 64 patients with available samples. According to this, PFS was longer in those who were MRD-negative on day 15 of cycle 4 than in the group retaining MRD-positive status (HR, 0.30; **Figure 1**). None of the 14 patients in the biomarker population who discontinued odronextamab due to disease progression achieved MRD negativity on or after day 15 of cycle 4. Another exploratory biomarker analysis investigated best overall response by CD20 expression. These data indicated that even patients with low or undetectable CD20 expression by immunohistochemistry or mRNA level measurement could achieve (complete) remission.

The treatment-emergent adverse events (TEAEs) were generally manageable and consistent with previous reports. CRS was the most common treatment-related TEAE (56 %), followed by neutropenia (30 %), infusion-related reactions (29 %), pyrexia (24 %) and anemia (20 %). CRS events were almost exclusively grade 1 or 2 and showed a median duration of 8 hours. Any-grade infections occurred in 80 %; here, 37 % were due to COVID-19. The rates of infections reflected a population with underlying B-cell functional impairment due to the malignancy and prior exposure to immunosuppressive therapy. Grade 2 immune effector cell-associated neurotoxicity syndrome (ICANS) was reported in one patient. TEAEs prompted treatment interruption/delay in 63 %. Four patients (3 %) died due to treatment-related TEAEs including pneumonia and progressive multifocal leukoencephalopathy.

According to the authors' conclusion, odronextamab might offer an important off-the-shelf treatment option for heavily pretreated patients with relapsed/refractory FL. At present, the phase III trials

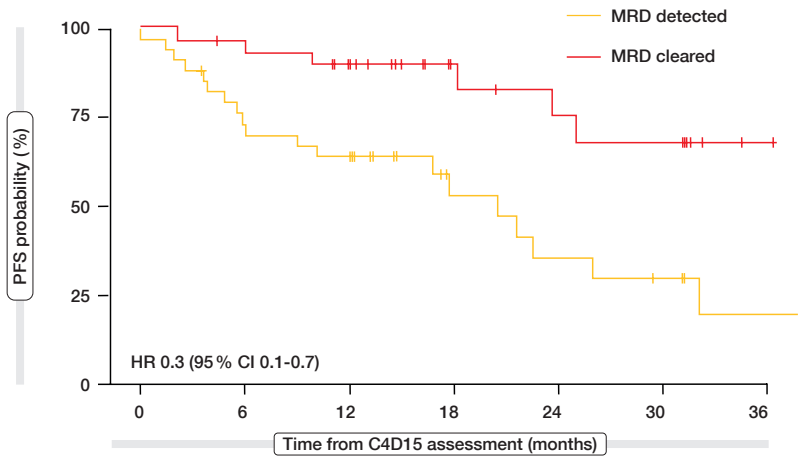

Figure 1: Odronextamab: progression-free survival by MRD status on day 15 of cycle 4

OLYMPIA-1 (NCT06091254), OLYMPIA-2 (NCT06097364) and OLYMPIA-5 (NCT06149286) are evaluating odronextamab in earlier lines of therapy.

Mosunetuzumab: efficacy across high-risk cohorts

The CD20 x CD3 bispecific antibody mosunetuzumab is in clinical use for the treatment of patients with relapsed/refractory FL after ≥ 2 prior therapies, representing an off-the-shelf, fixed-duration option without mandatory hospitalization. In the pivotal phase II setting, mosunetuzumab treatment has given rise to high ORR and CR rates as well as durable responses in a heavily pretreated population [3, 4]. A subgroup analysis of high-risk patients after > 3 years of follow-up was reported at EHA 2024 by Assouline et al. [5]. Patients with and without POD24 were compared to each other (n = 47 and 43, respectively), as were those in the third and fourth lines (n = 35 and 55, respectively) and patients aged < 65 and ≥ 65 years (n = 60 and 30, respectively). After step-up dosing in cycle 1, patients who achieved CR at cycle 8 discontinued mosunetuzumab at that time. Those who had either PR or stable disease at cycle 8 continued the treatment for a total of 17 cycles.

CR rates across the high-risk subgroups were consistent with the overall population (n = 90) that showed an ORR of 78 % and a CR rate of 60 % (**Figure 2**). Patients who received mosunetuzumab in the third line experienced the highest CR rate of 68.6 %. Median duration of CR had not been reached in the total group. At 30 months, duration of CR was 71 % overall and was again maintained across the subgroups, with the highest rate observed in the third-line cohort (77 %). Patients with POD24 and non-POD24 showed similar 36-month rates for PFS (44 % vs. 42 %) and OS (84 % vs. 81 %). Also, older patients did not have different outcomes compared to the younger cohort (36-month rates for PFS, 47 % vs. 42%; and for OS, 86 % vs. 81 %). For patients in the third line of treatment, as compared to those in the fourth line, the PFS benefit was numerically higher (36-month rates, 54 % vs. 36 %), while OS was comparable (85 % vs. 82 %). Together with the CR findings, these data suggest more favorable outcomes with mosunetuzumab in earlier *versus* later lines.

The safety profile across subgroups was consistent with that observed in the overall population. In patients aged ≥ 65 years, the rate of serious infections (17 %) did not exceed the respective overall rate (20 %). Grade ≥ 3 serious infections primarily included urinary tract infections (3 %), pneumonia (2 %), septic shock (2 %), COVID-19 (2 %) and Epstein-Barr viremia (2 %). Serious infections predominantly occurred in the first four cycles, with only three events being reported beyond cycle 8. Neutropenia was reported in 29 % overall. CRS events emerged in 44 %; most of them were graded as 1 or 2. In the group aged ≥ 65 years, the CRS rates were lower than in the younger age group (30 % vs. 52 %), suggesting that this treatment is safe in older patients. No mosunetuzumab-related fatal AEs occurred, and the rate of treatment-related AEs leading to discontinuation was low at 2 %.

A biomarker analysis showed that mosunetuzumab therapy allows for the recovery of B cells and immunoglobulins in patients with CR after completion of fixed-duration treatment. The authors concluded that mosunetuzumab offers a favorable benefit-risk ratio as an outpatient, fixed-duration regimen for patients with relapsed/refractory FL and a broad range of baseline and disease characteristics.

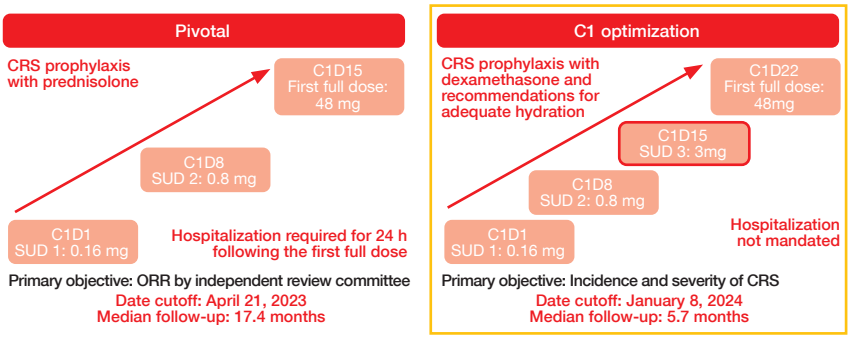

Figure 3: Step-up dosing (SUD) of epcoritamab in the pivotal and C1 OPT cohorts of the EPCORE NHL-1 trial

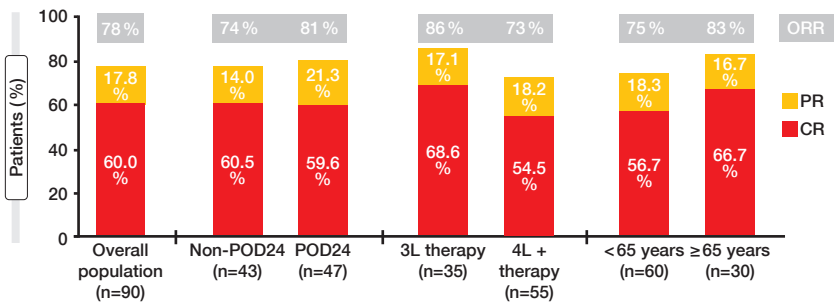

Figure 2: Consistent response rates with mosunetuzumab across high-risk subgroups

Optimizing treatment with epcoritamab

In the phase I/II EPCORE NHL-1 trial, treatment with the subcutaneous CD3 x CD20 bispecific antibody epcoritamab has led to deep and durable responses in patients with relapsed/refractory FL after ≥ 2 prior therapies [6]. The ORR was 82 %, with CRs occurring in 63 %. Seventy-two percent of complete responders were shown to maintain CR at 18 months. With respect to safety, the analysis yielded low-grade CRS and ICANS events that all resolved. However, further reductions in the incidence and severity of CRS and ICANS are an important goal as this may enhance accessibility and decrease healthcare resource utilization.

Therefore, Vitolo et al. compared the outcomes in the pivotal cohort of the EPCORE NHL-1 study (n = 128) with those in the cycle 1 optimization (C1 OPT) cohort (n = 86) [7]. In the pivotal cohort, step-up dosing included two steps in cycle 1 before administration of the first full dose of 48 mg on day 15 (**Figure 3**). CRS prophylaxis with prednisolone was

implemented. In the C1 OPT cohort, on the other hand, dosing was increased in three steps prior to the first full dose of 48 mg on day 22 of cycle 1. Here, CRS prophylaxis included dexamethasone and recommendations for adequate hydration. Hospitalization was not mandatory in this group, while patients in the pivotal cohort were hospitalized for 24 hours following the first full dose.

Both cohorts contained patients with relapsed/refractory FL grade 1-3a after ≥ 2 prior lines of therapy including ≥ 1 regimen with an anti-CD20 antibody. This was a high-risk population with a high unmet need. Approximately half of patients in each cohort had POD24, and most were double refractory to CD20-targeted treatment and an alkylating agent. Ann Arbor stage III-IV disease was present in 85 % and 92 % in the pivotal and C1 OPT cohorts, respectively. Sixty-one percent and 51 %, respectively, had Follicular Lymphoma International Prognostic Index scores of 3-5. The primary objective for the C1 OPT cohort was the incidence and severity of CRS, as well as feasibility of treatment in the outpatient setting. At the time of the analysis, treatment was ongoing in 74 % in the C1 OPT cohort after a median follow-up of 5.7 months. The first full dose had been administered in 95 %.

Reductions in CRS and ICANS rates

The study met its primary endpoint. CRS was reported in 66 % in the pivotal cohort vs. 49 % in th C1 OPT cohort, with lower rates of grade 2 and no 3 CRS events in the C1 OPT cohort. ICANS occurred in 6 % in the pivotal cohort, while no events were observed in the C1 OPT cohort (**Table**). In both cohorts, CRS emerged mostly after the first full dose and was essentially confined to cycle 1. All CRS events resolved, and none led to epcoritamab discontinuation. The decreased incidence and severity of CRS was reflected by lower IL-6 levels 24 hours after the first full dose in the C1 OPT cohort compared to the pivotal cohort.

Fifty-four percent of patients in the C1 OPT cohort received the first full dose in an outpatient setting while they were being closely monitored for CRS. Regardless of hospitalization status at the first full dose, 77 % of patients with CRS following the first full dose had CRS onset in the outpatient setting; all of them were able to identify CRS signs and symptoms in a timely manner and to receive adequate treatment. Overall, no grade 5 AEs were reported. Other common AEs included injection-site reactions, COVID-19, fatigue, neutropenia, diarrhea and pyrexia. No clinical tumor lysis syndrome occurred in either cohort.

The modified step-up in the C1 OPT cohort had no impact on the efficacy of treatment. In both cohorts, median time to response and median time to CR were 1.4 and 1.5 months, respectively. The ORRs were 83 % and 86 % for the pivotal and C1 OPT cohorts, respectively, and the MRD negativity rates were 67 % and 64 %, respectively. MRD negativity was associated with favorable PFS at all times. Taken together, cycle 1 optimization with three dosing steps prior to the full dose in addition to simple prophylactic measures substantially reduced the incidence and severity of CRS and ICANS. The treatment showed robust, clinically meaningful efficacy including deep responses in the largest relapsed/refractory FL dataset for a T-cell–engaging therapy to date. These data further support the feasibility and safety of epcoritamab as a potential outpatient treatment option in the setting of relapsed/refractory FL.

TABLE
Incidence and severity of CRS and ICANS in the pivotal cohort and the cohort that underwent cycle 1 optimization

Response	Pivotal cohort (n = 128)	C1 optimization cohort (n = 86)
CRS, n (%)	85 (66)	42 (49)
Grade 1	51 (40)	34 (40)
Grade 2	32 (25)	8 (9)
Grade 3	2 (2)	0
Treated with tocilizumab, n (%)	31 (24)	10 (12)
Leading to epcoritamab discontinuation, n (%)	0	0
Median time to CRS onset after first full dose	15 hours	2.5 days
CRS resolution, n/n (%)	85/85 (100)	42/42 (100)
Median time to resolution, days (range)	2 (1-54)	2 (1-14)
ICANS, n (%)	8 (6)	0

Sequences of treatment

Using data from the Optum® Clinformatics® Data Mart database, Gaballa et al. evaluated treatment patterns, time to next treatment (TTNT), healthcare resource utilization and cost of care for US residents with FL [8]. Patients were included who had received ≥ 1 line of treatment during the index period. A total of 4,525 individuals initiated first-line treatment; second-, third- and fourth-line therapies were started by 1,053, 304, and 97 patients, respectively. Rituxumab monotherapy (R-mono) was the most commonly used regimen in the first, second and third lines, followed by bendamustine/rituximab (BR) and R-CHOP. In the fourth line, BR and R-mono were most commonly prescribed, followed by R-CHOP.

Bendamustine plus obinutuzumab gave rise to the longest TTNT in the first line; in the second and third lines, this applied to BR and lenalidomide plus rituximab, respectively. R-mono demonstrated the longest TTNT in the fourth line. While median TTNT decreased by line of therapy across all regimens, inpatient admissions and outpatient visits increased with each subsequent line, as did the mean total cost of care that ranged from $ 40,538 to $ 74,466. The authors emphasized that these findings suggest a high disease burden and the need for better treatment options for patients with FL, especially in the third and fourth lines.

The randomized, phase II ROSEWOOD trial has shown superior efficacy of the combination of zanubrutinib and obinutuzumab compared to obinutuzumab monotherapy in patients with relapsed/refractory FL after ≥ 2 lines [9]. A post-hoc analysis assessed the efficacy

of the combination in the sequence of treatments administered in ROSEWOOD based on the Growth Modulation Index. This allowed for the generation of comparative efficacy evidence by comparing PFS durations with successive treatments, using each patient as their own control.

According to this analysis, the majority of patients receiving zanubrutinib plus obinutuzumab had significant improvement in PFS vs. PFS on their last prior regimen, irrespective of the number of previous treatments [10]. The median Growth Modulation Index of 2.7 in the overall population of the combination arm was more than double the 1.33 threshold for meaningful clinical activity versus the last prior line. In their summary, the authors noted that these data confirm the benefit of zanubrutinib plus obinutuzumab as a novel option for patients with relapsed/refractory FL. ■

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Relative efficacy of several treatment options in marginal zone lymphoma

Chemoimmunotherapy (CIT), immunotherapy and chemotherapy regimens are commonly used for the treatment of patients with marginal zone lymphoma. Moreover, the BTK inhibitor zanubrutinib has shown activity in the relapsed/refractory setting based on the phase II, single-arm MAGNOLIA and BGB-3111-AU-003 trials [1, 2]. Walewska et al. conducted a matching-adjusted indirect comparison (MAIC) to estimate the comparative efficacy of these treatment strategies in relapsed/refractory marginal zone lymphoma [3]. Individual patient-level data from 86 efficacy-evaluable patients enrolled in MAGNOLIA and BGB-3111-AU-003 were used to inform the zanubrutinib treatment group, resulting in an effective sample size of 38 individuals. Regarding CIT, immunotherapy and chemotherapy, aggregate data from a comparable cohort of 90 patients were identified from a UK cancer registry called the Haematological Malignancy Research Network. In both groups, a quarter of patients was refractory to the last therapy, and half had experienced progression within 24 months of initiation of treatment.

Relative to CIT, immunotherapy, or chemotherapy, zanubrutinib significantly reduced the risk of progression (adjusted HR, 0.30; p = 0.0014; **Figure**). The same applied to the endpoint of overall survival (adjusted HR, 0.23; p = 0.0002). Model results excluding patients who only received chemotherapy were consistent with these findings. The leave-one-out analyses showed that removing any one of the characteristics did not significantly alter the treatment effect estimates, although the number of prior lines of therapy had the largest impact. Taken together, these MAIC results suggest that zanubrutinib can be considered an effective alternative to CIT, immunotherapy, or chemotherapy, adding to a body of evidence that informs the relative efficacy of treatment options in patients with relapsed/refractory marginal zone lymphoma.

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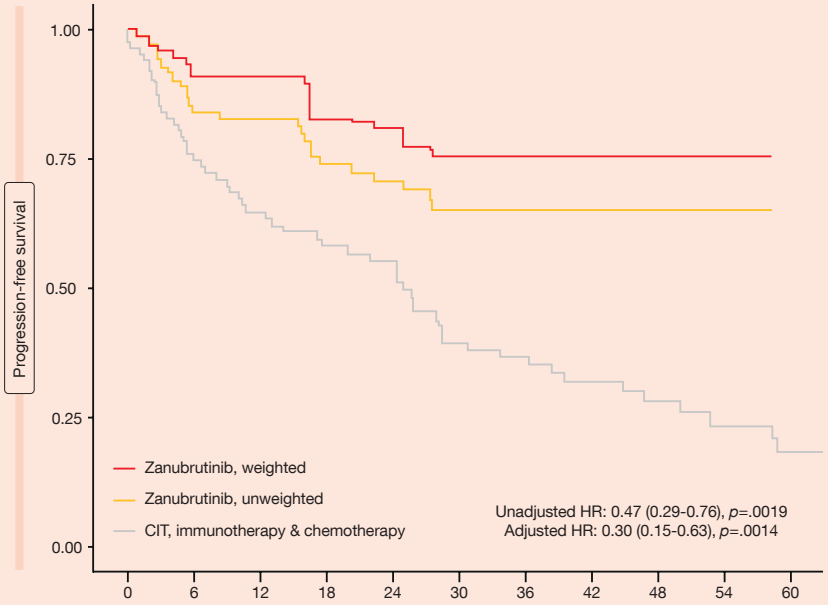

Figure: Matching-adjusted indirect comparison: zanubrutinib vs. chemoimmunotherapy, immunotherapy and chemotherapy

Economic analysis of zanubrutinib vs. acalabrutinib in B-cell malignancies

A recent meta-analysis by Hwang et al. provided a comprehensive comparison of adverse event (AE) profiles of zanubrutinib with acalabrutinib in patients with B-cell malignancies. Specific AEs seen more commonly with acalabrutinib than zanubrutinib included infections, atrial fibrillation, diarrhea, nausea/vomiting, headaches, cough, fatigue and pyrexia. On the other hand, hematuria, neutropenia, and hypertension were observed more frequently with zanubrutinib than with acalabrutinib [1]. Based on the AE profiles as reported by Hwang et al. and a health economic model developed from the UK's National Health Service perspective, the costs and quality-of-life outcomes associated with the use of zanubrutinib vs. acalabrutinib were evaluated [2]. The investigators estimated the total cost of managing AEs by summing the costs of grade ≥ 3 and grade 1/2 AEs. The loss of quality-adjusted life years (QALY) for each AE was calculated by multiplying the incidence rates with the disutility weights assigned to them and their duration. Base-case, scenario and sensitivity analyses were conducted.

Cost savings & QALY benefits

In the base-case setting, considering all AEs, treatment of a hypothetical cohort of 1,000 patients with zanubrutinib instead of acalabrutinib led to cost savings of £ 599K and 3.7 QALY gains. The scenario analysis for grade ≥ 3 AEs and grade 1/2 AEs revealed similar trends for cost savings and QALY savings, with consistent results in a scenario analysis limited to AEs that were significantly different between the two drugs (**Table**). In both base-case and scenario analyses, the relative contribution of grade 1/2 AEs in cost savings was higher than that of grade ≥ 3 AEs, whereas QALY savings were similar among grade ≥ 3 and grade 1/2 AEs. According to the one-way sensitivity analysis, incidence rates for infections represented the most influential parameter affecting cost savings, whereas disutility associated with headache or infections on acalabrutinib treatment was the most influential parameter affecting QALYs. The results of the probabilistic sensitivity analysis supported the robustness of the findings.

Overall, this economic analysis demonstrated that in patients with B-cell malignancies, zanubrutinib therapy is cost-saving and associated with QALY benefits compared to acalabrutinib in terms of AE management. These results are consistent with an identical analysis conducted from a US perspective, according to which treatment of a hypothetical cohort of 1,000 patients with zanubrutinib instead of acalabrutinib resulted in cost savings of $ 124K and 3.7 QALY gains in the base-case scenario [3]. The sensitivity analysis and probabilistic sensitivity analysis confirmed the robustness of this model.

TABLE
Scenario analyses: cost and QALY savings in hypothetical cohorts

Population	AE grade	Cost savings (zanubrutinib vs. acalabrutinib)	QALY savings (zanubrutinib vs. acalabrutinib)
Hypothetical cohort (n = 1,000) Specific-grade AEs	≥ 3	£ 215,331	1.8
	1/2	£ 383,240	1.9
Hypothetical cohort (n = 1,000) Significantly different AEs	All grades	£ 627,638	3.9
	≥ 3	£ 219,749	1.8
	1/2	£ 407,889	2.1

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