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Preface

Dear Colleagues,

The 64th Annual Meeting of the American Society of Hematology (ASH) took place as a hybrid event that hosted participants both online and on-site in New Orleans, Louisiana, USA. Among the multitude of updates and new insights presented from December 10th to 13th, 2022, attendees had access to thousands of scientific abstracts highlighting cutting-edge research in hematology. Thus, this issue of *memo* in Haematology summarizes results obtained for targeted therapies in B-cell malignancies including chronic lymphocytic leukemia, mantle cell lymphoma, Waldenström's macroglobulinemia, follicular lymphoma, and diffuse large B cell lymphoma (DLBCL), as well as acute myeloid leukemia.

The initial treatment in various types of hematologic malignancies is continuously evolving due to the introduction of new targeted agents, either as monotherapy or in combination with other agents, allowing for response-adapted adjustment of treatment intensity to minimize toxicity. While in the relapsed/refractory

setting, the therapeutic options following chemoimmunotherapy and covalent BTK inhibitor therapy are often limited, new potential strategies such as non-covalent BTK inhibitors or checkpoint inhibition are on the horizon.

In CLL patients, the second-generation BTK inhibitor zanubrutinib and the combination of ibrutinib and venetoclax are gaining ground, as well as a triplet consisting of BTK- and Bcl-2-inhibition and CD20-targeted therapy. Another class of drugs showing synergistic effects with venetoclax is PI3K- δ/γ inhibitors which are also highlighted in this report. Potential advances are further described in the setting of DLBCL.

The need for novel, efficacious and well tolerated agents is especially high for advanced-stage follicular lymphoma. This report outlines data from promising bispecific antibody, oral PI3K δ and BTK inhibitor regimens alone or in combination with other agents. Moreover, results for monotherapies and combinations in patients with mantle cell lymphoma are reported.

Last but not least, this issue looks closely at the efficacy and safety of new agents for the treatment of patients with acute myeloid leukemia whose standard



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therapy has long consisted of intensive chemotherapy followed by allogeneic hematopoietic stem cell transplant.

Once again, the ASH meeting facilitated the exchange of scientific information and clinical results related to the field of hematology while assisting physicians and scientists in developing and maintaining academic collaborations to generate new knowledge, ultimately benefiting patients.

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Potential strategies to overcome relapsed and refractory Waldenström's macroglobulinemia

Although covalent BTK inhibitors are increasingly important in the management of patients with Waldenström's macroglobulinemia (WM), progression and intolerance frequently necessitate treatment discontinuation. In the relapsed/refractory setting, the therapeutic options following chemoimmunotherapy and covalent BTK inhibitor therapy are limited, with no accepted standard of care [1, 2].

Non-covalent BTK inhibition with pirtobrutinib

According to the results of the phase I/II BRUIN study presented by Palomba et al. at ASH 2022, the highly selective, non-covalent (reversible) BTK inhibitor pirtobrutinib has demonstrated promising efficacy in heavily pretreated patients with relapsed/refractory WM including those

who had previously received chemoimmunotherapy and covalent BTK (cBTK) inhibitors [3]. In the dose-escalation and dose-expansion phase I part of BRUIN, pirtobrutinib 25 mg to 300 mg QD was tested in a population harboring various B-cell malignancies. Eighty patients with WM received pirtobrutinib 200 mg QD in the phase II part. Among these, 63 were cBTK-inhibitor-pretreated, with a median number of prior lines of 3; almost 80% had received both chemoimmunotherapy and BTK inhibition. Progressive disease was the reason for cBTK inhibitor discontinuation in two thirds of cases.

Pirtobrutinib demonstrated promising efficacy. Major response rates were 66.7% and 88.2% in the cBTK-inhibitor-pretreated and -naïve cohorts, respectively (**Table**). Notably, very good partial remission was obtained in 23.8% and

29.4%, respectively, which emphasized the depth of response achieved with pirtobrutinib even in the pretreated group. No substantial differences in major responses were observed according to patient and disease characteristics; this included prior therapy and reason for discontinuation of any prior cBTK inhibitor. At the time of the data cutoff, 55.6% of patients after cBTK inhibitor therapy remained on pirtobrutinib therapy. Median overall survival (OS) had not been reached yet in this group, while median progression-free survival (PFS) was 19.4 months. At 18 months, the OS and PFS rates were 81.7% and 57.1%, respectively.

Pirtobrutinib continued to be well tolerated, with low rates of treatment-related grade ≥ 3 adverse events (AEs) that were highest for neutropenia (11.5%). Among

TABLE
Remission rates with pirtobrutinib in the response-evaluable patient population according to pretreatment with covalent BTK inhibitors

	Prior cBTK inhibition (n = 63)	cBTK-inhibitor-naïve population (n = 17)
Major response rate*, %	66.7	88.2
Complete + very good partial response rate, %	23.8	29.4
Best response		
Very good partial response, n (%)	15 (23.8)	5 (29.4)
Partial response, n (%)	27 (42.9)	10 (58.8)
Minor response, n (%)	9 (14.3)	0 (0)
Stable disease, n (%)	9 (14.3)	2 (11.8)

* Complete response, very good partial response, or partial response

AEs of special interest (i.e., bruising, rash, arthralgia, hemorrhage, hypertension, atrial fibrillation/flutter), grade ≥ 3 treatment-related AEs ranged from 0.0% to 0.6%. Discontinuations and dose reductions due to treatment-related AEs occurred in 2.6% and 4.5%, respectively.

Pembrolizumab plus rituximab

The first clinical trial to investigate checkpoint inhibition in WM is the phase II, non-randomized, single-arm, open-label PEMBROWM study. Patients with relapsed/refractory WM who had received at least one prior line of treat-

ment and were not refractory to rituximab were treated with rituximab weekly for the first 28 days and then every 3 months for up to one year, while pembrolizumab was administered Q3W for a maximum of 18 cycles. After a median of 3 previous treatment lines, more than half of patients were refractory to BTK inhibitor therapy. The rationale for the trial resulted from the observation that PD-1 and PD-L1 is widely expressed in the bone marrow of WM patients, with soluble PD-1 ligands regulating T-cell function [4].

PEMBROWM closed early due to slow accrual, with a final total of 17 pa-

tients 5 of whom completed the full 18 cycles of treatment [5]. Nine responders at 24 weeks were required for the study to meet the primary endpoint, which was the overall response rate (ORR) at 24 weeks; however, at this time-point, only 8 patients responded. Nevertheless, the results indicated encouraging efficacy in this heavily pretreated population. The best ORR was 56%. After a median follow-up of 16 months, median PFS was 13 months and median OS had not been reached yet. The 1-year PFS and OS rates were 55% and 92%, respectively. Median time to next treatment (TTNT) was 18 months; at 1 year, the TTNT rate amounted to 71%.

The majority of AEs were grade 1 and 2 and most commonly included anemia (29%), fever (29%), infusion-related reactions (35%) and creatinine elevation (29%). Among grade ≥ 3 AEs, low blood counts and infection were observed most frequently. Only one grade 3 immune-related AE occurred. The quality-of-life scores according to the QLQ-30 questionnaire showed no significant differences between baseline and week 24. In their conclusion, the authors emphasized that a randomized study would be required to evaluate the added benefit of the PD-1 blockade to rituximab monotherapy in a highly relapsed/refractory WM patient population. ■

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Active monotherapies and combinations in mantle cell lymphoma

First-line triple combination: ALR

The initial treatment of patients with mantle-cell lymphoma (MCL) is continuously evolving due to the introduction of new targeted agents. Ruan et al. conducted a single-arm phase II study based

on the hypothesis that the addition of the next-generation BTK inhibitor acalabrutinib to lenalidomide plus rituximab (ALR) would synergize activity and accelerate minimal residual disease (MRD)-negative complete response (CR), thus allowing for response-adapt-

ed adjustment of treatment intensity to minimize toxicity.

The study included patients with untreated MCL and a tumor mass diameter of ≥ 1.5 cm. Those who benefited from induction (cycles 1-12) moved on to maintenance (cycle 13 until disease pro-

gression). Patients who achieved MRD-negative CR during maintenance had the option of treatment de-escalation after 24 cycles, i.e., discontinuation of the oral agents acalabrutinib and lenalidomide. Retreatment was possible in case of progression. Patients in whom MRD positivity persisted continued the triple combination. CR at the end of induction was defined as the primary endpoint.

At ASH 2022, data were presented after a median follow-up of 23 months for 24 patients with stage III/IV MCL who received ALR including maintenance [1]. Twelve of these had completed more than 24 cycles of treatment at the time of the analysis (Figure 1).

High CR and molecular response rates

The overall response rate (ORR) estimated at the end of induction was 100%, while CR was achieved in 83%. Molecular remission was measured using MRD clono-SEQ[®], with the detection limit set at $< 1 \times 10^{-6}$. According to this, most patients obtained MRD-negative CR. At the conclusion of induction, the MRD negativity rate was 67%; this increased to 83% at cycle 24. De-escalation was possible in 9 of 12 patients. The 2-year rates for progression-free survival (PFS) and overall survival (OS) were 86.7% and 100%, respectively.

Using next-generation sequencing, the researchers assessed the genomic mutation profile. The most common mutations included *IGLL5*, *ATM*, *CCND1* and *TP53* mutations. Five of six patients with *TP53* mutations achieved MRD negativity within 12 cycles, although one of them relapsed at cycle 20. MIPI score, Ki-67 index, or *TP53* mutational status did not affect response, while OS appeared to correlate with the *TP53* mutational status. These exploratory data suggest that *TP53* mutations might be associated with risk of lymphoma progression following initial response.

The treatment was well tolerated, with expected side effects that mainly included asymptomatic neutropenia, anemia, and thrombocytopenia. No cases of febrile neutropenia occurred. Most patients had COVID-19 infections, although all of them recovered with supportive care. Other adverse events (AEs) comprised rash, fatigue, and gastrointestinal side effects. The authors concluded

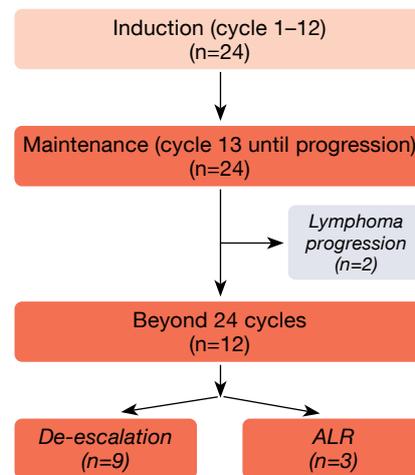


Figure 1: Acalabrutinib plus lenalidomide/rituximab: patient flow in the phase II setting

that real-time MRD analysis facilitates response-adapted treatment de-escalation during maintenance to minimize toxicity, which warrants further evaluation in larger studies. An expansion cohort receiving acalabrutinib plus lenalidomide and obinutuzumab is currently being launched (NCT03863184).

AVR: phase I results

Acalabrutinib in addition to venetoclax and rituximab (AVR) as first-line treatment in patients with MCL was assessed in the multicenter, open-label, phase IB ACE-LY-106 study that has already yielded high rates of clinical and molecular responses [2]. Wang et al. presented an update for 21 patients after a median follow-up of 25.8 months at ASH 2022 [3].

AVR was shown to be well tolerated and safe. The most common AEs were diarrhea, headache and fatigue, which were mostly grade 1 and 2. Grade 3/4 AEs included neutropenia (33%) and pneumonia (14%). Serious any-grade AEs occurred in 57%; these were COVID-19 infection (24%), pneumonia (14%), and pyrexia (10%). Four of seven patients contracting COVID-19 died from the infection. Temporary dose holds and permanent discontinuation of a study drug due to AEs were noted in 71% and 24%, respectively.

All of the patients responded to the treatment. The CR rate with bone marrow confirmation (Lugano criteria) was 71%, while the CR rate according to PET/CT amounted to 90%. Median duration of response had not been reached

yet, which also applied to median PFS and OS. At 2 years, 74% of patients were alive, and 54% were progression-free.

MRD data from peripheral blood were available for 16 patients. Fourteen of these (87.4%) achieved MRD negativity at least once during treatment. At cycles 6 and 12, 57.1% and 66.7% were MRD-negative, respectively. Among the 15 patients who obtained CR by PET/CT, 11 (73.3%) remained in CR at their last follow-up. As the authors noted in their summary, these findings warrant further investigations of AVR in the treatment-naïve setting.

Glofitamab monotherapy in heavily pretreated patients

In the setting of relapsed/refractory MCL, patient prognosis is poor, particularly after BTK inhibition [4]. Data from a phase I dose-escalation study presented by Phillips et al. demonstrated benefits of the CD20/CD3 bispecific antibody glofitamab in heavily pretreated patients with relapsed/refractory MCL [5]. Glofitamab was tested as monotherapy for a maximum of 12 cycles at a dose of 30 mg in cycles 2-12 after step-up dosing in cycle 1 (2.5 mg and 10 mg on days 8 and 15). For reasons of cytokine release syndrome (CRS) mitigation, the administration of obinutuzumab 1 x 1,000 mg or 1 x 2,000 mg preceded the treatment. While 16 patients received glofitamab after obinutuzumab 1,000 mg, 21 were treated with glofitamab after obinutuzumab 2,000 mg. The majority had previously received BTK inhibitor therapy and was refractory to any prior treatment.

Glofitamab monotherapy gave rise to high response rates in the overall population and in patients with prior BTK inhibitor therapy (Figure 2). Most responses were achieved early on and were durable. Median time to first response was 51 days. CRs lasted for a median of 10.0 months. At data cut-off, 74.1% of patients with CR remained in remission. After the exclusion of four COVID-19-related deaths, median duration of CR had not been reached, and 87% of CRs were ongoing. Moreover, durable CRs were maintained after cessation of therapy.

Glofitamab-related grade 3/4 AEs emerged in 62.2%. No grade 5 AEs related to glofitamab or AEs leading to

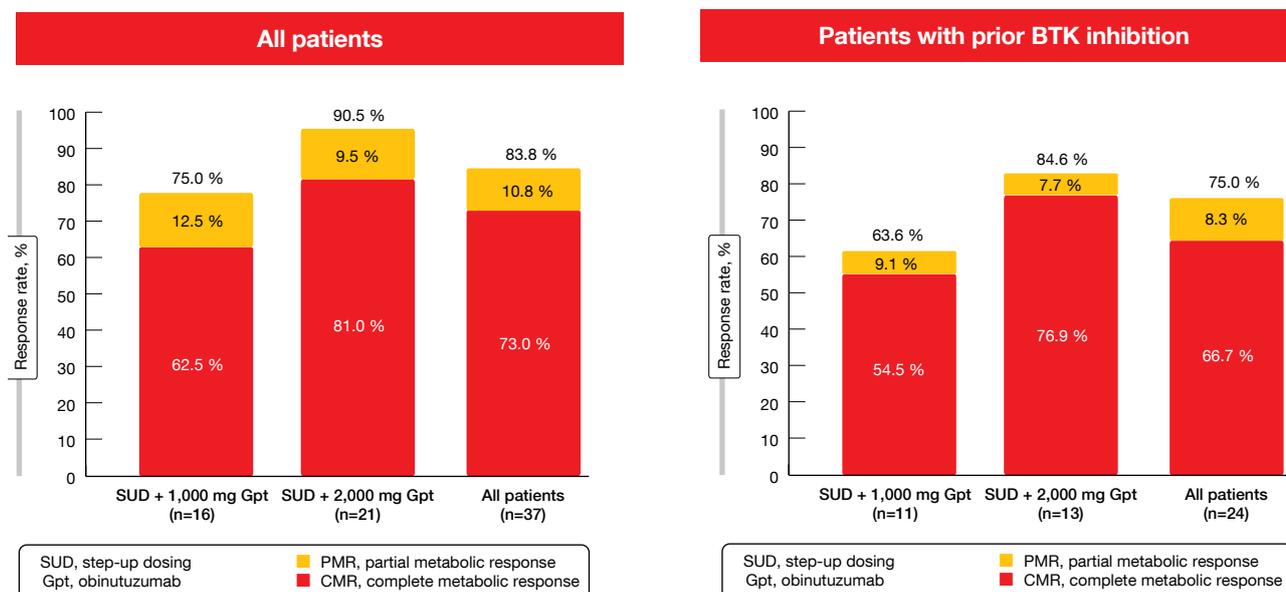


Figure 2: Complete and partial metabolic responses with glofitamab monotherapy in the total cohort and in the BTK-inhibitor-pretreated patients

treatment discontinuation occurred. The 2,000 mg obinutuzumab dose, as compared to the 1,000 mg dose, was associated with a lower rate of serious glofitamab-related AEs (52.4% vs. 75.0%) and grade 3/4 AEs (52.4% vs. 87.5%). CRS was the most common AE but was manageable and predominantly classified as grade 1 or 2. The cohort treated with obinutuzumab 2,000 mg experienced fewer instances of CRS than the cohort receiving obinutuzumab 1,000 mg (66.7% vs. 87.5%), and no grade-4 events were reported in the higher dose group. Other AEs of interest included infections, neutropenia and tumor flare. No grade ≥ 3 immune effector cell-associated neurotoxicity syndrome (ICANS) or tumor flare events occurred. A phase III study investigating glofitamab monotherapy is currently being planned for patients with relapsed/refractory MCL.

Second- vs. later-line zanubrutinib

Pooled data of 112 patients with relapsed/refractory MCL from the phase I BGB-3111-206 study and the phase II BGB-3111-AU-003 study that evaluated the next-generation BTK inhibitor zanubrutinib in the second line ($n = 41$) and in later lines ($n = 71$) have shown numerically improved PFS and OS with second-line zanubrutinib compared to later-line treatment [6]. The long-term follow-up analysis conducted at 35.2 months further confirmed these findings [7].

Inverse propensity score weighting was used to balance the baseline covariates. After weighting, OS was significantly improved in the second-line group vs. the later-line group (HR, 0.459; $p = 0.044$). Median OS had not been reached yet in either arm, and the 36-month OS rates were 82.0% vs.

66.5%. Second- and later-line groups experienced similar reductions in the risk of progression or death (HR, 0.78), although median PFS in the second-line cohort was numerically longer (27.8 vs. 22.1 months). At 36 months, 44.8% vs. 35.4% of patients were progression-free. The OS and PFS findings in the original sample were consistent with the post-weighting results. Both groups responded to a similar extent (ORRs, 88.6% vs. 85.7%), with median duration of response amounting to 25.2 vs. 25.1 months.

Furthermore, the safety profile was similar (all-grade AEs, 95.1% vs. 97.2%). Grade ≥ 3 AEs of special interest including atrial fibrillation/flutter, diarrhea, hemorrhage and hypertension occurred only infrequently in either group. Taken together, the data suggested that earlier treatment with zanubrutinib is associated with improved survival outcomes. ■

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Further steps to improve efficacy and safety in acute myeloid leukemia

Long-term follow-up of VIALE-A

Venetoclax 400 mg QD in combination with azacitidine 75 mg/m² on days 1–7 has been approved for the treatment of patients with newly diagnosed acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy based on the phase III VIALE-A trial that met its primary endpoint of overall survival (OS) at the time of the interim analysis conducted in March 2020 [1]. The study included patients aged ≥ 75 years or 18–74 years with comorbidities ineligible for standard induction regimens. While the experimental arm (n = 286) received the combination, the control arm was treated with placebo plus azacitidine (n = 145). At ASH 2022, the results of the 100% OS analysis were reported to determine the long-term survival benefit of venetoclax plus azacitidine [2].

After a median follow-up of approximately 43 months, no new safety signals had emerged for venetoclax plus azacitidine or azacitidine monotherapy compared to the previous analysis. Grade ≥ 3 adverse events (AEs) were observed in 98.6% vs. 96.5%. The overall AE rates were similar across the arms, while hematologic AEs occurred more frequently with the combination.

Venetoclax plus azacitidine continued to show significant OS improvement over azacitidine monotherapy, with a 42% mortality reduction (median OS, 14.7 vs. 9.6 months; HR, 0.58; p < 0.001). All subgroups derived continued OS benefit. In patients with *IDH1/2* mutations, median OS was 19.9 vs. 6.2 months, which translated into a 69% risk reduction (HR, 0.314; p < 0.001). Approximately 68% of patients treated with venetoclax plus azacitidine achieved complete remission (CR) or CR with incomplete hematologic recovery (CRi) as best response. The median duration of CR/CRi was 18.2 vs. 10.7 months. Within this group, median OS was longer in patients who had obtained MRD < 10⁻³ compared to those with MRD ≥ 10⁻³ (34.2 vs. 18.7 months). Median duration of CR for patients on the combination treatment (22.1 months) was approximately 5 months longer than the respective

result observed with venetoclax plus azacitidine at the time of the primary analysis (17.5 months). Both analyses yielded median duration of CR of approximately 13 months in the control arms.

The 7 + 7 scheme

The VIALE-A regimen which contains continuous venetoclax exposure confers considerable toxicity including high rates of grade 3/4 febrile neutropenia and post-remission grade 4 cytopenia [1]. Therefore, Willekens et al. assessed the efficacy and safety of a reduced venetoclax schedule as a potential means to improve tolerability [3]. This multicentric retrospective study included a frail first-line AML population in whom venetoclax had been restricted to 7 days per cycle and was administered concurrently with azacitidine (7 + 7 scheme). The patients' median age was comparable to the that of the VIALE-A study population, although 37% had ECOG performance status 2–4, and 29.3% showed comorbidities that had been defined as exclusion criteria in VIALE-A. Moreover, the group was enriched for patients with therapy-related AML (32%). In the cohort aged < 75 years, prior or concomitant neoplasia was mainly responsible for the ineligibility for intensive treatment (47%). Poor cytogenetic risk was present in 32.9%. Overall, nearly 70% of patients fell into the “adverse risk” category according to ELN 2022.

A total of 82 patients were included in the analysis. After a median follow-up of 4.8 months, 39 (48%) were still on treatment. Discontinuation was due to failure/relapse in 63% and toxicity in CR/CRi or morphologic leukemia-free state

(MLFS) in 30%. The median number of cycles was 4 (1–28). Increasing proportions of patients achieved CR/CRi with every cycle, which resulted in a global response of 68.3% that was similar to the results noted with conventional 28-day venetoclax exposure. CR/CRi rates ranged from 43.7% to 100% according to the genetic set-up, with a normal karyotype being associated with higher responses while the presence of *TP53* correlated with the lowest CR/CRi rate. Estimated OS and event-free survival (EFS) findings were encouraging and most favorable in the cohort with *NPM1* and/or *IDH2* mutations (**Table 1**).

Supplemental dose reductions remained frequent in the post-remission phase (60.7% of CR/CRi patients). The cycles were shortened to 5 days in almost all patients. Moreover, the venetoclax dose was reduced to 200 mg/d in half of them, and the interval between cycles was expanded to 35 days in approximately 30%. Seventy percent of patients with further dose reductions were still on therapy at the time of the analysis, and their estimated median OS was 25.8 months.

Early toxicity in cycle 1 was similar to the toxicity observed with the conventional venetoclax schedule. Febrile neutropenia occurred in 48.8%, and 88.3% of patients required platelet or erythrocyte transfusions. The median delay before cycle 2 was 13 days. Patients with CR/CRi had a median 36-day delay to neutrophil recovery > 1 G/L and a 31-day delay to platelet recovery > 100 G/L. As the authors emphasized, longer follow-up is necessary for the confirmation of the OS and EFS results as well as the assessment of toxicity after cycle 2.

TABLE 1

Overall survival and event-free survival with reduced venetoclax exposure in the total population and subgroups

Patient group	Median overall survival (months)	Median event-free survival (months)
Total population (n = 82)	12.8	7.5
Absence of VIALE-A exclusion criteria (n = 58)	13.8	11.4
Absence of <i>TP53</i> mutation (n = 66)	17.15	17.15
<i>NPM1</i> and/or <i>IDH2</i> mutations (n = 20)	25.76	25.76

BGB-11417 plus azacitidine

Another approach to optimize Bcl-2-inhibitor-based AML treatment is the use of improved agents such as the potent and selective Bcl-2 inhibitor BGB-11417. In an AML xenograft model, BGB-11417 has shown greater tumor reduction than venetoclax at the same dose level, both alone and when combined with azacitidine [4]. The phase IB/II dose-finding and dose-escalation study BGB-11417-103 is assessing BGB-11417 plus azacitidine in treatment-naïve AML patients unfit for intensive chemotherapy and patients with relapsed/refractory AML who had no prior Bcl-2-inhibitor or azacitidine exposure. As of the data cutoff, 57 patients were dosed in four cohorts (40 mg, 80 mg or 160 mg for 10 days or 160 mg for 28 days in 28-day cycles). The treatment-naïve and relapsed/refractory groups comprised 31 and 26 individuals, respectively.

According to the update presented at ASH 2022, BGB-11417 plus azacitidine was generally well tolerated [5]. Dose-limiting toxicities occurred only in the 80 mg cohort, and no clinical tumor lysis syndrome was observed. Laboratory tumor lysis syndrome emerged in one patient treated with 160 mg for 10 days who fully recovered. The analysis showed no dose-dependent toxicities, and the maximum tolerated dose was not reached. Neutropenia represented the most common treatment-emergent grade ≥ 3 AE (65%) but was manageable with dose

modifications. Grade ≥ 3 thrombocytopenia and anemia were observed in 51% and 35%, respectively. Nausea and constipation prevailed among the most common non-hematologic treatment-emergent AEs but were mostly grade 1 and 2.

BGB-11417 plus azacitidine proved active in both treatment-naïve and relapsed/refractory settings at the four dose levels tested. The combination gave rise to CR and CR with partial hematologic recovery (CRh) in 65% and 50% of treatment-naïve and relapsed/refractory patients, respectively. CR/CRh in the treatment-naïve group was mostly obtained by the end of cycle 1. The 80-mg cohort experienced the longest treatment duration (median, 7 cycles) and the highest CR rates (Figure 1). Almost half of 27 MRD-evaluable patients achieved MRD negativity. Efficacy analyses of molecular subgroups, safety expansion, and evaluation of higher doses of BGB-11417 are ongoing, and the inclusion of patients with AML who failed hypomethylating agents is planned.

Magrolimab on top of AV

Although the administration of Bcl-2 inhibition plus hypomethylating agents is undoubtedly effective in newly diagnosed AML patients ineligible for intensive chemotherapy, the survival rates beyond 2 years are low [1]. Jia et al. showed that combined blockade of the CD47-SIRPa axis by the first-in-class anti-CD47

antibody magrolimab plus azacitidine/venetoclax increases phagocytosis in AML cell lines regardless of *TP53* mutation status in AML preclinical models, thus facilitating macrophage-mediated anti-leukemia efficacy [6]. In the clinical setting, phase IB results have indicated efficacy and tolerability of magrolimab plus azacitidine in AML patients unfit for intensive chemotherapy [7].

Magrolimab plus azacitidine and venetoclax is being assessed in a phase I/II trial containing three phase II cohorts: patients with de novo and secondary AML (frontline cohort), those with relapsed/refractory venetoclax-naïve disease, and those with relapsed/refractory disease after prior venetoclax. The recommended phase II dose of magrolimab has been established at 1 mg/kg on days 1 and 4 followed by 15 mg/kg on day 8 and 30 mg/kg once weekly from day 11 of cycle 1 until the end of cycle 2. From cycles 3 onward, magrolimab 30 mg/kg was administered every 2 weeks. At ASH 2022, Daver et al. reported efficacy and safety findings for the frontline and relapsed/refractory AML groups [8].

Favorable results in frontline de novo AML

In the cohort treated in the frontline setting (n = 43), the disease was classified as adverse according to the ELN 2017 risk stratification in almost all of the patients, and high-risk cytogenetics were present

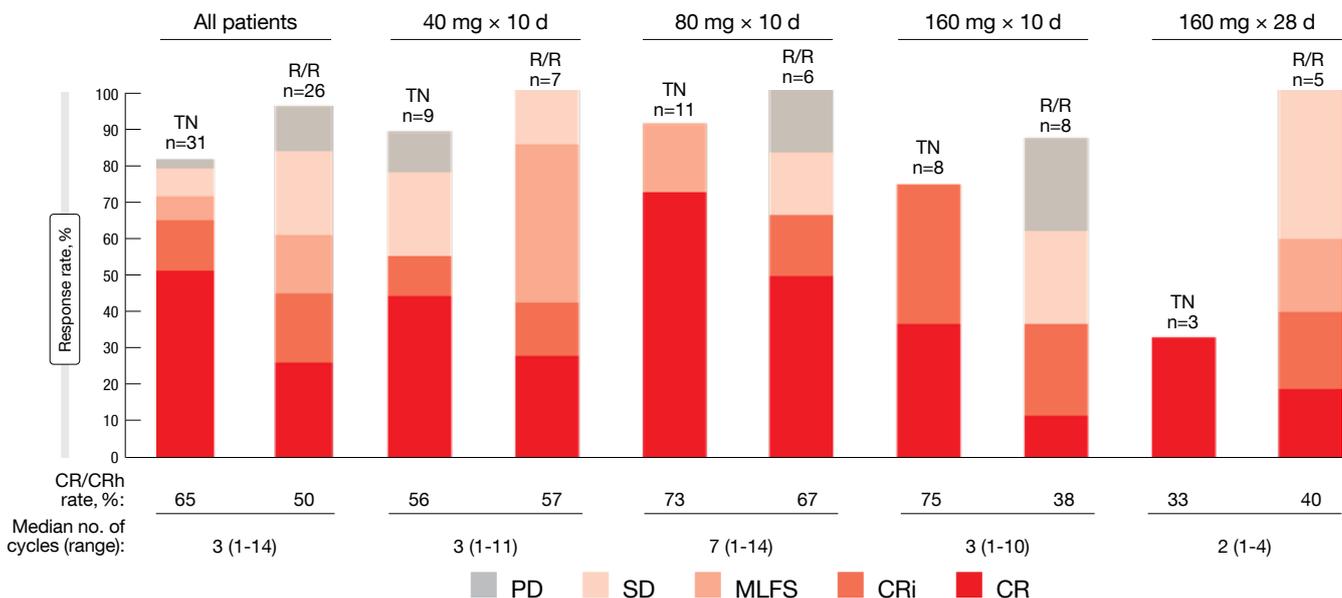


Figure 1: BGB-11417 plus azacitidine: response rates across the four dose levels

TABLE 2
Responses to treatment with magrolimab, azacitidine and venetoclax in the frontline setting

Responses	Full patient set (n = 43)	De novo AML		Secondary AML	
		TP53-mutant (n = 22)	TP53 wildtype (n = 11)	TP53-mutant (n = 5)	TP53 wildtype (n = 5)
n (%)					
Complete remission (CR)	21 (49)	10 (46)	6 (55)	2 (40)	3 (60)
Complete remission with incomplete hematologic recovery (CRi)	10 (23)	4 (18)	4 (36)	1 (20)	1 (20)
CR + CRi	31 (72)	14 (64)	10 (91)	3 (60)	4 (80)
Morphologic leukemia-free state	4 (9)	1 (5)	1 (9)	2 (40)	0 (0)

in the majority of cases. Nevertheless, 72% responded by achieving CR or CRi, with CR/CRi rates being similar across TP53-mutated and TP53-wildtype patients (Table 2). MRD negativity resulted in 67%. In patients with de novo AML, median duration of response and median OS had not been reached in either TP53 cohort at the time of the analysis. Twelve-month OS rates were 83% and 53% for the TP53-wildtype and TP53-mutant groups, respectively. The cohort with secondary AML fared worse than the de novo cohort; here, median OS was 9.6 and 7.6 months for the TP53-wildtype and TP53-mutant cohorts, respectively.

A propensity matched analysis demonstrated improved OS with the triple combination compared to venetoclax plus hypomethylating treatment in TP53-mutated patients ($p = 0.02$), although the median follow-up and numbers remained small. In the TP53 wildtype population, the sample size was insufficient for a historical comparison. TP53-mutated patients who went on to receive stem cell transplant (SCT) experienced higher recurrence-free survival compared to those who did not (16.3 vs. 4.2 months); the same applied to OS (16.6 vs. 9.8 months).

In patients with relapsed/refractory AML ($n = 36$), the activity of magrolimab plus azacitidine and venetoclax was modest. Only 11% and 44% developed CR/CRi in the venetoclax-exposed and venetoclax-naïve groups, respectively. Recurrence-free survival and OS were low in both cohorts.

Overall, the treatment with magrolimab plus venetoclax and azacitidine was safe in this population with very high risk. The analysis revealed no unex-

pected AEs, and none of the patients discontinued therapy due to treatment-related events. Infusion reactions occurred in 8 patients (10%), with three of them experiencing grade 3 events, although further reactions were effectively mitigated based on dexamethasone premedication. Eighteen individuals (23%) had grade ≥ 3 anemia; in the frontline cohort, hemoglobin levels decreased by a median of 1.2 g/dl (0–3.9 g/dl) after the first magrolimab infusion. The authors recommended careful monitoring of hemoglobin levels, especially between days 1 and 10 of cycle 1. The randomized phase III ENHANCE-2 (NCT04778397) and ENHANCE-3 (NCT05079230) studies are further assessing magrolimab in frontline AML.

Olutasidenib: relapsed/refractory IDH1-mutated disease

IDH1 mutations are found in 7–14% of patients with AML [9]. The potent, selective, oral, small-molecule IDH1 inhibitor olutasidenib has demonstrated a manageable tolerability profile and clinical activity in the completed phase I portion of the open-label, multicenter, phase I/II 2102-HEM-101 study [10]. Results from the pivotal phase II cohort of patients with relapsed/refractory AML who received olutasidenib 150 mg BID were reported at ASH 2022 [11]. The efficacy-evaluable and safety sets included 147 and 153 patients, respectively. They had received a median of 2 prior therapies, and 12% had undergone SCT. Refractory disease was present in 35%.

The CR/CRh rate, which constituted the primary endpoint, was 35%, with 32% of patients having developed CR. Median

duration of CR/CRh and CR was 25.9 and 28.1 months, respectively. Notably, response rates were similar for 12 patients who had received prior venetoclax; here, the CR/CRh and CR rates amounted to 33% and 25%, respectively. In the total population of 153 individuals, median OS was 11.6 months. The OS findings differed considerably according to the depth of response (Figure 2). In the group with CR/CRh, median OS had not been reached at the time of the analysis, and the 18-month OS rate was 78%. Across all response groups, 34% of patients who were platelet- and/or red blood cell-transfusion-dependent at baseline reached transfusion independence at 56 days. Those who achieved CR/CRh had comparatively higher rates of transfusion independence than other responders. Sixteen patients in the total population (11%) were able to proceed to SCT following olutasidenib treatment.

With regard to safety, the most common AEs included nausea, differentiation syndrome, and leukocytosis. Differentiation syndrome occurred in 14% of patients, with grade ≥ 3 events in 9% and one fatal case. However, most cases resolved with treatment interruption, dexamethasone therapy and/or supportive measures. Likewise, hepatic AEs that occurred in 25% (grade 3, 12%) were manageable with dose modifications and concomitant medications. QTc prolongation occurred in 8% (grade 3, 1%). In their summary, the authors pointed out that olutasidenib induced durable remissions and transfusion independence with a well-characterized and manageable safety profile. The observed activity was deemed to represent a therapeutic advance in this poor-prognosis patient population.

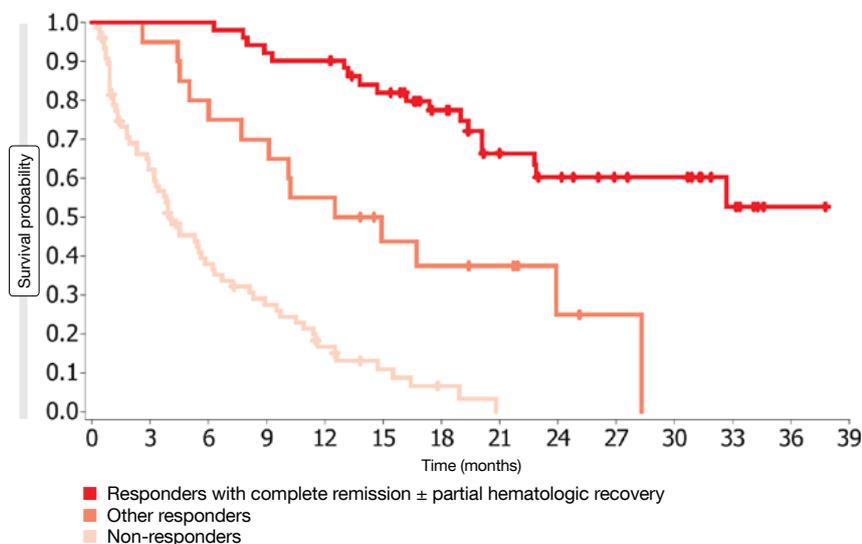


Figure 2: Overall survival according to the depth of response to olutasidenib therapy

MRD-guided pre-emptive FLT3-targeted therapy

FLT3-mutated AML confers a high risk of relapse [12]. Sequential MRD monitoring using quantitative PCR (qPCR) has the potential to enable pre-emptive intervention as it can identify impending hematologic relapse that inevitably follows untreated molecular relapse and is associated with poor outcomes [13, 14]. According to unpublished data from the UK NCRI AML19 study, most patients with *FLT3*-positive AML have co-mutations suitable for molecular qPCR MRD assessment, with *NPM1* mutations occurring most frequently in 55%.

Given the scarcity of data on whether and how to treat molecular relapse/per-

sistence, Othman et al. hypothesized that treatment with a *FLT3* inhibitor might be effective in patients who had *FLT3* mutation at diagnosis and experience molecular failure. The scientists retrospectively identified 51 AML patients from 27 UK hospitals who had *FLT3*-ITD or *FLT3*-TKD mutation at diagnosis, underwent MRD monitoring of *NPM1* or a fusion gene based on qPCR, and experienced molecular failure that was treated with single-agent *FLT3* inhibitor therapy (i.e., gilteritinib, sorafenib and quizartinib in 65%, 19% and 16%, respectively). Types of failure included molecular relapse, molecular persistence > 2 copies/100 *ABL* and molecular progression. Among the 51 patients assessed, most had molecular relapse (49%). In 51%, prior mi-

dostaurin therapy had been administered. Thirty-one percent had received allogeneic SCT.

FLT3 inhibitor monotherapy for molecular failure gave rise to high rates of molecular response and excellent OS [15]. In the total group, 63% of patients achieved CR or molecular response. The CR rate was as high as 93% in the group with prior allogeneic SCT. At 2 years, 79% of all patients were alive, 69% were event-free, and 58% had molecular EFS. After prior midostaurin, the molecular response rate was lower (54%) than in non-pretreated patients (74%). As many as 19 patients could be bridged to allogeneic SCT, and six were administered donor lymphocyte infusion (DLI) with *FLT3* inhibition. Responses deepened after SCT or DLI, with the overall CR rate increasing from 48% to 96% in these 25 patients.

The treatment was well tolerated. In the first 4 cycles, no neutropenia < 0.5 × 10⁹/L or thrombocytopenia < 25 × 10⁹/L was found in 25 patients for whom data were available. No transfusions were administered in this group. Eight patients underwent 12 hospital admissions, with a median length of stay of 4.5 days.

At the time the patients were treated, highly sensitive *FLT3* MRD assays had not been available. Data from 35 individuals showed that next-generation sequencing using the getITD assay allows for improved detection of *FLT3*-ITD and thus for better patient selection [16]. Overall, the authors noted that in the presence of an appropriate marker, sequential molecular MRD monitoring can be utilized to guide pre-emptive therapy.

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Chronic lymphocytic leukemia: moving towards new horizons

Final analysis of ALPINE: zanubrutinib vs. ibrutinib

The first-in-class, covalent BTK inhibitor ibrutinib has transformed the treatment of patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). However, toxicities frequently lead to treatment discontinuation [1-4]. Moreover, exposure coverage between dosing intervals falls below the IC_{50} threshold, and BTK occupancy at trough levels is variable [5]. The second-generation BTK inhibitor zanubrutinib has been designed to have greater BTK specificity than ibrutinib, with exposure coverage above its IC_{50} [6]. More sustained and complete BTK inhibition can be expected based on higher drug-concentration/ IC_{50} ratios. In patients with treatment-naïve CLL/SLL without del(17p), zanubrutinib has induced superior progression-free survival (PFS) compared with chemoimmunotherapy [7].

The randomized, phase III ALPINE study evaluated zanubrutinib in the setting of relapsed/refractory (r/r) CLL/SLL after ≥ 1 prior systemic therapy. Patients were randomized to either zanubrutinib 160 mg BID ($n = 327$) or ibrutinib 420 mg QD ($n = 325$). Overall response rate (ORR) non-inferiority and superiority as assessed by the investigators were defined as the primary endpoint. Brown et al. presented the final PFS analysis of the ALPINE trial at the ASH 2022 Congress [8]. PFS by independent review was significantly prolonged with zanubrutinib *versus* ibrutinib after a median follow-up of 29.6 months, resulting in 24-month PFS rates of 79.5% vs. 67.3% and a 35% reduction in the risk of progression or death (HR, 0.65; $p = 0.0024$; **Figure 1**). The findings favored the second-generation agent across subgroups including patients with del(17p)/*TP53* mutation; here, the 24-month rates were 77.6% vs. 55.7% (HR, 0.52; $p = 0.134$). The ORR according to independent review was 86.2% vs. 75.7% ($p = 0.0007$). Fewer deaths had occurred in the experimental arm, which gave rise to a 24% mortality reduction (HR, 0.76), although median overall survival (OS) had not been reached yet in either arm.

Compared with ibrutinib, zanubrutinib displayed a favorable safety profile, with lower rates of grade ≥ 3 adverse events (AEs; 67.3% vs. 70.4%) and serious AEs (42.0% vs. 50.0%). AEs led to dose reduction in 12.3% vs. 17.0% and treatment discontinuation in 15.4% vs. 22.2%. While hypertension and bleeding events occurred with comparable incidence across the arms, patients treated with zanubrutinib were less likely to experience cardiac AEs (21.3% vs. 29.6%) and serious cardiac AEs (1.9% vs. 7.7%). Cardiac events prompting treatment discontinuation were noted in 0.3% vs. 4.3% and fatal cardiac events in 0% vs. 1.9%. Atrial fibrillation/flutter was significantly less commonly observed (5.2% vs. 13.3%; $p = 0.0004$).

In their conclusion, the authors emphasized that ALPINE is the first study to demonstrate PFS superiority in a head-to-head comparison of BTK inhibitors in patients with r/r CLL/SLL. Superiority has now been proven with regard to both PFS and ORR.

CAPTIVATE: fixed-duration first-line treatment

The MRD cohort of the international, multicenter, phase II CAPTIVATE study assessed fixed-duration *versus* continued administration of ibrutinib following first-line treatment with ibrutinib plus venetoclax. Patients who had confirmed undetectable minimal residual disease (uMRD) after completion of the combination therapy were randomly

assigned in a double-blind manner to placebo ($n = 43$) or continued ibrutinib ($n = 43$). At ASH 2022, Allan et al. presented the findings after a median follow-up of 56 months [9].

Forty-one months after completion of treatment with ibrutinib plus venetoclax, 3-year disease-free survival (DFS) rates were similar across the arms (85% vs. 93%; HR, 0.435; $p = 0.1621$). DFS was defined as death from any cause, disease progression, or MRD conversion (MRD $>10^{-4}$). Likewise, complete response (CR) rates were stable or had increased further over time. Duration of CR did not differ significantly between the treatment arms. MRD negativity was sustained 3 years post-randomization, with the rates being similar across all patients. As the authors noted, the durability of MRD negativity and the 3-year DFS rate of 85% in the placebo arm further support the potential for durable treatment-free remissions in the majority of patients. At 48 months, PFS was 88% and 95% with placebo and continued ibrutinib, respectively. Patients with unmutated IGHV showed PFS rates similar to those in the total population. OS rates remained $\geq 98\%$ across the ibrutinib and placebo arms. In patients with del(17p), *TP53* mutation, or complex karyotype, median DFS, PFS and OS were consistent with the total population, although the sample size was small in the placebo arm.

Post-randomization AEs were generally infrequent. No new atrial fibrillation events occurred in the placebo arm,

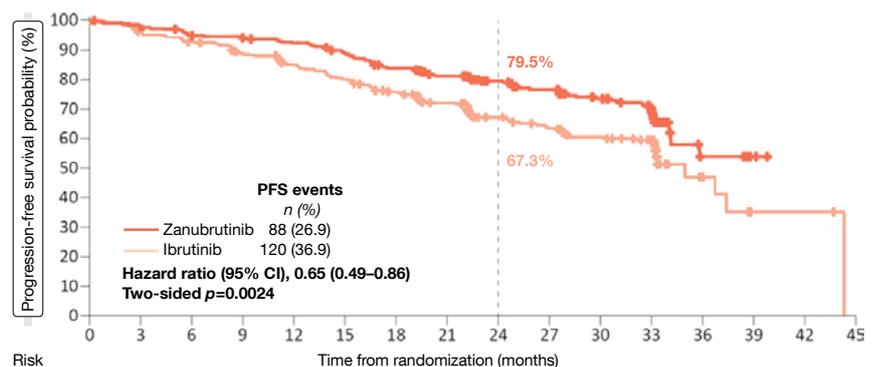


Figure 1: ALPINE study: superiority of zanubrutinib vs. ibrutinib regarding progression-free survival

while one such event was observed in the ibrutinib arm. Grade ≥ 3 hemorrhages were seen in neither arm. The authors concluded that the first-line combination of ibrutinib and venetoclax is an all-oral, once-daily, chemotherapy-free regimen with a favorable risk-benefit profile that continues to provide deep, durable responses.

Acalabrutinib, venetoclax & obinutuzumab

Therapeutic triplet regimens are evaluated in CLL based on a strong rationale indicating synergy between BTK inhibition and Bcl-2 inhibition on one hand and CD20-targeted treatment on the other [10–12]. However, *TP53*-aberrant CLL remains an area of unmet need.

Acalabrutinib plus venetoclax and obinutuzumab (AVO) is being tested in a treatment-naïve all-comer population in the phase II setting. The analysis of this group ($n = 37$) showed a high uMRD rate of 86% and a favorable toxicity profile [13]. Notably, uMRD outcomes in the bone marrow were similar regardless of *TP53* status.

Therefore, the researchers hypothesized that AVO would be an effective and well-tolerated novel-agent-only, time-limited frontline regimen for high-risk CLL, and opened an expansion cohort including 31 patients with *TP53*-aberrant disease only (i.e., del[17p] or *TP53* mutation). Prior to the initiation of obinutuzumab in cycle 2, patients received one cycle of acalabrutinib alone. Venetoclax was added at cycle 4. Obinutuzumab was administered for 6 cycles, venetoclax for 12 cycles, and acalabrutinib for 15 cycles. At cycle 16, the primary endpoint was

assessed, which was CR with uMRD in the bone marrow. Patients who achieved uMRD CR could discontinue therapy, while those who did not received another 9 cycles of acalabrutinib plus venetoclax. Restaging was performed at cycle 25, and patients again had the option to discontinue therapy if they had achieved uMRD. At ASH 2022, Ryan et al. presented longer-term follow-up data from the initial all-comer cohort and results from the expansion cohort [14].

In the entire group, 43% of patients achieved the primary endpoint, which was CR with uMRD in the bone marrow at cycle 16. For the *TP53*-aberrant group, this was 45%. AVO induced pronounced clinical responses, with a CR rate of 48% in the total population (Figure 2). Subgroup analyses showed similar CR rates irrespective of the *TP53* mutation status. uMRD was identified in 86% in both peripheral blood and bone marrow in all patients. Again, the results were consistent across the *TP53*-wildtype and *TP53*-aberrant groups. In patients who had reached cycle 25 on study, similar findings to those seen at cycle 16 emerged; the CR rate was 44%, and uMRD rates were 89% and 84% in the peripheral blood and bone marrow, respectively. MRD assessment via clonoSEQ® next-generation sequencing demonstrated durable MRD negativity in the blood, with uMRD $< 10^{-5}$ in 59% and 61% at cycles 16 and 25, respectively.

Lasting treatment effects

Among 43 patients who electively discontinued therapy after achieving uMRD in the bone marrow, 22 remained in CR or

partial remission (PR) at cycle 24 after a median time off therapy of 18.8 months. Four individuals who electively discontinued therapy after 15 cycles had disease recurrence, with three showing MRD recurrence only and one patient with overt CLL disease progression. Overall, at a median follow-up of 35 months, 92.6% of all patients were alive and progression-free.

The safety profile contained the expected toxicities of the three agents, including headache, fatigue, and bruising. Most of these were grade 1 or 2. Thirty-seven percent of patients had grade 3/4 neutropenia; however, no patient developed febrile neutropenia or opportunistic infections. Relatively low rates of grade ≥ 3 infections were observed, although one patient died of COVID-19 pneumonia. Two cases of atrial fibrillation occurred. Fourteen patients (21%) required any dose reduction.

In their summary, the scientists stated that AVO is a highly active, well-tolerated triplet regimen in a frontline CLL population enriched for high-risk disease. These findings provide a foundation for the MRD-guided, time-limited triplet therapy, particularly in high-risk CLL. AVO is currently being tested against acalabrutinib/venetoclax and chemoimmunotherapy in the phase III ACE-CL-311/AMPLIFY trial in non-high-risk CLL (NCT03836261).

GIVE regimen in high-risk patients

Another triplet is obinutuzumab, ibrutinib, and venetoclax (GIVE) that was assessed in previously untreated patients with del(17p)/*TP53* mutation in the phase II CLL2-GIVE trial. During the induction phase, obinutuzumab was administered for 6 cycles together with ibrutinib and venetoclax; the consolidation phase included ibrutinib plus venetoclax through cycle 12, after which ibrutinib continued for 3 more cycles. Patients who achieved uMRD at cycles 9 and 12 as well as CR or CR with incomplete count recovery (CRi) at cycle 15 could discontinue ibrutinib therapy at that time. Those who did not went on to receive ibrutinib for a maximum of 36 cycles. The CR rate at cycle 15 was defined as the primary endpoint.

According to the final analysis for 41 patients reported at ASH 2022 by Huber et al., time-limited therapy with the GIVE

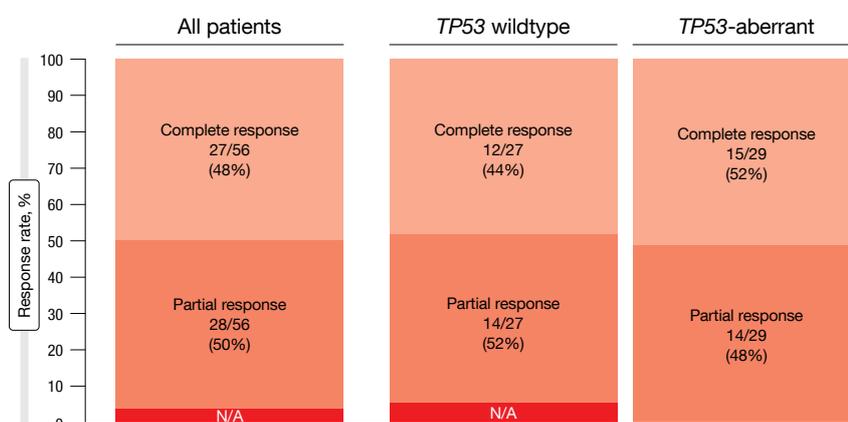


Figure 2: Acalabrutinib plus venetoclax and obinutuzumab: high clinical response rates at cycle 16 by iwCLL criteria

regimen represents a promising approach in high-risk patients [15]. At the time of the final restaging at cycle 15, all patients responded, with 58.5% and 41.5% achieving CR/CRi and PR, respectively. uMRD in the peripheral blood was present in 87.8% at cycles 9 and 12, and in 78.0% at cycle 15 (Figure 3). At cycle 36, this proportion had decreased to 43.9%, although 26.8% of samples were not assessable at that time due to omitted study visits during the COVID-19 pandemic. The 36-month PFS and OS rates amounted to 79.9% and 92.6%, respectively.

The most common hematologic AEs observed in the study included neutropenia (grade ≥ 3 , 48.8%) and thrombocytopenia (grade ≥ 3 , 17.1%). Among non-hematologic AEs, infections occurred in > 80% of patients and mainly comprised respiratory tract (33%), pathogen-unspecified (24%) as well as gastrointestinal and viral infections (9% each). Approximately 20% of infections were classified as grade ≥ 3 . Atrial fibrillation constituted the most common cardiac AE (14.6%; grade ≥ 3 , 2.4%). Any-grade AEs and grade ≥ 3 AEs emerged predominantly during induction therapy and decreased during consolidation and maintenance. The authors emphasized the importance of monitoring for infections and supportive measures, which might limit the utility of this regimen in younger and fitter patients. The GIVe regimen is being further assessed in the CLL13/GAIA trial that is comparing GIVe to chemoimmunotherapy, venetoclax/rituximab and venetoclax/obinutuzumab in patients without *TP53* deletion or mutation.

Phase I data for Bcl-2 inhibitor lisaftoclax

The novel Bcl-2 inhibitor lisaftoclax has been shown to be active in r/r CLL/SLL in a global phase I study, which included patients with *TP53* aberrations and/or progression after BTK inhibition [16]. Davids et al. reported the first analysis of a global phase I/II study investigating lisaftoclax as single agent (part 1; $n = 46$) or in combination (part 2) with rituximab ($n = 9$) or acalabrutinib ($n = 9$) in patients with r/r or treatment-naïve CLL/SLL [17]. The dose expansion part contained 100 additional patients who were treated with rituximab plus lisafto-

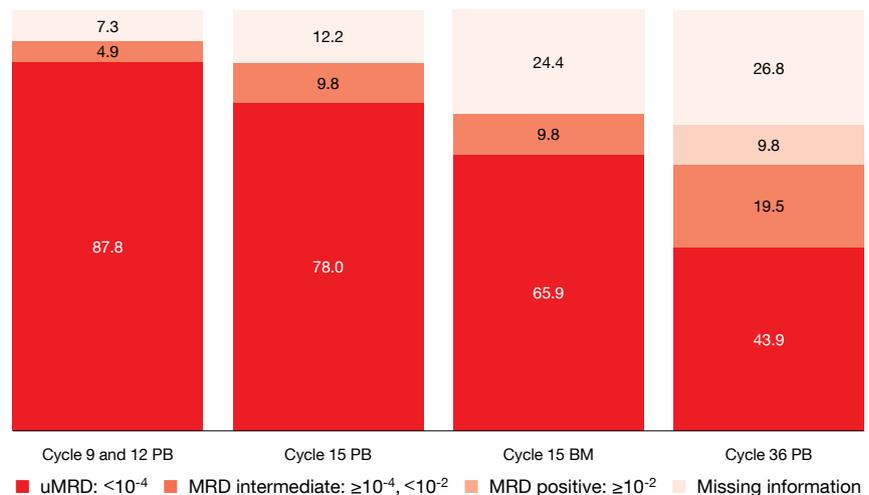


Figure 3: Minimal residual disease results for obinutuzumab plus ibrutinib and venetoclax in patients with *del(17p)/TP53* mutation. PB, peripheral blood; BM, bone marrow

clax ($n = 30$) or acalabrutinib plus lisaftoclax ($n = 70$). Overall, 46 patients received lisaftoclax monotherapy, while 39 and 79 were treated with the rituximab and acalabrutinib combinations, respectively. Each study part examined 3 lisaftoclax dose levels of 400 mg, 600 mg, and 800 mg.

Daily lisaftoclax ramp-up within a week was demonstrated to be feasible both in the monotherapy and combination settings. No dose-limiting toxicities have occurred to date. According to pharmacokinetic analyses, the drug exposure levels were dose-dependent and comparable between single agent and combination therapy. There were no significant drug-drug interactions between lisaftoclax and rituximab or acalabrutinib. The most common AEs included neutropenia, diarrhea, and COVID-19 infection. Grade 3/4 neutropenia occurred in 21.0% to 30.3% across the groups. Cytopenias generally abated from cycle 3 onward. Clinical tumor lysis syndrome (TLS) was observed in 2.5% but fully resolved.

Lisaftoclax proved to be active across the range of doses assessed. Almost all patients experienced decreases in lymph node diameters and absolute lymphocyte counts. In the r/r setting, ORRs were 67.4% for the monotherapy as well as 79.4% and 98% for the rituximab and acalabrutinib combinations, respectively. In the treatment-naïve group receiving lisaftoclax plus acalabrutinib, all patients responded. A registrational, phase III study evaluating lisaftoclax plus acalabrutinib in patients with r/r CLL is being planned.

BGB-11417 with and without zanubrutinib

The combination of ibrutinib and the Bcl-2 inhibitor venetoclax has proven effective in patients with CLL/SLL, although toxicities limit its use [18], thus leaving room for improvement in terms of more tolerable combination regimens. In vitro, the novel Bcl-2 inhibitor BGB-11417 has shown more potent and selective Bcl-2 inhibition and improved activity against Bcl-2 mutations than venetoclax [19]. Preliminary data from a first-in-human, multicenter, phase I study assessing BGB-11417 as monotherapy or together with zanubrutinib in patients with CLL/SLL were reported at ASH 2022 by Cheah et al. [20]. Parts 1 and 3 of the study investigated dose escalation including five dose levels (40 mg to 640 mg) for BGB-11417 alone and together with zanubrutinib, while parts 2 and 4 were expansions. In the combination cohort, both a weekly ramp-up schedule and an experimental daily ramp-up schedule were used. Among 79 CLL patients, 8 and 71 received BGB-11417 monotherapy and BGB-11417 plus zanubrutinib, respectively.

The treatment was well tolerated. At the time of the analysis, dose escalation continued to 640 mg with only one dose-limiting toxicity; the maximum tolerated dose had not been achieved. Preliminary pharmacokinetics revealed dose dependence throughout the dose range, fast absorption, and a short half-life of approximately 5 hours. The pharmacokinetics were similar with and without

TABLE
Responses observed for BGB-11417 as monotherapy and in combination with zanubrutinib

Response, n (%)	Relapsed/refractory BGB-11417 (n = 8)	Relapsed/refractory BGB-11417 + zanubrutinib (n = 25)	Treatment-naïve BGB-11417 + zanubrutinib (n = 46)
Efficacy-evaluable population	6	20	11
Overall response rate, n (%)	4 (67)	19 (95)	11 (100)
Complete response	2 (33)	6 (30)	2 (18)
Partial response	2 (33)	13 (65)	9 (82)
Stable disease	2 (33)	1 (5)	0
Progressive disease	0	0	0

zanubrutinib. In the group treated with single-agent BGB-11417, neutropenia, thrombocytopenia, headache and COVID-19 constituted the most common AEs, while for the combination, this was contusion, COVID-19, diarrhea, and neutropenia. Grade ≥ 3 neutropenia and grade ≥ 2 diarrhea were uncommon and readily manageable. No clinical TLS and a single instance of laboratory TLS occurred. The daily ramp-up group did not develop TLS.

BGB-11417 alone and combined with zanubrutinib demonstrated promising efficacy in patients with r/r and treatment-naïve CLL/SLL. After the weekly ramp-up to 40 mg, absolute lymphocyte counts decreased by approximately 90% within 6 weeks. The authors stated that this is similar to reductions observed with venetoclax 200 mg [21], theoretically suggesting a five-fold increase in potency. ORRs in efficacy-evaluable patients with r/r disease were 67% and 95% for the monotherapy and combination arms, respectively, and

100% in the treatment-naïve group receiving BGB-11417 plus zanubrutinib (Table). According to the preliminary MRD data, blood MRD negativity was observed at ≥ 80 mg after 6 months in both monotherapy and combination cohorts and increased with longer follow-up and higher dose. Longer observation periods are required to gain further insights here.

MRD-guided duvelisib plus venetoclax

Duvelisib, an oral inhibitor of PI3K- δ/γ , and venetoclax have shown synergistic effects in Richter's syndrome PDX models [22]. The recommended phase II dose of venetoclax 400 mg QD plus duvelisib 25 mg BID has already been established in a phase I/II study, with promising initial safety and efficacy results [23]. After a 7-day lead-in of duvelisib 25 mg, venetoclax treatment was started. The combination was administered for 12 cycles. On day 1 of cycle 13,

restaging was performed; patients with confirmed uMRD were able to discontinue treatment, with a view to resumption of venetoclax therapy in case of MRD recurrence, while those who remained MRD-positive continued on venetoclax. In the phase II, venetoclax was started at doses of 10 mg (outpatient) or 20 mg (inpatient) with weekly ramp-up to 400 mg QD, whereas patients with Richter's syndrome could undergo accelerated daily ramp-up to 400 mg over 5 days.

Ryan et al. performed an updated analysis of the data for the CLL/SLL cohort (n = 35) and the Richter's syndrome cohort (n = 8) based on the assumption that duvelisib plus venetoclax will achieve deep remissions with high rates of uMRD, thus allowing for an all-oral, time-limited therapy [24]. Indeed, 12 CLL patients (35%) achieved CR/CRi with uMRD in the bone marrow after 12 cycles, and 11 electively discontinued therapy. Half of CLL patients with TP53-aberrant disease responded to the treatment. This also applied to the group that had previously received BTK inhibition. At 2 years, 78% of all CLL patients were progression-free.

Two of the patients who electively discontinued treatment were found to have MRD-only recurrence in the peripheral blood at cycle 25. Both restarted venetoclax monotherapy, and one achieved uMRD. In the group with Richter's syndrome, two patients (25%) achieved CR, and one successfully underwent consolidative allogeneic stem cell transplantation. At the time of the analysis, five patients had died due to progressive disease.

Duvelisib plus venetoclax showed a manageable safety profile, with the most common AEs including cytopenias as well as grade 1 or 2 fatigue and diarrhea. Three cases of laboratory TLS were noted. Overall, further exploration of this regimen is warranted in patients with r/r CLL and Richter's syndrome.

Expanded phase I results for nembtabrutinib

Resistance to BTK inhibitor treatment is often due to mutations at the cysteine-binding residue (C481) on BTK or mutations in PLC γ 2 [25, 26]. Nembtabrutinib has been developed as a potent, reversible non-covalent inhibitor of wild-type

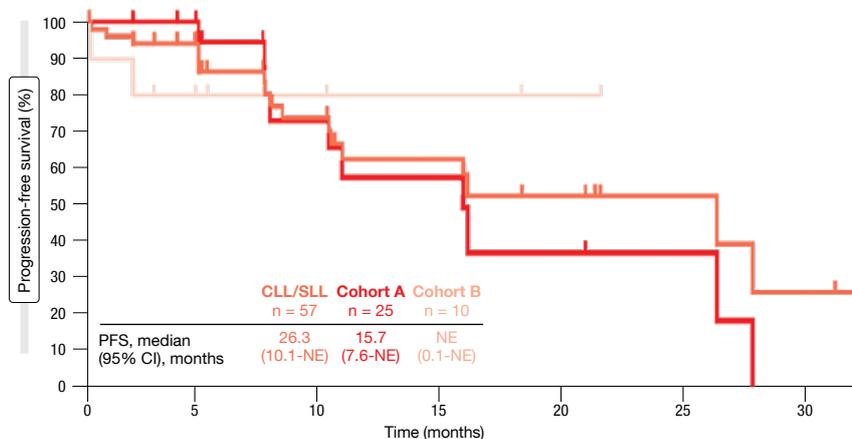


Figure 4: Progression-free survival with nembtabrutinib in the entire group as well as patients with C481S mutation (Cohort A) and without C481S mutation (Cohort B)

and ibrutinib-resistant *C481S*-mutated BTK [27]. The phase I/II BELLWAVE-001 study was designed to investigate nemtabrutinib in patients with relapsed or refractory hematologic malignancies. In patients with CLL/SLL, initial results from the dose-expansion phase revealed promising activity and a manageable AE profile [28].

According to the analysis presented at ASH 2022, nemtabrutinib at the recommended phase II dose of 65 mg QD continued to show promising and durable antitumor efficacy [29]. The ORR was

56% in the overall cohort ($n = 57$) and 58% in the BTK- and Bcl-2-pretreated individuals ($n = 24$), respectively. Patients with *C481S* mutation responded in 60% and those without *C481S* mutation in 40%. Median PFS was 26.3 months in the overall group, 15.7 months in the *C481S*-mutated cohort (Cohort A) and had not been reached in the group without *C481S* mutation (Cohort B) (Figure 4). Patients who were pretreated with BTK and Bcl-2 inhibitors experienced median PFS of 10.1 months and median duration of response of 8.5 months.

The AE profile of nemtabrutinib was manageable. Treatment-related AEs mainly comprised dysgeusia, decreased neutrophil counts, fatigue, decreased platelet counts and nausea. Among AEs of special interest, hypertension was most commonly observed (30%), followed by arthralgia (20%), maculopapular rash, and pneumonia (14% each). In their summary, the authors concluded that nemtabrutinib warrants further investigation in the subgroup of patients with CLL/SLL previously treated with BTK and Bcl-2 inhibitors.

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New approaches in relapsed and refractory DLBCL

Polatuzumab vedotin plus R-ICE

Approximately one third of patients with diffuse large B-cell lymphoma (DLBCL) develop relapsed or refractory disease, which remains a major cause of mortality [1]. In patients relapsing more than 1 year after first-line treatment, the standard of care is salvage treatment followed by autologous stem cell transplantation (ASCT), although responses to platinum-based salvage therapy are generally suboptimal. The CD79b-targeting antibody-drug conjugate polatuzumab vedotin was tested in the setting of relapsed/refractory DLBCL together with R-ICE (i. e., rituximab, ifosfamide, carboplatin, etoposide) as first salvage therapy based on the hypothesis that PolaR-ICE would be a safe and effective bridge to ASCT. At ASH 2022, Herrera et al. presented findings for 41 transplant-eligible patients with primary refractory (n = 20) or relapsed (n = 21) DLBCL after 1 prior anthracycline-based therapy [2].

According to the study schema, CT/PET staging was performed after 2 cycles of PolaR-ICE. Patients who obtained complete response (CR) or partial response (PR) could directly proceed to ASCT or undergo ASCT after they had received a third cycle of PolaR-ICE; this was at the discretion of the treating

investigator. ASCT was followed by polatuzumab vedotin consolidation for 3–4 cycles. The maximum overall number of polatuzumab vedotin cycles was 6. Primary endpoints included safety in the lead-in phase that established the recommended phase II dose of polatuzumab vedotin at 1.8 mg/kg, as well as CR after 2 cycles of PolaR-ICE.

Bridging to ASCT in 61 %

The safety lead-in identified no dose-limiting toxicities. After 2 cycles, 22 of 38 patients (54%) amenable to staging had developed CR (Figure). Together with a PR rate of 34%, this made for an overall response rate (ORR) of 88%. Twenty-three patients (56%) received 3 cycles of PolaR-ICE. At the end of salvage, ORR and CR rates were 80% and 56%, respectively. Overall, 22 patients (61%) underwent ASCT, and 16 (39%) proceeded to polatuzumab vedotin consolidation. In 10.7%, stem cell collection failure occurred. The impact of polatuzumab vedotin on stem cell collection remained unclear, as the authors noted. Patients with relapsed DLBCL had higher CR rates than those with primary refractory disease both after 2 cycles (76% vs. 30%) and at the end of salvage (76% vs. 35%). Preliminary analyses revealed a similar picture regarding PFS, although longer

follow-up is required to assess this endpoint adequately. After a median follow-up of 6.6 months, median PFS had not been reached in patients who went on to receive ASCT.

PolaR-ICE was shown to be a tolerable first salvage treatment option. Anemia, decreased platelet counts, and nausea were the most common attributable adverse events (AEs). The authors pointed out that a bridging rate of 61% compares favorably with historical results. It appears that in relapsed DLBCL, PolaR-ICE is a potent salvage regimen that should be considered for further study.

Zanubrutinib/lenalidomide: promising preliminary results

The ongoing open-label, multicenter, phase I dose-escalation and dose-expansion study BGB-3111-110 is investigating the next-generation BTK inhibitor zanubrutinib in addition to lenalidomide in Chinese patients with relapsed/refractory DLBCL after ≥ 1 line of systemic therapy. The patients were ineligible for high-dose therapy/stem cell transplantation if they had not received this previously. Zanubrutinib 160 mg BID was administered together with one of three doses of lenalidomide (i. e., 15 mg QD, 20 mg QD or 25 mg QD on days 1-21) in the dose escalation part. Preliminary results from

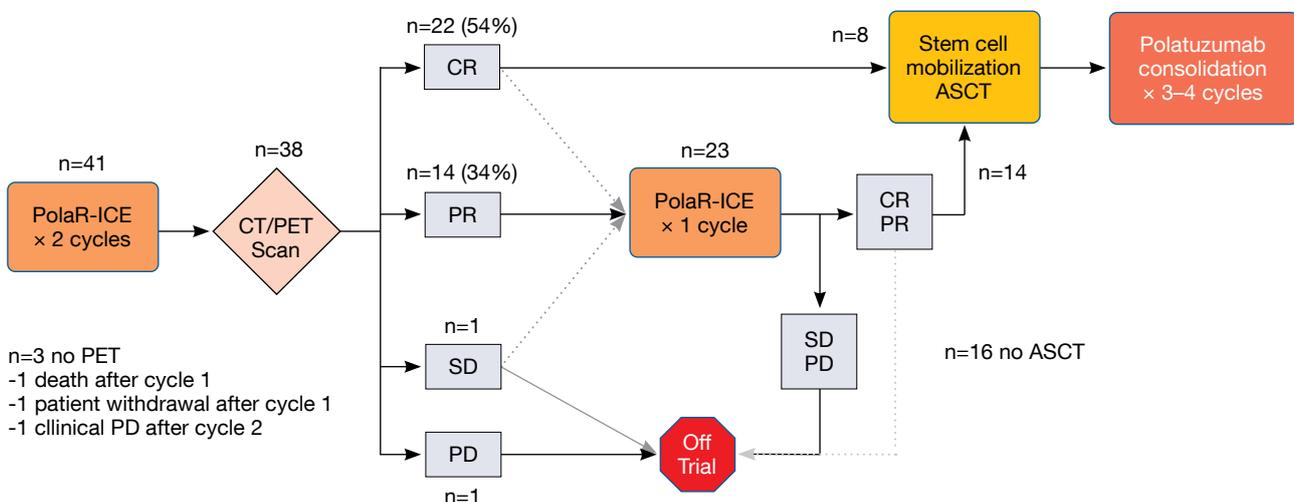


Figure: Responses to PolaR-ICE after 2 cycles and at the end of salvage treatment

this part of the study (n = 27) were reported at ASH 2022 by Zhang et al. [3]. The population included a total of 27 patients, with 6, 10, and 11 individuals being treated at the lenalidomide dose levels 1, 2, and 3, respectively. Seventy-four percent had stage III/IV disease, and 52% had refractory DLBCL.

The ORR identified in the overall cohort was 51.9%, and CR was achieved in 22.2%. Patients treated at dose level 3 showed the best ORR of 90.9% and the highest CR rate of 36.4%. Median duration of response had not been reached at the time of the analysis. Median PFS was 5.52 months in the overall group; for dose levels 1, 2, and 3, this was 2.79 months, 2.89 months, and not reached, respectively.

At the same time, zanubrutinib plus lenalidomide showed an acceptable safety profile. No patient experienced dose-limiting toxicity at any dose level, and the maximum tolerated dose was not reached. The incidence of any-grade treatment-emergent AEs (TEAEs) did not increase significantly with increasing dose. Grade ≥ 3 TEAEs occurred in 63%, were mostly hematologic events, and were generally manageable across all dose levels. Based on these efficacy and safety data, the recommended phase II dose of lenalidomide in this combination was determined to be dose level 3, i.e., lenalidomide 25 mg QD on days 1–21 of each 28-day cycle in addition to zanubrutinib 160 mg BID continuously. Patient recruitment for the dose

expansion part of the study that uses dose level 3 and will focus on the ORR as the primary endpoint is ongoing.

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Follicular lymphoma: bispecific and PI3K δ -targeted approaches

Advanced-stage follicular lymphoma (FL) remains incurable, with most patients eventually experiencing disease progression despite therapeutic advances. Relapsed or refractory FL is challenging to treat, particularly in high-risk patients who are refractory to prior treatments and have progressed within 24 months. The combination of rituximab and lenalidomide (R²) is commonly used in this setting, although complete response (CR) rates are suboptimal [1]. This raises the need for novel, efficacious and well tolerated agents.

Epcoritamab plus R² in relapsed/refractory FL ...

Epcoritamab, a subcutaneously administered CD3/CD20 T-cell-engaging, bispecific antibody is being investigated together with R² in the phase I/II EPCORE NHL-2 study based on the rationale that epcoritamab and R² might synergize and have non-overlapping toxicities [2–4]. Arm 2b of the EPCORE NHL-2 study contains patients with relapsed/refractory CD20-positive, grade I–IIIA, stage II–IV FL. Epcoritamab 48 mg is administered weekly in cycles 1 and 2 followed by Q4W treatment for up to 2 years. At the same time, the patients re-

ceive rituximab until cycle 5 and lenalidomide for a maximum of 12 cycles. Among the 76 patients included in the analysis, 59% had stage IV disease, and 51% had FLIPI scores 3–5. Primary refractory and double refractory FL was present in 38% and 39%, respectively. In 42%, progression had occurred within 24 months of the initiation of first-line treatment (POD24). Thirty-eight percent were refractory to their last line of therapy.

In this massively pretreated cohort, the combination of epcoritamab and R² showed potent antitumor activity according to the update presented at ASH 2022 by Falchi et al. [5]. Overall, responses occurred in 96.2%, and complete metabolic responses were seen in 83.5%. Treatment was ongoing in 88% of patients at the time of the analysis, and median duration of response had not been reached. Notably, the majority of remissions were obtained at the first assessment already, which made for a median time to response of 1.4 months. Moreover, deep responses occurred across high-risk subgroups including double refractory patients and those with a history of POD24 (Figure 1).

The safety of the combined treatment remained consistent with previous re-

ports. Epcoritamab-related treatment-emergent adverse events (TEAEs) led to dose delays in 25%, while none of these TEAEs gave rise to discontinuation. Neutropenia was the most common TEAE (all grades, 47%); grade 3 and grade 4 neutropenic events were reported in 20% each. Cytokine release syndrome (CRS) occurred in 43%, although none of these patients experienced grade ≥ 3 events, and CRS did not necessitate treatment discontinuation. Most CRS events emerged after the first full dose. The authors pointed out that these data support outpatient administration. Furthermore, no cases of clinical tumor lysis syndrome were observed. The ongoing phase III EPCORE FL-1 trial is evaluating fully outpatient epcoritamab plus R² treatment in patients with relapsed/refractory FL (NCT05409066).

... and treatment-naïve disease

Arm 6 of the EPCORE NHL-2 study is investigating epcoritamab + R² in adults with previously untreated CD20-positive, grade I–IIIA FL. In the expansion phase, 41 patients received epcoritamab weekly in cycles 1 and 2 and Q4W from cycle 3 for up to 2 years combined with rituximab weekly in cycle 1 followed by

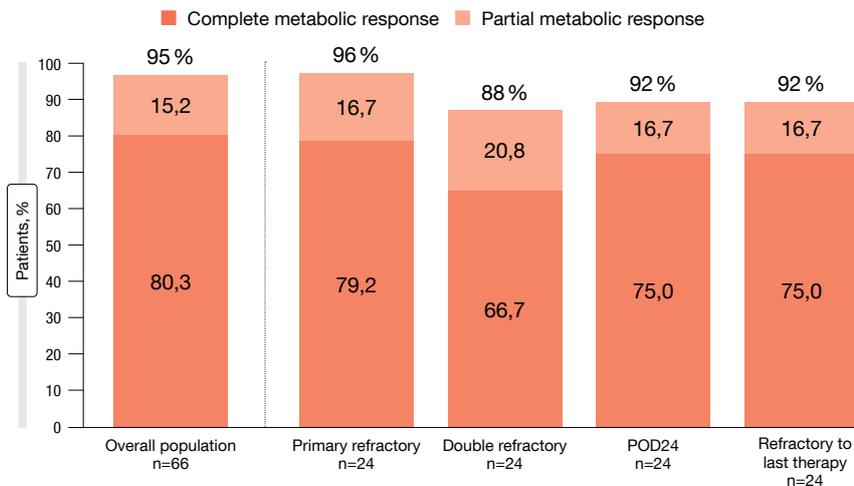


Figure 1: Responses to epicoritamab across high-risk subgroups with relapsed/refractory follicular lymphoma

Q4W administration in cycles 2–6 and oral lenalidomide in cycles 1–12. Almost all patients had stage III/IV disease, and FLIPI scores 3–5 were present in one third of the population.

As the first analysis of the data from arm 6 of the EPCORE NHL-2 study showed, epicoritamab + R² gave rise to high overall response and complete metabolic response rates of 94% and 86%, respectively [6]. Almost all responses had occurred at the time of the first assessment and were maintained, with 80% of patients still being on treatment after a median follow-up of 8.1 months. Median duration of response had not been reached yet.

No new safety findings were reported. CRS showed predictable timing, with most events noted after the first full dose, and was restricted to grade 1 and 2. Dose delays and treatment discontinuation related to epicoritamab therapy were seen in 17% and 7%, respectively. No clinical tumor lysis syndrome emerged. In their summary, the authors emphasized that these results support further clinical evaluation of epicoritamab + R² as a chemotherapy-free regimen in previously untreated patients with FL.

Single-agent mosunetuzumab

The CD20/CD3 bispecific antibody mosunetuzumab is being assessed in a pivotal single-arm, multicenter, phase II study that includes patients with relapsed or refractory grade I–IIIA FL who had received ≥ 2 systemic therapies in-

cluding an anti-CD20 antibody and an alkylator. Mosunetuzumab was administered as fixed-duration treatment at a dose of 30 mg Q3W after step-up dosing in cycle 1. In patients who achieved CR after 8 cycles, treatment was discontinued; in case of partial response or stable disease, mosunetuzumab was administered for a maximum of 17 cycles. As this treatment can be performed in the outpatient setting, hospitalization was not mandatory. Ninety patients participated most of whom had stage III/IV disease. After a median of 3 lines of prior therapy, 69% were refractory to their last treatment, and 79% were refractory to any prior anti-CD20 therapy. In 52%, a history of POD24 was present. Mosunetuzumab therapy gave rise to an overall response rate (ORR) of 80% and a complete response (CR) rate of 60%, which meant that the primary endpoint of CR superiority vs. historical control was met [7].

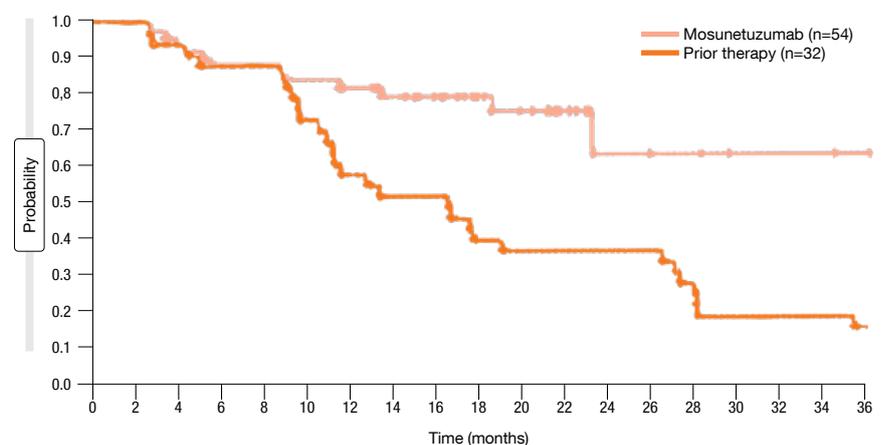


Figure 2: Duration of complete remission with mosunetuzumab vs. prior treatment

The updated outcomes presented at ASH 2022 after a median follow-up of 28.3 months demonstrated that only 18% of patients required treatment beyond 8 cycles [8]. Overall, 78% responded and 60% obtained CR, which was consistent with the published findings [7]. Responses proved durable; at 24 months, 63% of patients were in ongoing CR. Median overall survival and median time to next treatment had not been reached yet. Clinically meaningful response rates were observed in patients with common mutations including those associated with poor prognosis, such as *TP53* mutations. Furthermore, mosunetuzumab induced substantially improved response rates compared to the last prior therapy (ORR, 78% vs. 56%; CR, 60% vs. 36%), with longer duration of CR (median, not reached vs. 15 months; **Figure 2**) and improved progression-free survival (24 vs. 12 months).

The analysis demonstrated a manageable safety profile without new serious AEs, grade ≥ 3 AEs, or treatment-related AEs. No additional CRS events had been noted. Occurrence of CRS and tumor response showed no correlation. In their conclusion, the authors emphasized that mosunetuzumab is a promising option as an off-the-shelf, outpatient therapy with fixed duration of treatment.

Intermittent dosing of zandelisib

The clinical pharmacology of the oral PI3K δ inhibitor zandelisib allows for dosing on a non-continuous schedule [9]. Zelenetz et al. reported results for patients with FL grade I–IIIA who received zandelisib 60 mg on an intermittent

schedule in the open-label, phase II TIDAL study. Zandelisib was administered daily during cycles 1 and 2 (i. e., the induction phase) followed by dosing on days 1–7 of 28-day cycles from cycle 3 onward. The patients showed progressive disease after ≥ 2 prior therapies, which must have included an anti-CD20 antibody and an alkylating agent. Overall, 121 individuals were analyzed. This was a heavily pretreated population, with a median of 3 previous therapies. Almost all had received prior chemoimmunotherapy, and 56.2% had a history of POD24.

Single-agent zandelisib gave rise to high rates of durable remissions. Overall, 72.7% of patients responded, and CR resulted in 38.0%. Eighty-five percent

achieved disease control. Median duration of response and median progression-free survival were 16.4 and 11.6 months, respectively. Remissions occurred in patients with poor prognostic factors such as history of POD24 (ORR, 73.5%) and refractory disease (ORR, 68.5%). In the group after 2 prior lines of treatment, the ORR was 84.2%, with CR achieved in 43.9%. Moreover, remissions were seen early, as 87.5% of responses emerged by the end of cycle 2. Almost all patients with post-baseline disease assessment experienced tumor reduction.

Grade ≥ 3 TEAEs of special interest primarily occurred in cycles 1–3, which represented the continuous dosing period and the washout phase during the

first intermittent dosing cycle, while their cumulative incidence decreased substantially thereafter. Diarrhea represented the most common TEAE, followed by nausea, fatigue, pyrexia and neutropenia. In 13.2%, patients discontinued treatment due to treatment-related AEs.

As the authors pointed out, these data support the evaluation of zandelisib on an intermittent dosing schedule as a single agent or in combination in various B-cell malignancies, both in relapsed disease and earlier lines of treatment. The phase III COASTAL trial investigating zandelisib plus rituximab vs. chemoimmunotherapy is ongoing in patients with relapsed/refractory FL and marginal zone lymphoma (NCT04745832).

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Clinical findings with sundry targets in various B-cell malignancies

AUGMENT: 5-year results

Recurrent follicular lymphoma (FL) and marginal zone lymphoma (MZL) are treated similarly, mostly with single-agent rituximab. In patients with relapsed/refractory FL, the combination of lenalidomide with rituximab (R²) has previously demonstrated promising efficacy [1]. The multicenter, double-blind, randomized, phase III AUGMENT study was initiated to compare time-limited treatment for approximately one year with R² vs. rituximab plus placebo in patients with FL grade I-IIIa or MZL who had already received ≥ 1 prior systemic chemotherapy, immunotherapy or chemoimmunotherapy but who were not

refractory to rituximab. While lenalidomide 20 mg was taken orally on 21 days of twelve 28-day cycles, rituximab was administered on days 1, 8, 15 and 22 in cycle 1, as well as on day 1 in cycles 2–5. Approximately 180 patients were treated in each arm. At the time of the primary analysis, R², as compared with R-placebo, induced a higher overall response rate (ORR; 78% vs. 53%) and complete remission (CR) rate (34% vs. 18%) [2]. Leonard et al. reported updated findings from the AUGMENT trial at ASH 2022 [3].

After a median follow-up of 65.9 months, 70% and 61% of patients in the R² and R-placebo arms, respectively, had completed the treatment. R² continued to demonstrate superior efficacy over R-pla-

cebo. Progression-free survival (PFS), which was defined as the primary endpoint, was significantly improved in the experimental arm (median PFS, 27.6 vs. 14.3 months; HR, 0.50; $p < 0.0001$). For overall survival (OS), the Kaplan-Meier curve separation after five years continued to favor R², thus providing evidence for a survival benefit of the combination. Median OS had not been reached in either arm, but the OS rates amounted to 83.2% vs. 77.3% at 5 years (HR, 0.59; $p = 0.0285$).

Notably, fewer R²-treated patients required ≥ 1 subsequent therapy (41% vs. 61%), with rituximab being the most common agent (25% and 34%, respectively). Median time to next lymphoma treatment was 73.1 vs. 31.8 months (HR,

0.53; $p < 0.0001$; **Figure 1**), which implied that the treatment-free period extended well beyond the 1-year active treatment period in the experimental arm.

Lower rates of SPMs and histologic transformation

The safety profiles remained consistent with the primary analysis. Grade 3/4 treatment-emergent adverse events (TEAEs) were observed more commonly in the R²-treated population (69% vs. 32%), with neutropenia occurring most frequently (50% vs. 13%). Not surprisingly, patients on lenalidomide treatment were more likely to require dose reductions (26% vs. 3% of placebo dose reductions). Also, a greater proportion of patients had dose interruptions with lenalidomide (64%) vs. placebo (26%) or rituximab (34%).

Compared to historical experience, the rates of second primary malignancies (SPMs) and histologic transformations continued to be lower. SPMs occurred in 7% vs. 12% of patients treated with R² and R-placebo, which represented an increase from 3% and 6%, respectively, in the primary analysis [2]. The incidence rate of SPMs per 100 patient-years was lower with R² than with rituximab alone (1.62% vs. 2.66%). Six vs. 8% of patients developed histologic transformations, which resulted in a lower updated incidence rate in the R² arm (1.24% vs. 1.85% per 100 patient-years).

Overall, fewer patients treated with R² died (15% vs. 26%), with most deaths occurring off treatment. Disease progression or disease complication was more commonly the cause of death in the control arm (14%) than in the experimental arm (5%). In their summary, the authors pointed out that these updated

results, including the OS data, further support the use of the R² regimen as a standard of care for patients with relapsed/refractory indolent non-Hodgkin lymphoma (NHL).

Zandelisib plus zanubrutinib

The PI3K δ inhibitor zandelisib has shown durable responses in patients with relapsed/refractory FL in two studies [4, 5]. Preclinical data suggest that dual inhibition of PI3K δ and BTK results in synergistic efficacy [6]. At ASH 2022, Soumerai et al. presented results from an open-label, multi-arm, phase IB study for the combination of zandelisib with the selective next-generation BTK inhibitor zanubrutinib [7]. The study population consisted of patients with relapsed/refractory FL Grade I-IIIa ($n = 31$) or relapsed/refractory mantle cell lymphoma (MCL; $n = 19$) after ≥ 1 prior treatment line. Zandelisib was administered at a daily dose of 60 mg on an intermittent dosing schedule (i.e., days 1–7 of each 28-day cycle) starting from cycle 1 in addition to zanubrutinib 80 mg BID. Intermittent dosing of zandelisib has been shown to improve tolerability, particularly in terms of immune-related AEs, without compromising efficacy [4, 5].

In the group with FL, 86.7% of patients responded, with 23.3% and 63.3% developing CR and partial remission (PR), respectively. Responses lasted for a median of 20.6 months, and median PFS was 22.4 months. Likewise, patients with MCL experienced pronounced and durable responses. The ORR in this group was 72.2%, and 27.8% developed CR. Median duration of response had not been reached at the time of the analysis,

while median PFS was 10.1 months. Tumor reduction was observed in almost all patients who underwent post-baseline disease assessment in both cohorts. Deepening of responses occurred over time, which calls for longer follow-up to estimate the true CR rates.

The combination of zandelisib and zanubrutinib was tolerated well without an increase in the rate or severity of class-related AEs. TEAEs in the total population most commonly included diarrhea, decreased blood cell counts, and increased blood creatinine levels. Most events were grade 1 and 2, although grade-4 neutrophil count decreases occurred in 12%. Only 2 patients (4%) discontinued treatment due to treatment-related TEAEs. One patient died due to COVID-19-related complications. The analysis showed low rates of AEs of special interest; here, transaminase elevations were most common (8.0%). As the authors concluded, these encouraging preliminary findings support further evaluation of zandelisib plus zanubrutinib in relapsed/refractory FL, MCL and other B-cell malignancies.

Zanubrutinib after acalabrutinib intolerance

Compared to ibrutinib and acalabrutinib, zanubrutinib has shown higher kinase selectivity, which is thought to improve tolerability as many AEs of the less selective BTK inhibitors are potentially caused by off-target inhibition. In the ongoing phase II BGB-3111-215 study, zanubrutinib 160 mg BID or 320 QD was well tolerated in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), MCL, MZL, or Waldenström's macroglobulinemia (WM) intolerant to their prior BTK inhibitor therapy [8]. At ASH 2022, Shadman et al. reported an update for cohort 2 of the study that included 21 patients intolerant to acalabrutinib [9]. The primary endpoint was the safety of zanubrutinib as assessed by the recurrence and change in severity of the patients' acalabrutinib intolerance AEs.

After a median zanubrutinib exposure of 7.6 months, which was longer than the reported cumulative acalabrutinib exposure before discontinuation (4.6 months), 67% of patients had not experienced any recurrence of their prior acalabrutinib intolerance events. Among the acalabrutinib intolerance events, 75% did not recur

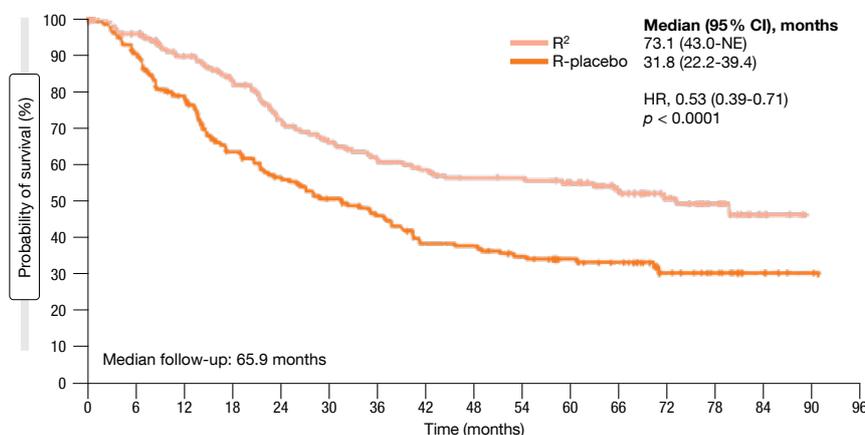


Figure 1: Time to next lymphoma treatment for R² vs. rituximab plus placebo

on zanubrutinib at any grade, and none recurred at higher severity. The most common grade ≥ 3 AE was neutrophil count decrease (10%). In terms of efficacy, zanubrutinib gave rise to an ORR of 61%, with 94% of patients achieving at least disease stabilization. According to the authors, these outcomes suggest that patients who are intolerant to acalabrutinib can attain clinical benefit if their treatment is switched to zanubrutinib.

Moreover, Xu et al. evaluated blood samples from 71 patients included in the BGB-3111-215 study to assess the mutational landscape of patients intolerant to BTK inhibitors [10]. This exploratory analysis suggested that mutations of cell cycle, DNA damage, and NOTCH1 pathway genes are frequent in patients intolerant to ibrutinib and/or acalabrutinib. The top mutated genes were *TP53* (32%), *SF3B1* (23%), *ATM* (18%), *NOTCH1* (17%), and *CHEK2* (15%). Baseline alterations in cell cycle/DNA damage and epigenetic modifier pathways were associated with inferior response to BTK inhibition (Figure 2) and inferior PFS. Patients who progressed on zanubrutinib showed higher likelihood of *BTK* mutations that convey resistance to BTK inhibitors or other mutations known to be associated with poor prognosis.

Findings in Japanese patients

In the ongoing, multicenter, phase I/II BGB-3111-111 study, zanubrutinib is being investigated in Japanese patients with mature B-cell malignancies including WM, CLL/SLL, relapsed/refractory MCL, FL, and MZL. Part 1 of the study was dedicated to confirming the safety, tolerability, and pharmacokinetics of zanubrutinib, while part 2 evaluated efficacy and safety in disease-specific cohorts.

Investigator-assessed data presented at ASH 2022 for a total of 53 patients [11] indicated that the plasma exposure was comparable to exposures observed in published global zanubrutinib trials at equivalent doses [12-16]. Moreover, the efficacy data were comparable with those observed in these studies. Zanubrutinib was shown to be highly active in Japanese patients. Across the disease-specific cohorts, the ORRs ranged from 82% to 100%. Median duration of response and median PFS had not been reached for any cohort.

The treatment was generally well tolerated. Platelet count decreases represented the most common any-grade AE, followed by pyrexia and neutrophil count decreases. Neutropenia and infections were the most common grade ≥ 3 AEs of special interest. Overall, these preliminary data support the use of zanubrutinib in Japanese patients with WM, CLL/SLL, and relapsed/refractory MCL.

Biomarker analysis of zanubrutinib and tislelizumab

Zanubrutinib in combination with the anti-PD-1 antibody tislelizumab has shown antitumor activity in B-cell malignancies, including DLBCL [17, 18]. In the phase I dose-escalation/dose-expansion BGB-3111-A317 study, zanubrutinib plus tislelizumab is being assessed in patients with various relapsed/refractory B-cell malignancies. Lyu et al. performed an exploratory analysis based on samples from 24 patients with DLBCL included in BGB-3111-A317 to identify biomarkers associated with response and resistance to the combination therapy [19].

According to the preliminary results, patients with *PD-L1* gene amplification, PD-L1-positive tumor cells, and high

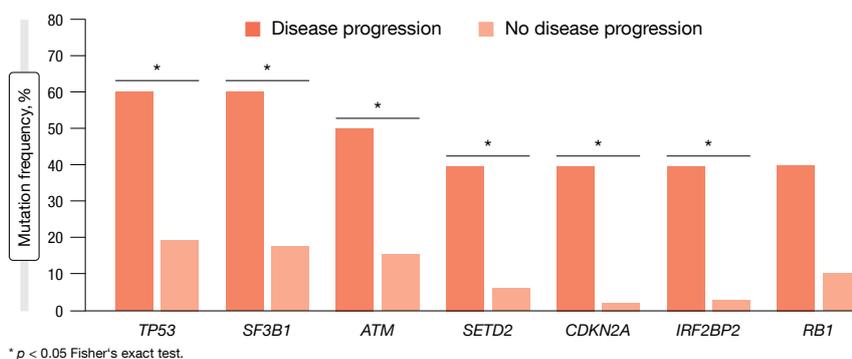
mRNA levels of *CD3D*, *HLA-DRA*, and *LAG3* in baseline tumor tissue might be more responsive to zanubrutinib plus tislelizumab. Enrichment of *CD3D*, *HLA-DRA*, and *LAG3* suggests an inflamed tumor microenvironment (TME). Non-responders, on the other hand, had high mRNA levels of *REL*, which were associated with poor clinical outcomes, and higher occurrence of *TP53* mutations. The authors noted that the inhibition of B-cell and BCR-related signatures and induction of NK signatures in tumor samples that were observed on zanubrutinib treatment indicate the on-target effect of this agent and its potential TME-modulating effect. However, due to the limited number of samples, these findings must be interpreted with caution.

Zilovertamab plus ibrutinib

The anti-ROR1 antibody zilovertamab has been designed to inhibit signaling related to ROR1, an onco-embryonic kinase-like receptor that is highly expressed in many solid and hematologic malignancies, but not in normal adult tissues [20]. Zilovertamab has been shown to inhibit expression of downstream genes that promote the survival and growth of CLL cells with mutated *TP53* in patients treated with BTK inhibitors.

The phase I/II study reported at ASH 2022 by Lee et al. demonstrated safety and robust efficacy of the combined use of zilovertamab and ibrutinib in patients with relapsed/refractory MCL and treatment-naïve or relapsed/refractory CLL [21]. Parts 1 and 2 of the study were dedicated to dose finding and dose expansion; here, patients with CLL (n = 34) and MCL (n = 33) were treated with zilovertamab plus ibrutinib, while an MZL cohort was still enrolling at the time of the analysis. The recommended phase II regimen included 3 doses of zilovertamab 600 mg Q2W followed by 600 mg Q4W plus the approved doses of ibrutinib for the treatment of CLL or MCL. In the third part of the study, zilovertamab plus ibrutinib was tested against ibrutinib monotherapy in patients with CLL. Eighteen individuals received the combination, while 10 were treated with single-agent ibrutinib. Overall, this was a heavily pretreated population with high-risk disease.

Across the study parts, zilovertamab plus ibrutinib gave rise to robust and du-



* $p < 0.05$ Fisher's exact test.

Figure 2: Exploratory analysis: correlation between the presence of baseline genetic alterations and disease progression

rable responses (**Table 1**). ORRs ranged from 89.3% to 100.0%. Median duration of response was almost 3 years in the MCL and CLL cohorts, while it had not been reached yet by either treatment arm in the randomized comparison. The safety profile of the combination was consistent with that of ibrutinib monotherapy. Diarrhea and fatigue occurred most often, and grade 3/4 events were rare. Atrial fibrillation was seen in 9.4% of patients. The majority of laboratory abnormalities was grade 1 or 2. In part 3 of the study, the combination induced grade 3/4 decreases in neutrophil counts in 5.6%, while this rate was much higher in the ibrutinib-only arm (20.0%). Febrile neutropenia was observed in 1.2% of patients treatment with zilovetamab plus ibrutinib.

Activity for MCL and CLL

The scientists analyzed the efficacy of zilovetamab plus ibrutinib separately for MCL patients and CLL patients. In the MCL population, the combination led to rapid responses, with CR and PR rates of 17.9% and 60.7%, respectively, already at month 3. At 26 months, the ORR and CR rate were 89.3% and 42.9%, respectively. In contrast, historical ibrutinib has given rise to response rates that plateaued at a markedly lower level after increasing slowly over the course of one year [22].

Also, the combination elicited favorable PFS compared to ibrutinib alone, as > 70% of MCL patients were progression-free at 24 months. Analyses of PFS by prior line of therapy demonstrated durable results maintained in the second line that again exceeded the historical findings shown for ibrutinib [23]. Moreover, zilovetamab plus ibrutinib displayed robust efficacy with regard to PFS across subgroups with poor prognosis including

patients with Ki-67% index $\geq 30\%$ (median PFS, 33.21 months) and *TP53* mutation (median PFS, not reached). Median OS in the total MCL cohort had not been reached after a median follow-up of 19.5 months; at 25 months, 70% of patients were alive. Historical ibrutinib has given rise to a median OS of 25.0 months in the same setting [22]. Based on these data, the global, placebo-controlled phase III ZILO-301 trial investigating ibrutinib with or without zilovetamab has been initiated in patients with relapsed/refractory MCL (NCT05431179).

In the group with CLL, the median PFS for zilovetamab plus ibrutinib had not been reached after a median follow-up of 40 months. At 24 months, 95% of patients were progression-free. For reference, the ALPINE study showed 24-month PFS rates of 79.5% and 67.3% for zanubrutinib and ibrutinib, respectively, in patients with relapsed/refractory CLL [24]. The pooled landmark analysis for CLL patients with *TP53* mutation/17p deletion across all study parts yielded encouraging findings, as the entire group remained progression-free at 42 months.

BGB-11417 monotherapy

Although the efficacy of Bcl-2 inhibitors in CLL/SLL has been established by the approval of agents such as venetoclax across all lines of therapy, AEs and the development of *BCL2* mutations leading to resistance limit the utility of this treatment in clinical practice [25, 26]. BGB-11417 has been developed as a more potent and highly selective Bcl-2 inhibitor than venetoclax, with the potential to achieve deeper target inhibition and clinical responses [27, 28]. According to preliminary data obtained from the phase I BGB-11417-102 study, BGB-11417 monother-

apy is well tolerated at all tested doses of up to 640 mg/d and shows promising efficacy in patients with mature B-cell malignancies [29]. Escalating doses with a weekly ramp-up for CLL/SLL (n = 18) and a daily ramp-up for NHL (i.e., FL, MZL, DLBCL or TF-NHL; n = 30) were investigated in the relapsed/refractory setting.

At the time of the analysis, the majority of treatment-related AEs were grade 1/2 events. No treatment-related AEs led to treatment discontinuation or death for both CLL/SLL and NHL patients (**Table 2**). The most common grade ≥ 3 TEAE was decreased neutrophil counts (22.9%), although this was transient and controllable. None of the patients developed clinical TLS. The data did not suggest any dose-dependent toxicity increases.

Among the 10 patients with CLL/SLL who were available for tumor assessment, 6 responded already at the lower dose levels. At the 80 mg/d dose level, 2 and 1 obtained CR and PR, respectively, while 3 developed PR at the 160 mg/d dose level. Owing to the short follow-up, no response data were available for the 320 mg/d and 640 mg/d cohorts yet. Two out of 7 patients assessable for MRD negativity achieved undetectable MRD. Preliminary activity was noted in the NHL patients, with 5 responding in the group of 25 individuals available for assessment. Further expansion data are being generated here, as the authors emphasized. Dose escalation is still ongoing, and the maximum tolerated dose/maximum absorbable dose has not been determined to date.

BGB11417 with and without zanubrutinib

Preliminary results from the first-in-human, phase I, dose-escalation and dose-

TABLE 1

High response rates and durable responses with zilovetamab plus ibrutinib in patients with MCL and CLL

Endpoints	MCL (Parts 1 & 2) Zilovetamab + ibrutinib (n = 28)	CLL (Parts 1 & 2) Zilovetamab + ibrutinib (n = 34)	CLL (Part 3) Zilovetamab + ibrutinib (n = 16)	CLL (Part 3) Ibrutinib (n = 7)
Overall response rate (ORR), n (%)	25 (89.3)	31 (91.2)	15 (93.8)	7 (100.0)
Complete response, n (%)	12 (42.9)	3 (8.8)	0	1 (14.3)
Partial response, n (%)	13 (46.4)	27 (79.4)	15 (93.8)	6 (85.7)
Stable disease, n (%)	1 (3.6)	3 (8.8)	1 (6.3)	0
Median duration of response, months	34.1	33.5	Not reached	Not reached
Median duration of follow-up, months	19.5	40.0	29.2	30.0

TABLE 2
Treatment-related adverse events observed with single-agent BGB-11417

n (%)	NHL (n = 30)	CLL/SLL (n = 18)	All (n = 48)
Patients with any treatment-related AEs	25 (83.3)	15 (83.3)	40 (83.3)
Grade \geq 3 AEs	12 (40.0)	8 (44.4)	20 (41.7)
Serious AEs	1 (3.3)	1 (5.6)	2 (4.2)
Leading to death	0	0	0
Leading to treatment discontinuation	0	0	0
Leading to dose modification	3 (10.0)	3 (16.7)	6 (12.5)

expansion BGB-11417-101 study were presented by Soumerai et al. for patients with relapsed/refractory NHL or WM who received BGB-11417 either as a single agent (parts 1 and 2) or in combination with zanubrutinib (parts 3 and 4) [30]. In the total group of 59 individuals, 43 and 16 received the monotherapy and the combination, respectively. NHL included DLBCL, FL, MZL, and MCL. Only patients with MCL were treated with the combination.

BGB-11417 was shown to be tolerable at doses of up to 640 mg/d. In the group with

NHL that was treated with single-agent BGB-11417, only 1 dose-limiting toxicity of febrile neutropenia occurred, and the maximum tolerated dose was not reached. BGB-11417 plus zanubrutinib was also well tolerated at doses of BGB-11417 \leq 320 mg; here, dose escalation is ongoing in patients with MCL. No clinical TLS emerged. Gastrointestinal AEs represented the most common monotherapy toxicity, although all cases were mild. Likewise, neutropenic events, which were the most common AE with the combined regimen, typically remained in the grade 1/2 range.

Responses occurred in 43% of WM patients and 10% of NHL patients treated with the monotherapy; in the group that received BGB-11417 plus zanubrutinib, the ORR was 81%. Complete remissions resulted in 67% of the patients who received the combination. Taken together, these data demonstrate the efficacy of BGB-11417 monotherapy in NHL and WM as well as that of BGB-11417 plus zanubrutinib in MCL. The study continues to determine the recommended phase II dose in the monotherapy and combination therapy settings.

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Final analysis of the MAGNOLIA trial: zanubrutinib in marginal zone lymphoma

The global, open-label, single-arm, phase II MAGNOLIA trial was designed to assess the next-generation BTK inhibitor zanubrutinib in patients with relapsed/refractory marginal zone lymphoma (MZL) who had previously received ≥ 1 CD20-directed regimen. After a median follow-up of 15.7 months, the overall response rate (ORR) according to independent review was 68.2%, with complete remissions resulting in 25.8% [1]. Median duration of response and median progression-free survival had not been reached yet. At both 12 and 15 months, 82.5% of patients were alive and progression-free. Opat et al. presented the final analysis of the MAGNOLIA study at a median follow-up of 28 months at ASH 2022 [2]. The safety and efficacy populations comprised 68 and 66 individuals, respectively. Thirty-one were continuing zanubrutinib treatment on the long-term extension study at the time of the analysis.

Zanubrutinib was generally well tolerated, and no new safety signals emerged. Contusion, diarrhea and constipation were reported as the most common treatment-emergent AEs (TEAEs), with almost all cases rated as mild or moderate. Neutropenia occurred in 16%; here, 12% of events were grade ≥ 3 . TEAEs of clinical interest mainly included infections (all grades, 56%; grade ≥ 3 , 22%) and hemorrhage (all grades, 41%; grade ≥ 3 , 1.5%). Hypertension and atrial fibrillation/flutter were infrequent and showed lower rates than reported for ibrutinib [3]. All-grade second primary malignancies were noted in 7%.

Zanubrutinib treatment gave rise to high response rates and durable disease control. The ORR according to PET and/or CT by independent review committee (i.e., the primary endpoint) was 68%, with complete responses being achieved in 26%. Median time to response was relatively short at 2.8 months. According to CT only, 67% of patients responded. Remissions were seen across MZL subtypes (Figure) as well as regardless of age, disease stage, presence of bone marrow involvement, and prior treatment. Median progression-free survival, median overall survival and median duration of response had not been reached. At 24 months, 86% of patients in the entire group were alive, and 71% were progression-free.

In 73% of cases, responses lasted through 2 years. For all of these endpoints, no obvious differences emerged across MZL subtypes.

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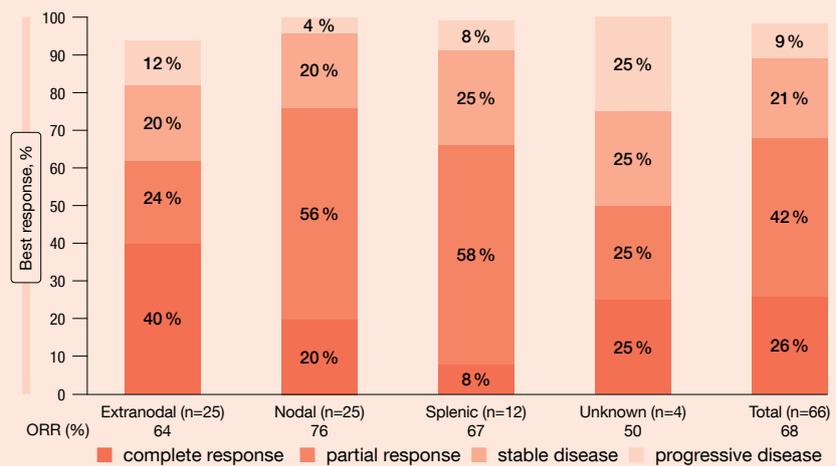


Figure: Best overall responses across marginal zone lymphoma subtypes by independent review

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Shirley D'Sa discusses the results of the first clinical trial investigating checkpoint inhibition in relapsed/refractory Waldenström's macroglobulinemia as well as other immunotherapeutic agents or combinations that might be worth investigating in this setting and explains the association of type I cryoglobulinemia with WM, IgM monoclonal gammopathy of undetermined significance or non-Hodgkin Lymphoma.

The ASH 2022 slide deck is now available! It contains summaries of selected posters and presentations from this years' congress focusing on emergent therapeutic options for B-cell malignancies, in particular the use of Bcl-2 and BTK inhibitors. The slide deck also highlights the potential of Bcl-2 inhibitors for the treatment of AML.

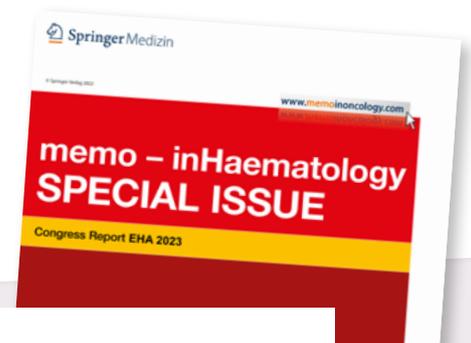
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This special issue will be offering a synopsis from the EHA 2023 that will be held in June 2023. The report promises to make for stimulating reading, as the EHA Congress itself draws on the input from a number of partner organizations, representing a multidisciplinary approach to cancer treatment and care. Stay tuned for the latest news in hematologic diseases and its subspecialties.



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