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02/22

memo – inHaematology SPECIAL ISSUE

Congress Report ASCO 2022 • EHA 2022

A GLOBAL CONGRESS DIGEST ON TARGETED AND IMMUNE-DIRECTED THERAPIES IN HAEMATOLOGICAL MALIGNANCIES

Report from the American Society of Clinical Oncology (ASCO) Annual Meeting (hybrid), 2nd–6th June 2022, and the 30th European Hematology Association (EHA) 2022 Congress (hybrid), 9th–12th June 2022

IMPRESSUM/PUBLISHER

Media owner and publisher: Springer-Verlag GmbH, Professional Media, Prinz-Eugen-Straße 8–10, 1040 Vienna, Austria, **Tel.:** +43(0)1/330 24 15-0, **Fax:** +43(0)1/330 24 26, **Internet:** www.springernature.com, www.SpringerMedizin.at. **Copyright:** © 2022 Springer-Verlag GmbH Austria. Springer Medizin is a Part of Springer Nature. **Managing Directors:** Joachim Krieger, Juliane Ritt, Dr. Alois Sillaber. **Medical Writer:** Judith Moser, MD. **Corporate Publishing:** Claudia Aigner. **Publishing Editor:** Anna Fenzl, PhD. **Layout:** Katharina Bruckner. **Published in:** Vienna. **Produced in:** Fulda. **Printer:** Druckerei Rindt GmbH & Co KG, Fulda, Germany; The editors of "memo, magazine of european medical oncology" assume no responsibility for this supplement.

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Supported by BeiGene Ltd. in the form of an unrestricted grant

Preface

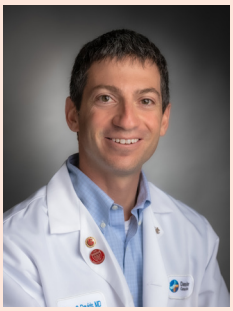
Dear Colleagues,

After 2 years of the COVID-19 pandemic, the Annual Meeting of the American Society of Clinical Oncology, held in Chicago, USA, and virtually from 3rd–7th June 2022, featured nearly 250 oral as well as over 2,200 poster presentations. Shortly thereafter, the 27th Congress of the European Hematology Association 2022, held in Vienna, Austria, and virtually, from 9th–12th June 2022, saw leading experts from around the world gather again to further discuss the most exciting updates in the field of hematology with key updates summarized in 200 oral presentations and 1,400 posters.

Over the last two decades, several new drugs have been approved for the management of CLL, and the field continues to undergo highly relevant improvements. The use of drug combinations with synergistic or at least additive efficacy but non-overlapping toxicity helps to keep an eye on health-related quality of life, not only for untreated but also for heavily pretreated patients. This issue of memo inHaematology offers a synopsis of treatments including BTK inhibitors that represent an essential pillar in the management of CLL and play an important role in other B-cell malignancies including marginal zone lymphoma.

Early-phase trials are outlined that demonstrate encouraging results with high response rates in patients with relapsed or refractory large B-cell lymphoma including DLBCL independent of age, disease subgroups, previous CAR-T therapy, and treatment lines. New strategies to overcome on-target resistance mutations emerging from BTK inhibitor treatment are introduced, as well as trial updates and real-world insights in the setting of Waldenström's macroglobulinemia. Next-generation BTK inhibitors for the treatment of mantle cell and follicular lymphoma are on the rise. Novel PI3Kδ inhibitors continued to be explored in relapsed and refractory follicular lymphoma.

Last but not least, this issue looks closely at patients with acute myeloid leukemia whose standard therapy has long consisted of intensive chemotherapy followed by allogeneic hematopoietic stem cell transplant. Recent years have seen major advances due to accurate genetic classification and treatment with hypomethylating agents, venetoclax, and nucleoside analogues. Lately, a first-in-class anti-CD47 antibody and a potent, highly selective investigational BCL2 inhibitor have shown encouraging antitumor activity.



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Once again, the two congresses showed that education on the latest advances in oncology accompanied by the best practices and promoting equal access to optimal cancer care for all patients is necessary to get closer to fulfilling the core mission of oncologists worldwide, who all pull together to improve the quality of cancer treatment, from prevention and diagnosis all the way to palliative care and patient follow-up.

Matthew S. Davids, MD, MMSc
Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Updates and ancillary analyses in the setting of chronic lymphocytic leukemia

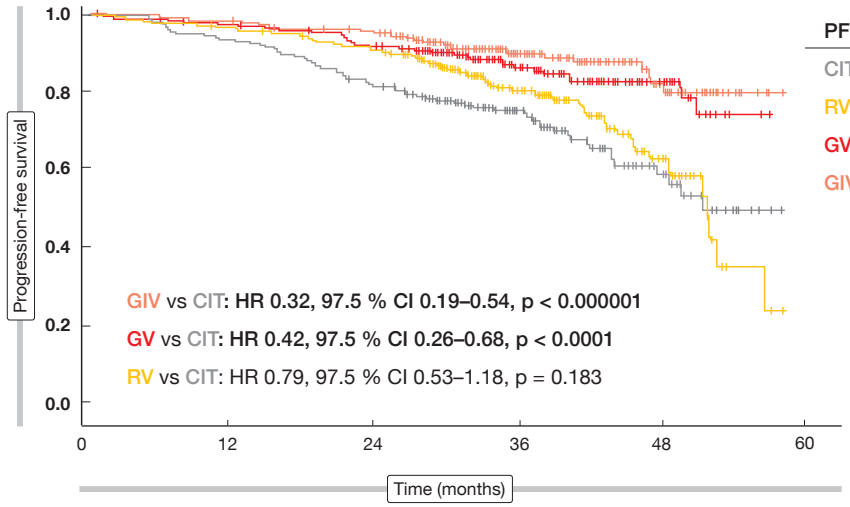
Progression-free survival in GAIA/CLL13

In fit patients with advanced CLL of favorable genetic risk, chemoimmunotherapy (CIT) consisting of fludarabine/cyclophosphamide/rituximab (FCR) or bendamustine/rituximab (BR) still represents the treatment standard. Another potential strategy, however, is time-limited therapy consisting of obinutuzumab plus venetoclax (GV) with or without a BTK inhibitor. The four-arm, randomized, phase III GAIA/CLL13 trial compared GV and GV plus ibrutinib (GIV) to 6 cycles of FCR (patient age ≤ 65 years) or BR (> 65 years) in fit patients (i.e., CIRS scores ≤ 6 and normal creatinine clearance) in whom *TP53* mutation and deletion 17p had been excluded. In the fourth study arm, rituximab plus venetoclax (RV) was administered. Overall, the trial contained 926 patients. The regimens were administered for a maximum of 12 cycles; only ibrutinib was allowed to be continued for up to 36 cycles in case of minimal residual disease (MRD) persistence.

The coprimary endpoint of undetectable MRD (uMRD) at 15 months in peripheral blood has been presented at the ASH 2021 congress [1]. This showed significantly higher uMRD rates with GIV and GV compared to CIT ($p < 0.0001$ each), while RV was not superior to CIT. At EHA 2022, Eichhorst et al. reported the second coprimary endpoint of the GAIA/CLL13 trial, which was interim progression-free survival (PFS) for GIV vs. CIT, as well as other study outcomes [2].

Broad clinical benefits with GV-based treatment

In keeping with the uMRD results, the PFS interim analysis demonstrated superior results for both GV-based regimens vs. CIT after a median follow-up of 38.8 months **(Figure 1)**. Median PFS had not been reached for GIV or GV,



PFS	Median months	3-year PFS (%)
CIT	52.0	75.5
RV	52.3	80.8
GV	Not reached	87.7
GIV	Not reached	90.5

Figure 1: GAIA/CLL13: superior progression-free survival with GV-based regimens vs. RV and CIT

while it was 52 months for both CIT and RV. At 3 years, 90.5 % and 87.7 % of the patients treated with GIV and GV, respectively, were progression-free (vs. 75.5 % with CIT). GV-based treatment prolonged PFS in almost all subgroups compared to CIT. The analysis according to the IGHV mutation status showed that PFS benefits due to GIV and GV occurred particularly in the unmutated IGHV setting, with rates of 86.6 % and 82.9 % vs. 65.5 % for CIT. In the group with mutated IGHV, the treatments showed no considerable differences. Patients aged ≤ 65 years in the mutated IGHV cohort derived equal PFS benefits from CIT, GIV, and GV therapy.

Time to next treatment (TTNT) was longer with the GV-based regimens than with CIT. At 3 years, 98.3 % and 94.1 % of patients in the GIV and GV arms, respectively, had not received any subsequent therapy (vs. 87.2 % with CIT). No differences in overall survival (OS) were observed between the study arms, although the overall number of events and the follow-up were still immature.

Grade ≥ 3 AEs occurred with similar incidence in the GIV, GV and CIT arms (83.5 %, 84.2 % and 81.5 %, respectively). The lower rate observed with RV (73.0 %) was particularly due to fewer blood and lymphatic system AEs. Rates for infections were highest with CIT (20.4 %) and GIV (22.1 %), which also applied to febrile neutropenia (11.1 % and 7.8 %, respectively). Hypertension, which is known to be an ibrutinib-specific AE, was noted in 5.6 % in the GIV arm. Second primary malignancies showed an increased incidence after CIT (49 cases vs. 29, 27 and 24 with GIV, GV, and RV, respectively). This was mainly based on a larger number of solid tumors and non-melanoma skin cancers. For Richter transformation, no distinct differences were noted across the four arms.

CLL14: 5-year update

In contrast to CLL13, the CLL14 study was designed to assess first-line treatment with GV in patients who had coexisting medical conditions as evidenced by CIRS scores > 6 and/or creatinine clearance < 70 mL/min. In the experimental arm, patients were treated with GV for 6 cycles followed by venetoclax monotherapy for another 6 cycles. Those in the control arm received 6 cycles of chlorambucil plus obinutuzumab followed by 6 cycles of chlorambucil. Each arm contained 216 patients. PFS was defined as the primary endpoint. At EHA 2022, Al-Sawaf et al. reported the 5-year analysis of CLL14 after a median observation time of 65.4 months [3].

At least 4 years after treatment cessation, the median PFS had still not been reached with GV and was 36.4 months with chlorambucil/obinutuzumab. The 5-year PFS rates amounted to 62.6 % vs. 27.0 %, translating into a 65 % reduction in the risk of progression or death (HR, 0.35; p < 0.0001). In the experimental arm, median PFS had not been reached yet in patients without *TP53* deletion and/or mutation, and was 49.0 months in those with these risk factors. Patients in the control arm showed median PFS of 38.9 and 19.8 months, respectively, for the two subgroups. Similarly, PFS was longest in the IGHV-mutated group treated with GV (not reached) followed by the GV-treated patients with unmutated IGHV (64.2 months), whereas the patients on chlorambucil/obinutuzumab experienced poorer PFS outcomes across the IGHV subgroups (59.9 and 26.9 months, respectively). These findings imply that the combined fixed-duration approach is feasible even in the presence of high-risk genomics.

A multivariable model identified pretreatment disease burden and deletion 17p as independent prognostic factors for PFS in the context of GV treatment. For pretreatment disease burden, the threshold was defined as a maximum lymph node size of > 5 cm and absolute lymphocyte counts > 25 G/L. Prognostic variables for chlorambucil/obinutuzumab, on the other hand, included IGHV mutational status, deletion 17p, deletion 11q, complex karyotype, and serum β2 microglobulin.

Deeper and sustained MRD rates after GV

Median TTNT had not been reached with GV and was 52.9 months with chlorambucil/obinutuzumab. At 5 years, 72.09 % vs. 42.84 % of patients were alive and had not received any further line of therapy (HR, 0.42; p < 0.0001). When viewed according to genomic risk groups, the course of disease was again more favorable in the absence of high-risk features, with TTNT being longest in the GV-treated cohort.

Second-line treatments in both arms comprised mainly targeted agents including several BTK inhibitors, although 26-31 % of patients received chemo(immuno)therapy, which reflects the limited access to second-line targeted drugs and can be expected to confound the OS observations to a certain degree. Median OS had not been reached yet; at 5 years, 81.9 % vs. 77.0 % of patients were alive (HR, 0.72). Only 8 patients in the experimental arm died due to CLL-related causes (vs. 23 in the control arm), which suggests that upfront use of BCL2 inhibitors can effectively contribute to controlling CLL-related mortality.

The updated analysis yielded no new safety signals after the prolonged follow-up. After the end of treatment, the AE rates remained very low. The cumulative incidence of second primary malignancies did not differ significantly between the two study arms.

Four years after treatment discontinuation, 18.1 % vs. 1.9 % of patients had sustained MRD < 10^{-4} in the peripheral blood. The depth of remission beyond 10^{-4} was shown to significantly correlate with long-term PFS, thus indicating the value of ultra-sensitive MRD assessments. Likewise, within the GV-treated group, patients with MRD ≥ 10^{-4} had a shorter OS than those with MRD < 10^{-4}; this highlights the need for dedicated MRD-guided approaches. Tailored strategies need to be developed for patients who remain MRD-positive after GV treatment.

MRD endpoint of the FLAIR study

The phase III NCRI FLAIR trial was initiated to compare ibrutinib plus rituximab with FCR in untreated, fit CLL patients. Indeed, the combination gave rise to improved PFS [4]. Two additional arms were added later on that tested ibrutinib plus venetoclax against ibrutinib monotherapy, the primary endpoint being MRD eradication. This population was ≤ 75 years old, considered fit for FCR, and was previously untreated but required therapy by IWCLL criteria. In patients who achieved MRD negativity, ibrutinib was not stopped immediately but was continued for the same duration that had passed until the negative assessment, to ensure further cell reduction and to enhance the likelihood of cure. Patients with MRD negativity in the peripheral blood underwent repeat testing after 3 months as well as blood and bone marrow testing at 6 months; if all of these assessments were negative, the first result was considered the time to MRD negativity.

The patients in the ibrutinib/venetoclax arm (n = 136) were treated for 2-6 years depending on the time to MRD negativity. Ibrutinib monotherapy (n = 138) was administered for a maximum of 6 years. If MRD positivity returned prior to year 6 according to periodic MRD measurements, ibrutinib was restarted. Hillmen et al. presented the interim data at EHA 2022 [5].

454-fold higher chance of achieving MRD negativity

Regarding the primary endpoint, which was MRD negativity at 2 years, the NCRI FLAIR trial revealed significant superiority of ibrutinib/venetoclax. MRD negativity was achieved in the blood and bone marrow in 71.3 % and 65.4 %, respectively, whereas none of the ibrutinib-treated patients had turned MRD-negative after 2 years' time **(Figure 2)**. Due to this highly significant difference (p < 0.0001), penalized logistic regression models were fitted to enable finite parameter estimation. This showed that the odds of achieving MRD negativity in the bone marrow were 454 times higher for patients receiving the combination than for those treated with ibrutinib monotherapy. Median time to MRD eradication was 12 and 19 months in the blood and bone marrow, respectively, for ibrutinib/venetoclax, and had not been reached with ibrutinib in either compartment. Almost 43 % patients treated with the combination stopped therapy due to meeting MRD stopping rules (vs. 0 % in the control arm).

While factors such as age and gender did not affect the outcomes, mutational status did. In the combination arm, MRD negativity was obtained more frequently by IGHV-unmutated than IGHV-mutated patients (79.7 % vs. 56.4 %). MRD eradication emerged in 82.8 % of patients with 11q deletion but only in 54.5 % of those with 13q deletion. The IWCLL response 9 months after randomization constituted a secondary endpoint. Approximately 90 % of the entire study population responded, although the patients in the experimental arm achieved a considerably higher CR rate than those in the control arm (59.6 % vs. 8 %).

The combination was well tolerated, with higher rates of diarrhea, nausea, anemia and leukopenia in ibrutinib/venetoclax-treated patients. Among grade ≥ 3 AEs, only leukopenia was notably increased in the experimental arm (27.4 % vs. 5.1 %). No cases of clinical tumor lysis syndrome occurred; laboratory TLS was reported in 4.4 % in the combination arm vs. 0 % in the control arm.

BRUIN: pirtobrutinib after BTK failure

Although BTK inhibitors have revolutionized the outcomes in leukemia, re-

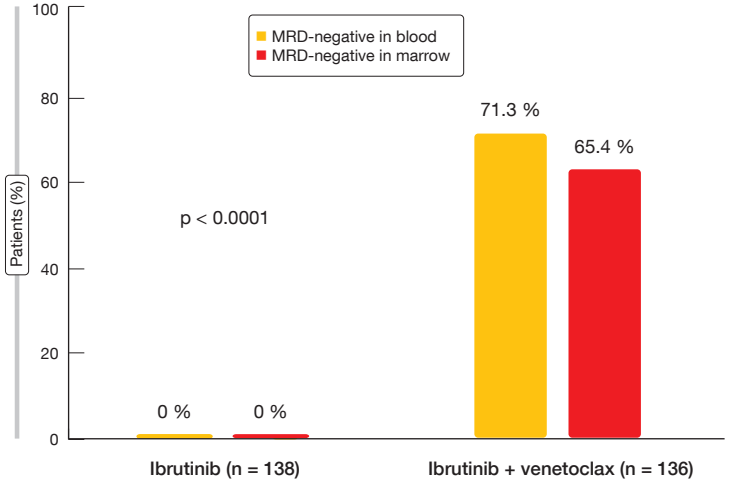


Figure 2: : MRD negativity with ibrutinib/venetoclax vs. ibrutinib at 2 years in the NCRI FLAIR trial

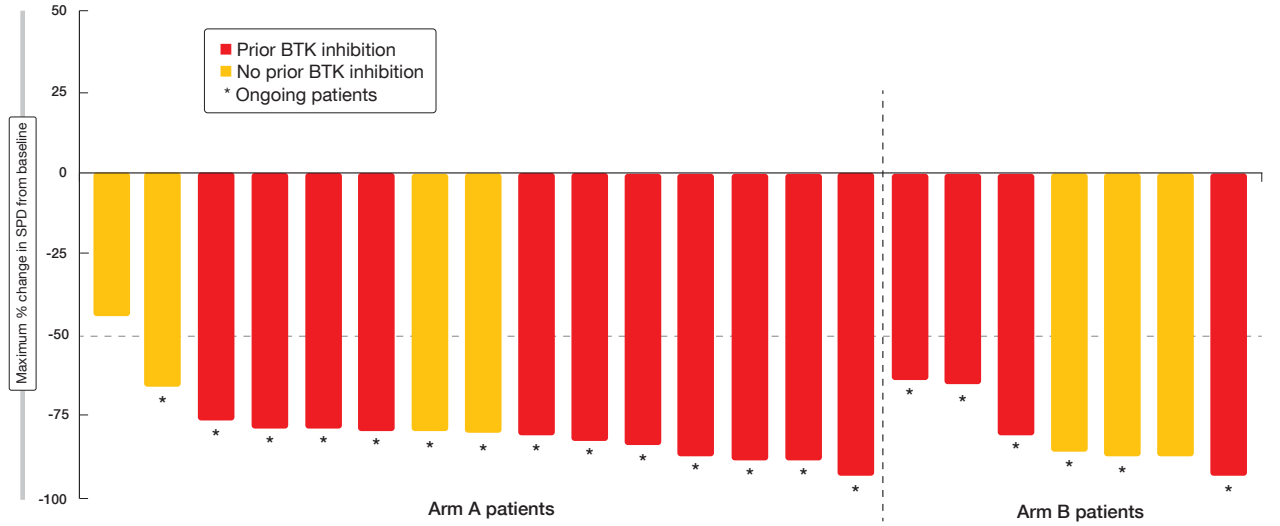


Figure 3: Reductions in tumor size achieved with pirtobrutinib/venetoclax (Arm A) and pirtobrutinib/venetoclax plus rituximab (Arm B)

sistance and intolerance limit their clinical benefits. Ibrutinib discontinuation rates at 5 years have been estimated at 41 % and 54 % for the frontline and relapsed/refractory settings, respectively [6, 7]. Available options following covalent BTK inhibitor treatment are limited.

The phase I/II BRUIN study is evaluating the highly selective, potent, non-covalent BTK inhibitor pirtobrutinib (LOXO-305) in patients with previously treated, advanced B-cell malignancies. The analysis presented by Mato et al. at EHA 2022 related to the group of 261 BTK-inhibitor–pretreated individuals with CLL/small lymphocytic lymphoma (SLL) [8]. In addition to BTK inhibition, most of them had previously received anti-CD20 antibody therapy and chemotherapy. BCL2 inhibitors had been administered in 41 %. Furthermore, high-risk molecular characteristics were present in a considerable proportion of patients.

Pirtobrutinib demonstrated promising efficacy in this heavily pretreated population, with an overall response rate (ORR) of 68 %. Responses were shown to be independent of the BTK C481 status, the reason for prior BTK discontinuation (i.e., progression vs. intolerance), and other classes of prior therapy including covalent BTK inhibitors, BCL2 inhibitors, and PI3Kδ inhibitors. Also, the responses appeared to deepen over time. The ORR increased to 73 % in the patient group with ≥ 12 months of follow-up.

In terms of PFS, the treatment induced durable disease control. Median PFS in at least BTK-inhibitor–treated patients (prior lines, 3) had not been reached yet, and in those who had received at least prior BTK plus BCL2 inhibitor treatment (prior lines, 5), median PFS was 18 months. Seventy-four percent remained on pirtobrutinib therapy at the time of the analysis. The treatment with the novel BTK inhibitor was extremely well tolerated. Any-grade treatment-emergent AEs included fatigue (23 %), diarrhea (19 %), neutropenia (18 %), and contusion (17 %). AEs of special interest were rare and mainly low-grade. No dose-limiting toxicities occurred, and the maximum tolerated dose was not reached. Only 1 % of patients permanently discontinued therapy due to treatment-related AEs.

Pirtobrutinib plus venetoclax ± rituximab

The phase IB part of the BRUIN study assessed pirtobrutinib-based combinations in patients with relapsed/refractory CLL. Fifteen individuals received pirtobrutinib plus venetoclax (Arm A), while 10 were treated with pirtobrutinib plus venetoclax and rituximab (Arm B). Early results reported at EHA 2022 indicated promising efficacy of the combination approach [9]. All patients experienced reductions in tumor size irrespective of BTK inhibitor pretreatment **(Figure 3)**. Partial remissions were achieved in 93.3 % and 100 % in Arms A and B, respectively. The median time to best response was short at 1.9 across the two arms. All responding patients except for two remained on therapy at the time of the analysis. Median time on treatment was 9.8 and 6.0 months, respectively.

Pirtobrutinib plus venetoclax ± rituximab was well tolerated, with a safety profile consistent with known drug class findings and no clear additive toxicities in this patient group. The most common any-grade treatment-emergent AEs included fatigue, nausea, and decreased neutrophil counts in Arm A, as well as constipation, diarrhea, infusion-related reactions and decreased neutrophil counts in Arm B. No dose-limiting toxicities occurred, and no patient discontinued treatment due to drug-related AEs. According to the pharmacokinetics assessed, there was no apparent interaction between pirtobrutinib ± rituximab and venetoclax. Randomized, global, phase III trials are currently evaluating pirtobrutinib in CLL/SLL as monotherapy and in combination with other targeted drugs.

3-year data from CAPTIVATE

First-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib and venetoclax was evaluated by the international, phase II CAPTIVATE trial. The open-label, single-arm FD Cohort of the study assessed the fixed-duration administration of the combination for 12 cycles after a 3-cycle ibrutinib lead-in. The primary endpoint, which was the CR rate including complete response with incomplete bone marrow recovery (CRi) per investi-

gator assessment in patients with del(17p), was met [10]. CR/CRi resulted in 56 %, with similarly high rates overall and in patients with high-risk features. Wierda et al. presented the 3-year follow-up of the FD Cohort after a median time on the study of 38.7 months, which included a median of 24.9 months after completion of treatment [11].

The data revealed that the CR rate had increased from 55 % at the time of the primary analysis to 57 %. Similar results were obtained for patients with deletion 17/*TP53* mutation and unmutated IGHV **(Figure 4)**. Median duration of CR had not been reached, with the 24-month estimate being 94 %. Seventy-nine percent of patients had a best response of uMRD in blood and/or bone marrow. Within the group of those with uMRD in the blood 3 months after treatment, 78 % of evaluable patients maintained uMRD through another 9 months.

The 36-month PFS rate was as high as 88 % overall, with similar rates in patients with del(17p)/*TP53* mutation (80 %) and unmutated IGHV (86 %). No patient died during the prolonged follow-up. At 36 months, 98 % of the total population were alive. Again, the 36-month rates for OS were similar for patients with del(17p)/*TP53* mutation and unmutated IGHV (96 % and 97 %, respectively). Twelve patients who progressed after the combination received retreatment with single-agent ibrutinib. Nine of 11 evaluable patients achieved partial response, and one each obtained partial response with lymphocytosis and disease stabilization. Successful retreatment thus appears to be feasible.

The safety profile of the ibrutinib/venetoclax combination proved manageable and unchanged from that previously reported, with the majority of AEs being mild and resolving quickly.

The authors noted in their summary that the treatment continued to demonstrate deep and durable responses, as well as clinically meaningful PFS, including in patients with high-risk features. Ibrutinib/venetoclax represents an all-oral, once-daily, chemotherapy-free, fixed-duration regimen for previously untreated patients with CLL/SLL.

ELEVATE TN: significant OS benefit after 5 years

The randomized, open-label, phase III ELEVATE TN trial evaluated the next-generation BTK inhibitor acalabrutinib with or without obinutuzumab *versus* chlorambucil/obinutuzumab in treatment-naïve CLL patients who were aged ≥ 65 years or < 65 years and had CIRS scores > 6 or creatinine clearance of 30-69 mL/min. Both the acalabrutinib combination and the monotherapy improved PFS compared to the chemoimmunotherapy regimen at a median follow-up of 28.3 months ($p < 0.0001$ each) [12].

According to the 5-year follow-up presented at EHA 2022, efficacy and safety of acalabrutinib/obinutuzumab and single-agent acalabrutinib were maintained [13]. Median PFS had not been reached yet with either regimen, resulting in 89 % and 79 % risk reductions with the combination and the monotherapy, respectively, compared to chlorambucil/obinutuzumab (HRs, 0.11 and 0.21, respectively; $p < 0.0001$ each). The estimated 60-month PFS rates were 84 %, 72 %, and 21 %, respectively. Particularly profound benefits were achieved in the subgroup with unmutated IGHV; here, the median PFS had not been reached for both acalabrutinib/obinutuzumab and single-agent acalabrutinib, while it was 22.2 months among patients in the chlorambucil/obinutuzumab arm, which gave rise to risk reductions of 94 % and 88 %, respectively (HRs, 0.06 and 0.12, respectively; $p < 0.0001$ each). At 60 months, 82 % and 72 % vs. 6 % of patients were progression-free.

Although median OS had not been reached yet in any of the treatment arms, the combination was shown to induce a significant benefit compared to chemoimmunotherapy (HR, 0.55; $p = 0.0474$), with 60-month OS rates of 90 %, 84 %, and 82 %. The treatment is ongoing in 65 % and 60 % of patients treated with acalabrutinib/obinutuzumab and single-agent acalabrutinib, respectively.

Long-term efficacy of acalabrutinib-based regimens

A pooled analysis of data from 7 clinical trials assessed the long-term efficacy of acalabrutinib-based regimens in patients with treatment-naïve or relapsed/refractory CLL and higher-risk genomic features including deletion 17p and/or *TP53* mutation, unmutated IGHV, and complex karyotype [14]. The data of 809 patients treated with acalabrutinib or acalabrutinib/obinutuzumab were analyzed. Within this group, 321 and 488 had newly diagnosed and relapsed/refractory disease, respectively.

At a median follow-up of almost 4 years, PFS and OS rates were shown to be high in all genomic subgroups. In treatment-naïve patients, at 48 months, the PFS and OS rates ranged from 76 % to 91 % and 88 % to 95 %, respectively, depending on the genetic setup. At 36 months, 73 % to 82 % of patients with relapsed/refractory disease were alive, and 54 % to 65 % showed freedom from progression. The ORRs were consistent across the treatment-naïve and pretreated cohorts **(Table 1)**. Despite the presence of higher-risk genomic features, discontinuation rates due to Richter's transformation were low in both

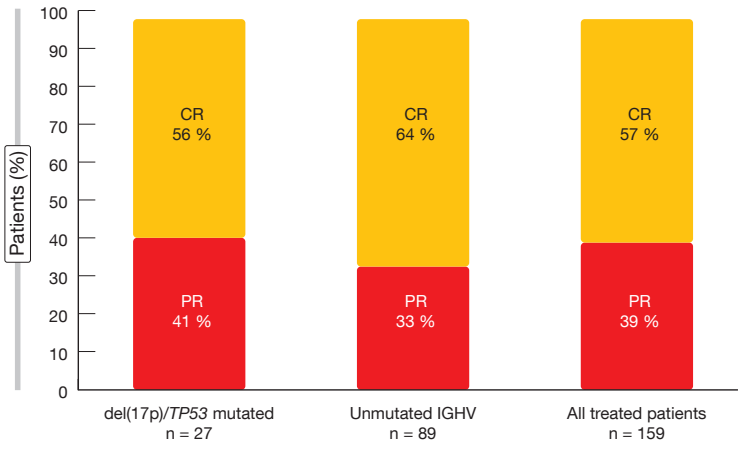


Figure 4: Best overall response to fixed-duration treatment with ibrutinib/venetoclax in the CAPTIVATE study 2 years after the end of treatment

TABLE 1
Responses to acalabrutinib-based therapy by higher-risk genomic features in patients with treatment-naïve and relapsed/refractory CLL

	Treatment-naïve CLL (acalabrutinib-based regimens)		
Response	del(17)/*TP53*mutated (n = 64)	Unmutated IGHV (n = 288)	Complex karyotype (n = 80)
ORR, %	91	96	91
CR, %	23.4	19.8	17.5
PR, %	67.2	76.0	73.8
	Relapsed/refractory CLL (acalabrutinib monotherapy)		
Response	del(17)/*TP53*mutated (n = 214)	Unmutated IGHV (n = 408)	Complex karyotype (n = 146)
ORR, %	86	87	84
CR, %	5.1	7.8	10.3
PR, %	80.8	79.4	73.3

ORR, overall response rate; CR, complete response; PR, partial response

treatment-naïve and relapsed/refractory cohorts (0.3 % and 0.4 %, respectively).

The safety profile of acalabrutinib in this analysis was similar to the reported overall safety profile, with low rates of atrial fibrillation/flutter and major hemorrhage. At the time of the analysis, more than half of the patients in the treatment-naïve cohort remained on treatment, with up to 82 months of follow-up. Overall, these findings illustrate the long-term benefit of acalabrutinib-based regimens in patients with CLL and higher-risk genomic features regardless of treatment line.

HRQOL with first-line zanubrutinib: SEQUOIA

The international, open-label, randomized, phase III SEQUOIA trial examined the next-generation BTK inhibitor zanubrutinib compared to BR in patients with treatment-naïve CLL/SLL. After a median follow-up of 26.2 months, PFS was significantly prolonged with zanubrutinib vs. BR (HR, 0.42; p < 0.0001) [15]. At EHA 2022, Ghia et al. presented health-related quality of life data from baseline through week 24 in patients without deletion 17p in cohort 1 who received either zanubrutinib (n = 241) or BR (n = 238) [16]. Patient-reported outcomes were collected using the EORTC QLQ-C30 questionnaire and the EuroQol EQ-5D 5-level visual analog scale.

By week 12, patients in the experimental arm were shown to experience greater improvement in global health status and in physical function and role function compared to those in the control arm. Additionally, symptoms of diarrhea, fatigue and nausea/vomiting decreased from baseline to a larger extent. This symptom reduction was also observed at week 24 **(Figure 5)**. However, at week 12, patients who received BR experienced better outcomes with respect to pain than those treated with zanubrutinib; at week 24, the effects of the two treatments on pain were similar. The authors concluded that with improved selectivity and fewer off-target effects, zanubrutinib might improve health-related quality of life outcomes in treatment-naïve patients with CLL/SLL.

ALPINE: PROs for zanubrutinib vs. ibrutinib

Zanubrutinib was compared to ibrutinib in patients with relapsed/refractory CLL/SLL in the international, open-label, randomized, phase III ALPINE trial. The interim analysis of the first 415 patients showed superiority of zanubrutinib over ibrutinib in terms of ORR, 12-month PFS, OS, and improved tolerability [17].

Health-related quality of life data based on the EORTC QLQ-C30 questionnaire and the EuroQol EQ-5D 5-level visual analog scale demonstrated greater improvements from baseline in global health status in the zanubrutinib arm compared to the ibrutinib arm by cycle 7 [18]. This also applied to physical functioning and role functioning. Moreover, zanubrutinib-treated patients experienced greater reductions in diarrhea, fatigue, nausea/vomiting, and pain. By cycle 13, findings for physical functioning and role functioning continued to favor zanubrutinib, which also applied to symptom scores for diarrhea and pain, while the

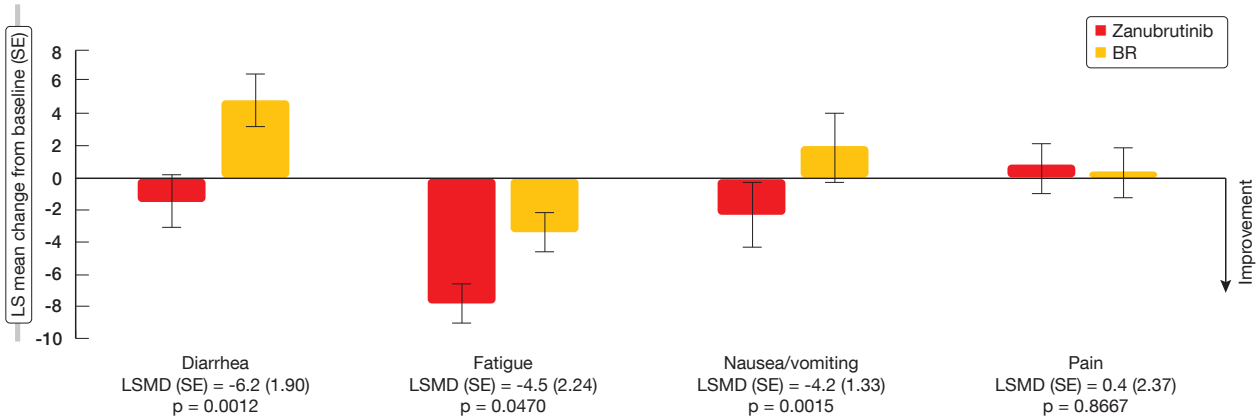


Figure 5: EORTC QLQ-C30 LS mean change from baseline in symptom scales at week 24 for zanubrutinib vs. bendamustine/rituximab

two arms were comparable regarding improvements in fatigue and nausea/vomiting. With respect to the EuroQol EQ-5D 5-level visual analog scale, the analysis suggested similar patterns of improvement from baseline with zanubrutinib and ibrutinib up to cycle 13.

In their conclusion, the scientists pointed out that the more pronounced improvements of health-related quality of life in cycle 7, i.e. 6 months after the initiation of therapy, indicate that treatment with zanubrutinib could potentially alleviate disease burden earlier than ibrutinib in this patient population. The results align with the interim data obtained in ALPINE that showed lower rates of AEs such as atrial fibrillation, major bleeding, and AEs leading to discontinuation or death in patients treated with zanubrutinib vs. ibrutinib [16]. However, further analyses are warranted to assess the relationships between the health-related quality of life results and AEs as well as other clinical endpoints in this patient population. ■

REFERENCES

1 Eichhorst B et al., A randomized phase III study of venetoclax-based time-limited combination treatments vs. standard chemoimmunotherapy in frontline chronic lymphocytic leukemia of fit patients: first co-primary endpoint analysis of the international intergroup GAIA (CLL13) trial. ASH 2021, abstract 71
2 Eichhorst B et al., Time-limited venetoclax-obinutuzumab ± ibrutinib is superior to chemoimmunotherapy in frontline chronic lymphocytic leukemia: PFS co-primary endpoint of the randomized phase 3 GAIA/CLL13 trial. EHA 2022, LBA2365
3 Al-Sawaf O et al., Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 5-year results of the randomized CLL 14 study. EHA 2022, S148
4 Hillmen P et al., Ibrutinib plus rituximab is superior to FCR in previously untreated CLL: results of the phase III NCRI FLAIR trial. ASH 2021, abstract 642
5 Hillmen P et al., The combination of ibrutinib plus venetoclax results in a high rate of MRD negativity in previously untreated CLL: the results of the planned interim analysis of the phase III NCRI FLAIR trial. EHA 2022, S145
6 Woyach J et al., BTK^{C481S}-mediated resistance to ibrutinib in chronic lymphocytic leukemia. J Clin Oncol 2017; 35(13): 1437-1443
7 Burger JA et al., Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia 2020; 34(3): 787-798
8 Mato AR et al., Pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in previously treated CLL/SLL: updated results from the phase 1/2 BRUIN study. EHA 2022, S147
9 Roeker LE et al., Pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in combination with venetoclax ± rituximab in relapsed/refractory chronic lymphocytic leukemia: results from the BRUIN phase 1b study. EHA 2022, P640
10 Wierda WG et al., Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia: primary analysis results from the minimal residual disease cohort of the randomized phase II CAPTIVATE study. J Clin Oncol 2021; 39(34): 3853-3865
11 Wierda WG et al., Fixed-duration ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma: 3-year follow-up from the FD Cohort of the phase 2 CAPTIVATE study. J Clin Oncol 40, 2022 (suppl 16; abstr 7519)
12 Sharman JP et al., Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet 2020; 395: 1278-1291
13 Sharman JP et al., Acalabrutinib ± obinutuzumab vs obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: 5-year follow-up of ELEVATE-TN. EHA 2022, P666
14 Davids MS et al., Long-term efficacy of acalabrutinib-based regimens in patients with chronic lymphocytic leukemia and higher-risk genomic features: pooled analysis of clinical trial data. EHA 2022, P667
15 Tam CS et al., SEQUOIA: results of a phase 3 randomized study of zanubrutinib versus bendamustine + rituximab in patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma. Blood 2021; 138: 396
16 Ghia P et al., Patient-reported outcomes from a phase 3 randomized study of zanubrutinib vs. bendamustine plus rituximab in patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma. EHA 2022, P662
17 Hillmen P et al., First interim analysis of ALPINE study: results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. EHA 2021, LB1900
18 Hillmen P et al., Health-related quality of life outcomes associated with zanubrutinib vs. ibrutinib monotherapy in patients with relapsed/refractory CLL/SLL: results from the randomized phase 3 ALPINE trial. EHA 2022, P663

Marginal zone lymphoma: benefits of BTK inhibition in later lines

Zanubrutinib in patients ≥ 65 years

Patients with marginal zone lymphoma (MZL) usually show an indolent course of disease, although MZL remains largely incurable, particularly in the relapsed/refractory setting [1, 2]. BTK inhibition offers a potent treatment option in this situation. The single-arm, multicenter, phase II MAGNOLIA study tested the next-generation BTK inhibitor zanubrutinib in patients with relapsed/refractory MZL who had received ≥ 1 CD20-based regimen, demonstrating high response rates and durable disease control [3]. As MZL is the second most common lymphoma in older patients, patient- or disease-related risk factors and treatment-related toxicities can make the selection of an optimal treatment challenging [4]. Opat et al. investigated zanubrutinib in the subgroup of patients aged ≥ 65 years included in the MAGNOLIA trial (n = 40) [5].

Zanubrutinib proved well tolerated and highly effective in the older population. In the group aged ≥ 65 years, the overall response rate (ORR) was 75 %, and in those aged ≥ 75 years (n =18), 94.4 %. Complete remissions resulted in 25 % and 22.2 %, respectively. Responses were observed across all subgroups independent of line of treatment, time since the last anti-lymphoma therapy, disease status (relapsed vs. refractory), the presence of bulky disease, the type of prior treatment, and MZL subtype **(Table 1)**. Median progression-free survival (PFS) and duration of response had not been reached yet. At 15

months, 86.6 % of patients were alive and progression-free.

Treatment-emergent AEs were mostly grade 1 and 2, and none gave rise to dose reductions. Events leading to dose interruption and study drug discontinuation were reported in 32.5 % and 5.0 %, respectively. Atrial flutter/fibrillation and hypertension occurred in 2 cases each but did not lead to treatment withdrawal. No major hemorrhage was observed. At a median study follow-up of 15.8 months, 87.5 % of patients were still on treatment. In their summary, the authors pointed out that these results are consistent with previously published findings [3].

TABLE 1
Responses to zanubrutinib treatment by MZL subtypes in patients aged ≥ 65 years treated in the MAGNOLIA trial

Best response, n (%)	Extranodal (n = 17)	Nodal (n = 14)	Splenic (n = 8)	Unknown (n = 1)	Total (n = 40)
ORR (CR or PR)	12 (70.6)	12 (85.7)	6 (75.0)	0	30 (75.0)
Complete response	7 (41.2)	3 (21.4)	0	0	10 (25.0)
Partial response	5 (29.4)	9 (64.3)	6 (75.0)	0	20 (50.0)
Stable disease	4 (23.5)	2 (14.3)	1 (12.5)	0	7 (17.5)
Progressive disease	1 (5.9)	0	1 (12.5)	1 (100.0)	3 (7.5)

Proof-of-concept study for acalabrutinib

A multicenter, open-label, phase II study examined monotherapy with the next-generation BTK inhibitor acalabrutinib in patients with relapsed/refractory MZL after ≥ 1 systemic treatment line containing ≥ 1 CD-20–directed regimen. ORR as assessed by the investigator constituted the primary endpoint. At ASCO 2022, Budde et al. presented an interim report of the trial after a median follow-up of 13.3 months [6].

Among 40 evaluable patients, the ORR was 52.5 %, including complete and partial responses in 13 % and 40 %, respectively. The subgroup with the extranodal subtype fared best (ORR, 64.7 %); ORRs for those with nodal and splenic MZL were 41.7 % and 45.5 %, respectively. Ninety-three percent of patients experienced tumor reductions. Median duration of response had not been reached yet, which also applied to median overall survival. Median PFS was 27.4 months.

The AEs reported were consistent with the known safety profile of acalabrutinib. Most events were rated as grade 1 or 2. The most common grade ≥ 3 AEs included fatigue, neutropenia, anemia, dyspnea, and thrombocytopenia. Among events of special clinical interest, infections (34.9 %) and bleeding (23.3 %) were most common. AEs led to acalabrutinib discontinuation in 7 %. One patient died due to an AE, which was septic shock occurring after approximately 5.2 months of acalabrutinib treatment. No cases of atrial fibrillation/flutter, ventricular arrhythmias, or major hemorrhage were reported. Overall, the results of this study support acalabrutinib as a safe and feasible chemotherapy-free option.

Economic burden of MZL

Based on the IBM MarketScan® commercial and Medicare supplemental claims dataset, a retrospective, observational study assessed real-world treatment patterns, costs, and healthcare resource utilization in US patients with MZL between 2017 and 2020 [7]. Overall, 2,491 patients with a median age of 63 years were identified. Among these, 59 % were commercially insured (median age, 57), while 41 % received Medicare-supplemented care (median age, 76).

The findings suggested that real-world treatment patterns in the US across lines of therapy follow the regimen recommendations by the National Comprehensive Cancer Network clini-

TABLE 2
Use of regimens across the treatment lines in the management of US patients with MZL

	Overall (n = 2,491)			Commercially insured (n = 1,480)			Medicare supplemented (n = 1,011)		
Treatment (%)	1st line	2nd line	3rd line	1st line	2nd line	3rd line	1st line	2nd line	3rd line
R mono	44.6	71.0	79.9	43.2	70.0	78.9	46.6	72.6	81.5
R-CHOP	20.3	3.5	2.1	22.1	4.6	2.7	17.5	1.9	1.1
BR	19.7	9.5	4.2	20.2	9.2	9.2	18.9	9.8	4.4
Ibrutinib	1.0	3.9	4.2	0.8	3.6	4.6	1.4	4.2	3.3
Other	14.4	12.2	9.6	13.7	12.5	12.5	15.6	11.6	9.8

REFERENCES

1 Cheah CY et al., Marginal zone lymphoma: present status and future perspectives. Haematologica 2022; 107(1): 35-43
2 National Cancer Institute 2020 https://seer.cancer.gov/archive/csr/1975_2017/, accessed April 2022
3 Opat S et al., The MAGNOLIA trial: zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor, demonstrates safety and efficacy in relapsed/refractory marginal zone lymphoma. Clin Cancer Res 2021; 27(23): 6323-6332
4 Bron D et al., Marginal zone lymphomas: second most common lymphomas in older patients. Curr Opin Oncol 2019; 31(5): 386-393
5 Opat S et al., Zanubrutinib in older patients with relapsed/refractory marginal zone lymphoma: subgroup analysis of the MAGNOLIA study. EHA 2022, P1162
6 Budde LE et al., Acalabrutinib in patients with relapsed/refractory marginal zone lymphoma: results of a phase 2, multicenter, open-label trial. J Clin Oncol 40, 2022 (suppl 16; abstr 7549)
7 Yang K et al., Real-world treatment patterns and economic burden of patients with marginal zone lymphoma. J Clin Oncol 40, 2022 (suppl 16; abstr e18730)

cal practice guidelines. First-line, second-line and third-line treatment was administered in 72 %, 29 %, and 13 %, respectively. Single-agent rituximab represented the most common regimen across both commercial and Medicare patients and all treatment lines **(Table 2)**. R-CHOP and bendamustine/rituximab were the second most commonly used regimens in first line with decreased use in later lines, where ibrutinib showed increasing use although it had lower per person per month (PPMM) cost in the first-line setting than other treatments.

MZL patients were demonstrated to incur a high economic burden. Overall, they had 4.6 outpatient visits PPMM, as well as 0.5 hospitalizations with a mean length of stay of 2.6 days. The total PPMM healthcare costs amounted to $ 19,896. Multivariable regression showed that baseline comorbidities such as atrial fibrillation, renal disease and neutropenia, as well as treatment discontinuation, were significant predictors of higher costs and healthcare resource utilization. According to the authors, future studies are needed to evaluate long-term outcomes and the impact of heterogenous MZL subtypes. ■

Early-phase trials investigating novel agents in miscellaneous B-cell malignancies

Large B-cell lymphoma: subcutaneous epcoritamab

The prognosis is still poor for most patients with relapsed or refractory large B-cell lymphoma (LBCL) irrespective of therapeutic advances that have recently been achieved. There is a need for convenient, efficacious, well-tolerated, and readily available treatment options. Epcoritamab, a subcutaneously administered bispecific antibody, has been designed to simultaneously bind to CD3 and CD20, thus inducing T-cell–mediated cytotoxic activity against CD20-positive, malignant B cells. The phase I/II EPCORE NHL-1 study was initiated to establish the recommended phase II dose and to assess the safety and efficacy of subcutaneous epcoritamab, as well as pharmacokinetics and immune biomarkers, in patients with relapsed or refractory CD20-positive B-cell non-Hodgkin lymphoma (NHL). In the dose-escalation part, notable single-agent activity with clinically meaningful overall response rates (ORRs) and complete responses (CRs) was found, as well as a manageable safety profile [1].

Thieblemont et al. reported pivotal dose-expansion findings in patients with relapsed/refractory LBCL at EHA 2022 [2]. This cohort included 157 individuals with diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B. They had received ≥ 2 prior lines of antineoplastic therapy, including ≥ 1 anti-CD20 antibody.

This was a challenging-to-treat and highly refractory population. Primary refractory disease was present in 61 %, and 71 % had already been treated with ≥ 3 lines of therapy. Prior CAR-T cell therapy had been performed in 39 %, with 75 % of patients progressing within 6 months thereafter. The study treatment consisted of epcoritamab 48 mg QW in cycles 1-3, Q2W in cycles 4-9, and Q4W from cycle 10. ORR by independent review committee constituted the primary endpoint.

Deep and durable complete remissions

Single-agent epcoritamab demonstrated high response rates, with an ORR of 63 % and CRs in 39 %. Deep responses were achieved independent of age, disease subgroups, previous CAR-T therapy and response to it, and treatment lines **(Figure 1)**. Epcoritamab was shown to drive deep and durable CRs. The majority of CRs were obtained by the time of the first or second assessment; however, some conversions from partial to complete remissions still took place at ≥ 36 weeks. The median duration of response for patients in CR had not been reached yet. At 9 months, 89 % of complete responders remained in CR.

Progression-free survival (PFS) varied according to best response; in the group with CR, it had not been reached yet, while it was 4.4 months in the entire group. Overall survival (OS) data were immature, with a 12-month OS rate of 56.9 %. Minimal residual disease (MRD) negativity resulted in 45.8 % in the total population. An exploratory ctDNA analysis demonstrated that MRD-negative responses were durable and correlated with PFS.

Moreover, epcoritamab was shown to be well tolerated. Most adverse events (AEs) were low grade and occurred early in treatment, in cycles 1-3. Among treatment-emergent AEs, cytokine-release syndrome was observed most commonly, but was mainly grade 1/2 and predictable, with events mainly seen after the first full dose. Ten patients (6.4 %) experienced immune effector cell-associated neurotoxicity syndrome. In 9 cases, these were grade 1 and 2 and resolved, while 1 patient died, which was confounded by multiple factors. The analysis yielded few discontinuations due to AEs (7 %); 32 % of patients remained on treatment. In all, epcoritamab is well tolerated and drives deep and durable responses in challenging-to-treat, highly refractory patients with relapsed/refractory LBCL.

Phase II data on nemtabrutinib

BTK inhibitors are highly effective against several B-cell malignancies, although their use is limited by AEs, potentially due to off-target inhibition of other kinases. Also, BTK mutations can

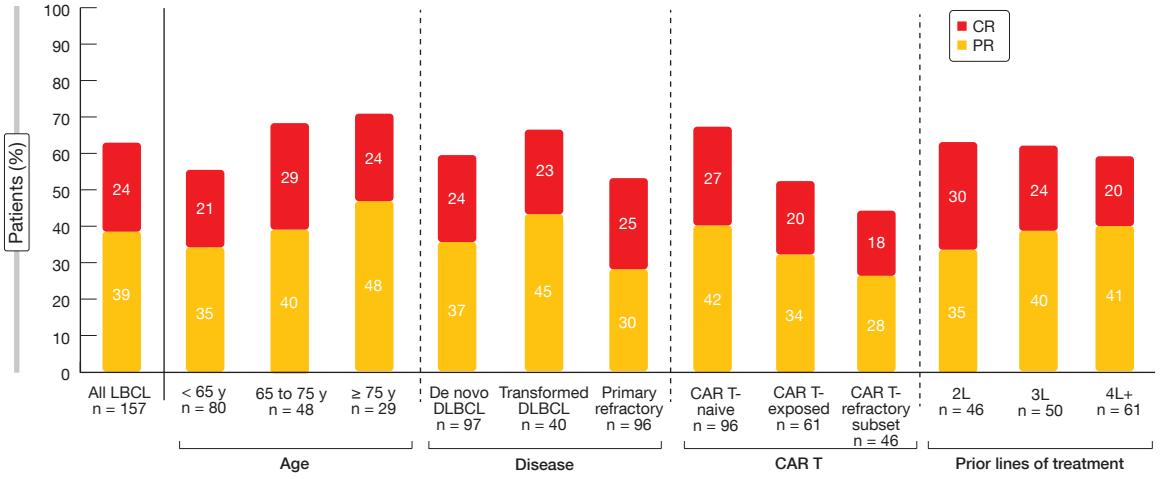


Figure 1: Deep responses with subcutaneous epcoritamab across key subgroups in the EPCORE NHL-1 study

abrogate the binding capacity of the drug, resulting in resistance that might limit subsequent treatment options [3-5]. Nemtabrutinib is a potent, reversible inhibitor of both wild-type and ibrutinib-resistant C481S-mutated BTK [6]. The phase I/II dose-escalation and dose-expansion BELLWAVE-001 study is investigating nemtabrutinib in pretreated patients with CLL/SLL and various types of B-cell NHL. Preliminary results from the dose-expansion phase after a median follow-up of 6.18 months revealed promising antitumor activity and manageable safety of nemtabrutinib 65 mg QD in patients with pretreated CLL/SLL [7].

According to the update reported at EHA 2022, nemtabrutinib continued to show favorable activity, with responses observed in heavily pretreated patients and those progressing on prior covalent BTK inhibitors [8]. The ORR was 53 % in the entire cohort of 57 CLL/SLL patients treated with 65 mg QD. In Cohort A, which comprised patients with C481S mutation who had received ≥ 2 prior therapies including covalent BTK inhibitors (n = 25), 60 % of patients responded; in Cohort B including patients without C481S mutation after ≥ 2 prior therapies and intolerance to BTK inhibitors (n = 10), the ORR was 40 %. Median duration of response had not been reached in all patients and in Cohort B, while it was 13.9 months in Cohort A **(Figure 2)**. Likewise, median PFS was 15.7 months in Cohort A and had not been reached yet in the other groups.

AEs proved manageable, with the most common grade ≥ 3 treatment-emergent AEs including decreased neutrophil counts (27 %), thrombocytopenia, hypertension, and pneumonia (14 % each). Two patients developed atrial fibrillation that was grade ≥ 3 in 1 case. The investigation of nemtabrutinib at doses ≥ 65 mg for the treatment of B-cell malignancies is continuing.

Zanubrutinib after acalabrutinib intolerance

The ongoing, multicenter, single-arm, phase II BGB-3111-215 study is assessing the safety and efficacy of the next-generation BTK inhibitor zanubrutinib in patients with CLL/SLL, Waldenström's macroglobulinemia (WM), mantle cell lymphoma (MCL), or marginal zone lymphoma who have discontinued ibrutinib and/or acalabrutinib treatment due to AEs. Previous findings demonstrated that zanubrutinib was well tolerated in this patient group [9]. At EHA 2022, Shadman et al. presented updated results for cohort 2 of the study that included acalabrutinib-intolerant patients [10]. The safety of zanubrutinib was assessed based on the recurrence and change in severity of AEs that had led to acalabrutinib intolerance.

The results obtained in 13 patients showed that 73 % of acalabrutinib-related intolerance events did not recur on zanubrutinib treatment **(Figure 3)**, which meant that 62 % of patients did not experience recurrence of any event. Among 6 events that recurred, 5 were rated as the same grade and 1 as lower grade. One patient discontinued treatment due to recurrence of myalgia of the same grade. Three patients who experienced the same intolerance events on ibrutinib and acalabrutinib (i.e., pain in extremity, diarrhea, and atrial fibrillation) did not develop recurrence of these on zanubrutinib therapy. Eighty percent of the 10 zanubrutinib-treated patients

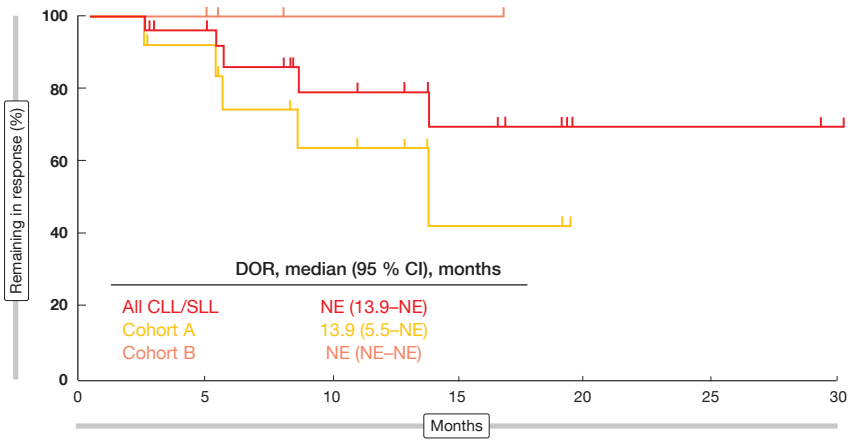


Figure 2: BELLWAVE-001 study: duration of response on nemtabrutinib treatment in all patients and in Cohorts A and B

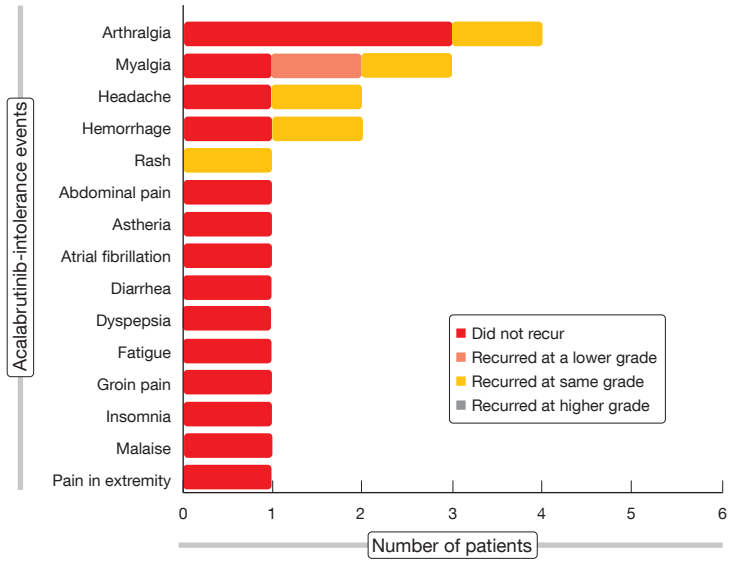


Figure 3: Recurrence and severity of acalabrutinib-related intolerance events on treatment with zanubrutinib

with ≥ 90 days of follow-up achieved at least stable disease, and 70 % experienced deepening of response. The authors concluded that zanubrutinib might be a viable therapeutic option for patients who are intolerant to acalabrutinib. Enrollment and follow-up of the study are ongoing.

A novel strategy to overcome on-target resistance mutations emerging from BTK inhibitor treatment is the use of BGB-16673, an investigational BTK-targeting chimeric degradation activation compound active against both wild-type and mutant *BTK* [11]. The phase I, open-label, dose-escalation and dose-expansion study BGB-16673-101 will assess BGB-16673 as the first-in-human study (NCT05006716). Adult patients with select relapsed/refractory B-cell malignancies are eligible. After determination of the recommended phase II dose, Cohort 1 will contain patients with relapsed/refractory CLL/SLL after BTK inhibition, while Cohort 2 will enroll those with relapsed/refractory MCL post BTK inhibitor treatment.

BGB-11417 as monotherapy and plus zanubrutinib in phase I

Treatment with the BCL2 inhibitor venetoclax can be impeded by gastrointestinal toxicities, neutropenia, and the emergence of specific *BCL2* mutations resulting in resistance [12, 13]. The potent and highly selective BCL2 inhibitor BGB-11417 has shown more pronounced antitumor activity than venetoclax in human acute lymphatic leukemia, MCL and DLBCL in xenograft mouse models [14]. In addition, BGB-11417 has a broad therapeutic index and tolerable safety profile.

The first-in-human, open-label, multicenter, dose-escalation and dose-expansion phase I trial BGB-11417-101 investigated BGB-11417 as monotherapy (parts 1 and 2) and in combination with zanubrutinib (parts 3 and 4) in patients with NHL, WM, and CLL/SLL. All patients had relapsed/refractory disease except for those with CLL/SLL who were divided into a treatment-naïve and a relapsed/refractory cohort. Disease-specific dose-escalation cohorts assessing up to 5 potential dose levels of BGB-11417 (i.e., 40 mg, 80 mg, 160 mg, 320 mg, 640 mg QD) are followed by the corresponding expansion cohorts.

At the time of the cutoff for the preliminary analysis reported at EHA 2022, 78 patients had been treated, with 34 and 44 in the monotherapy and combination cohorts, respectively [15]. Transient neutropenia was the most common grade ≥ 3 AE; overall, grade ≥ 3 AEs were infrequent and manageable. The risk of tumor lysis syndrome appeared limited, with laboratory TLS observed in only 1 CLL patient with high TLS risk who received monotherapy. The available data indicated that the combination of BGB-11417 with zanubrutinib is well tolerated, similar to single-agent BGB-11417, at the dose levels tested.

With respect to efficacy, responses were observed at the preliminary dose levels as dose escalation had not yet been completed for any cohort. Significant reductions in absolute lymphocyte counts occurred during ramp-up for all patients with CLL. In the relapsed/refractory setting, the combination treatment gave rise to promising early response rates, with 80 % of patients achieving partial response with rebound lymphocytosis or better across the dose levels ranging from 40 to 320 mg. ■

REFERENCES

1 Hutchings M et al., Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. Lancet 2021; 398(10306): 1157-1169
2 Thieblemont C et al., Subcutaneous epcoritamab in patients with relapsed or refractory large B-cell lymphoma (EPCORE NHL-1): pivotal results from a phase 2 study. EHA 2022, LB2364
3 Preetesh J et al., Long-term outcomes and mutation profiling of patients with mantle cell lymphoma (MCL) who discontinued ibrutinib. Br J Haematol 2018; 183(4): 578-587
4 Xu L et al., Acquired mutations associated with ibrutinib resistance in Waldenström macroglobulinemia. Blood 2017; 129(18): 2519-2525
5 Woyach J et al., Resistance to acalabrutinib in CLL is mediated primarily by BTK mutations. Blood 2019; 134(suppl_1): 504
6 Woyach J et al., Final results of phase 1, dose escalation study evaluating ARQ 531 in patients with relapsed or refractory B-cell lymphoid malignancies. Blood 2019; 134: 4928
7 Woyach JA et al., Preliminary efficacy and safety of MK-1026, a non-covalent inhibitor of wild-type and C481S mutated Bruton tyrosine kinase, in B-cell malignancies: a phase 2 dose expansion study. Blood 2021; 138: 392
8 Woyach J et al., Nemtabrutinib (MK-1026), a noncovalent inhibitor of wild-type and C481S-mutated Bruton tyrosine kinase for B-cell malignancies: efficacy and safety of the phase 2 dose-expansion BELLWAVE-001 study. EHA 2022, P682
9 Shadman M et al., Phase 2 study of zanubrutinib in BTK inhibitor-intolerant patients with relapsed/refractory B-cell malignancies. Blood 2021; 138(suppl 1): 1410
10 Shadman M et al., Zanubrutinib in acalabrutinib-intolerant patients with B-cell malignancies. EHA 2022, PB1890
11 Tam CS et al., A phase 1 first-in-human study of BGB-16673, a Bruton tyrosine kinase protein degrader, in patients with B-cell malignancies (Trial in Progress). EHA 2022, P686
12 Davids et al., Comprehensive safety analysis of venetoclax monotherapy for patients with relapsed/refractory chronic lymphocytic leukemia. Clin Cancer Res 2018; 24(18): 4371-4379
13 Blombery P et al., Acquisition of the recurrent Gly101Val mutation in BCL2 confers resistance to venetoclax in patients with progressive chronic lymphocytic leukemia. Cancer Discov 2019; 9(3): 342-353
14 Hu N et al., Preclinical characterization of BGB-11417, a potent and selective Bcl-2 inhibitor with superior antitumor activities in haematological tumor models. AACR 2020, abstract 3077
15 Opat S et al., A phase 1 study with the novel BCL2 inhibitor BGB-11417 as monotherapy or in combination with zanubrutinib in patients with B-cell malignancies: preliminary data. EHA 2022, P687

BTK inhibition in Waldenström's macroglobulinemia: trial updates and real-world insights

The open-label, multicenter, randomized phase III ASPEN trial was set up to assess the efficacy and safety of the potent, selective, irreversible next-generation BTK inhibitor zanubrutinib in Waldenström's macroglobulinemia (WM). Cohort 1 of the study included patients with *MYD88*-mutated disease (n = 201); here, zanubrutinib was compared to ibrutinib after 1:1 randomization. In Cohort 2, 28 patients with *MYD88* wildtype received zanubrutinib in a non-randomized manner. Both treatment-naïve and pretreated patients participated, although no prior BTK inhibition was allowed. Untreated patients were eligible when considered unsuitable for standard chemoimmunotherapy.

With respect to the primary endpoint, which was complete response (CR) plus very good partial response (VGPR) for zanubrutinib vs. ibrutinib, no significant difference resulted at the time of the primary analysis [1], although the findings indicated clinically meaningful efficacy and improved tolerability of the newer BTK inhibitor.

42-month follow-up of ASPEN

This impression was corroborated by the long-term follow-up reported at EHA 2022 [2]. In Cohort 1, the CR plus VGPR rate was numerically higher at all time points with zanubrutinib vs. ibrutinib. At 44.1 months, this was 36.3 % vs. 25.3 %, with shorter median time to CR plus VGPR (6.7 vs. 16.6 months). Zanubrutinib elicited a higher event-free rate for the duration of CR plus VGPR at 24 months (90.6 % vs. 79.3 %). Median PFS and OS had not yet been reached, with hazard ratios favoring zanubrutinib (PFS, 0.63; OS, 0.75). At 42 months, 87.5 % vs. 85.2 % of patients were alive, and 78.3 % vs. 69.7 % were progression-free. After almost 4 years, 66 % vs. 52 % remained on treatment.

Assessments by *CXCR4* status demonstrated that patients with *CXCR4* mutation derived benefits from zanubrutinib compared to ibrutinib regarding VGPR or better (21.2 % vs. 10.0 %), major response (78.8 % vs. 65.0 %), time to major response (3.4 vs. 6.6 months), and PFS (HR, 0.50). Seventy-three percent of these patients treated with zanubrutinib enjoyed freedom from progression at 42 months, while only 49.0 % in the ibrutinib arm did.

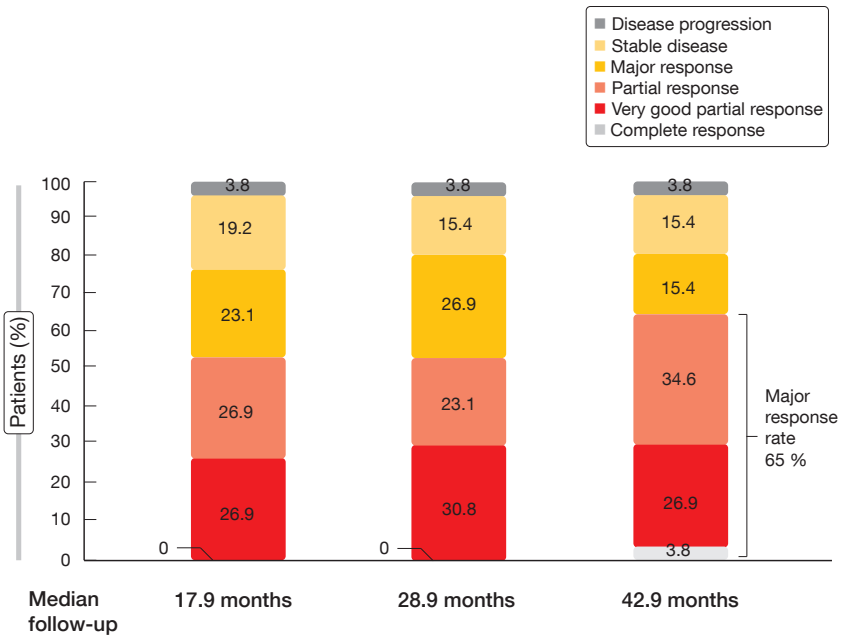


Figure: ASPEN trial: deepening of responses to zanubrutinib treatment over time

In Cohort 2, responses to zanubrutinib treatment continued to deepen over time **(Figure)**. At 42.9 months of follow-up, one patient had achieved complete response, and the rate of major responses had risen to 65 %. Event-free rates of PFS and OS at 42 months were 53.8 % and 83.9 %, respectively.

Likewise, the safety advantages of zanubrutinib remained consistent over time, with less off-target activity *versus* ibrutinib. Zanubrutinib-treated patients showed lower cumulative incidences of atrial fibrillation, diarrhea, hypertension, muscle spasms, and pneumonia, and had fewer AEs leading to death, treatment discontinuation, or dose reductions. Among AEs of special interest observed in cohort 1, neutropenia was more common with zanubrutinib (all grades, 34.7 % vs. 20.4 %), although infection rates were similar across the arms (all grades, 79.2 % vs. 79.6 %), with grade 3/4 events occurring less frequently in the experimental arm (21.8 % vs. 27.6 %). The authors noted that over time, zanubrutinib showed a consistent trend of deeper, earlier, and more durable responses compared with ibrutinib.

Expanded access study of zanubrutinib

A phase II, expanded access study was initiated at 10 academic and community medical centers across the United States to provide real-world experience with zanubrutinib in patients with WM for whom no other clinical trials were available. Castillo et al. presented results for 17 treatment-naïve and 33 pretreated patients at EHA 2022 [3]. Forty-one were assigned to receive zanubrutinib 160 mg BID, while 9 received zanubrutinib 320 mg QD. Compared to the population recruited into the ASPEN trial, the patients were older on average, had worse ECOG performance status, longer disease duration,

TABLE
Responses to acalabrutinib in patients with untreated and relapsed/refractory WM at 5 years

	Modified 3rd IWWM criteria		6th IWWM criteria	
	Treatment-naïve (n = 14)	Relapsed/refractory (n = 92)	Treatment-naïve (n =14)	Relapsed/refractory (n = 92)
Response, %				
ORR (≥ MR)	93	95	93	95
MRR, %	79	82	79	84
CR, %	0	2	0	4
VGPR, %	7	41	7	23
PR, %	71	38	71	57
MR, %	14	13	14	11
SD, %	0	4	0	5
Time to initial response, months	1.0	1.0	1.0	1.8

ORR, overall response rate; MRR, major response rate; CR, complete response; VGPR, very good partial response; PR, partial response; MR; minor response; SD, stable disease

and poorer prognosis. Most of them had either intermediate-risk or high-risk disease (54.0 % and 40.0 %, respectively). In the group with relapsed/refractory disease, the median number of prior therapies was 2.

Nevertheless, the response rates and toxicity profile were comparable to the findings obtained in the ASPEN study. Overall, 85.4 % of patients responded to treatment, with 73.2 % achieving a major response and 39.0 % obtaining VGPR. Responses were similar across the treatment lines, as well as in patients receiving 160 mg BID and 320 mg QD. The ORR was lower than that observed in ASPEN, which had bordered on 100 %. According to the authors, this difference might be attributed to less frequent response assessments (every 6 months), as any responses arising in between would not have been captured. For instance, 3 of 4 patients with disease progression as best response had IgM levels indicating improvement during the first 6 months, i.e., prior to the first response assessment. Median PFS and OS had not been reached yet at the time of the analysis.

No new safety signals emerged during the study period. Overall, 6.0 % and 8.0 % of treatment-emergent AEs led to treatment discontinuation and dose reductions, respectively; dose interruptions became necessary in 12.0 %. No fatal TEAEs were reported. The safety profile did not differ in any meaningful way between patients with untreated or relapsed/refractory disease and those assigned to 160 mg BID or 320 QD. The authors concluded that these findings were consistent with the established zanubrutinib profile in WM and other B-cell malignancies when administered as monotherapy at a daily dose of 320 mg orally in patients with intermediate-risk or high-risk, treatment-naïve or relapsed/refractory WM.

Long-term findings for single-agent acalabrutinib

In the phase II ACE-WM-001 study, monotherapy with the highly selective, potent, covalent BTK inhibitor acalabrutinib has shown durable responses and a tolerable safety profile in patients with treatment-naïve (n = 14) and relapsed/refractory (n = 92) WM [4]. Acalabrutinib was administered at doses of 100 mg BID or 200 mg QD until disease progression. Owen et al. reported the final results of the trial after a median follow-up of 63.7 months [5]. Approximately half of patients remained on treatment at the time of data cutoff.

Acalabrutinib therapy induced ORRs of 93 % and 95 % in patients with untreated and relapsed/refractory WM, respectively **(Table)**. Responses were consistent irrespective of age, baseline ECOG performance status, baseline hemoglobin and IgM levels, and prior treatment lines. The PFS and OS benefits were maintained over time in both cohorts. At 66 months, PFS rates were 84 % and 52 % for treatment-naïve and relapsed/refractory patients, respectively; OS rates amounted to 91 % and 71 %, respectively.

Acalabrutinib exhibited a tolerable safety profile with no new toxicities and a low incidence of individual cardiovascular events. The most common grade 3/4 AEs were neutropenia (17 %), pneumonia (9 %), anemia (6 %), and hyponatremia (5 %). Key events of clinical interest included cardiac events (all grades, 21 %; grade 3/4, 8 %), bleeding (62 %; 6 %), and hypertension (7 %; 4 %). Atrial fibrillation and hypertension showed low cumulative incidences over time, while infections and bleeding events slightly increased, although these were mostly low-grade. AEs led to treatment discontinuation in 29 % and 17 % of untreated and pretreated patients, respectively. Overall, acalabrutinib appeared to be a highly effective treatment that provides durable responses with a tolerable safety profile in patients with treatment-naïve or relapsed/refractory WM. ■

REFERENCES

1 Tam CS et al., A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinema: the ASPEN study. Blood 2020; 136(18): 2038-2050
2 Dimopoulos M et al., ASPEN: long-term follow-up results of a phase 3 randomized trial of zanubrutinib versus ibrutinib in patients with Waldenström macroglobulinemia. EHA 2022, P1161
3 Castillo JJ et al., Results of a phase 2 expanded access study of zanubrutinib in patients with Waldenström macroglobulinemia. EHA 2022, P1160
4 Byrd JC et al., Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. J Clin Oncol 2021; 39(31): 3441-3452
5 Owen R et al., Acalabrutinib in treatment-naïve or relapsed/refractory Waldenström macroglobulinemia: 5-year follow-up of a phase 2, single-arm study. EHA 2022, P1130

Prolonging remission in relapsed and refractory follicular lymphoma

Follicular lymphoma (FL) is a common indolent form of non-Hodgkin lymphoma that accounts for 20-25 % of all new NHL cases in Western countries [1]. Although patients with FL generally respond well to first-line anti-CD20-based chemotherapy regimens, recurrence is common. Approved treatment options are limited in the relapsed and refractory setting. Studies suggest that each subsequent relapse involves shorter duration of response [2].

ROSEWOOD: durable responses with zanubrutinib/obinutuzumab

The combination of obinutuzumab with the next-generation BTK inhibitor zanubrutinib was investigated in the phase II, randomized ROSEWOOD trial after phase Ib data had provided an early efficacy signal for this regimen, with good tolerability [3]. Zinzani et al. reported the primary analysis of ROSEWOOD at EHA 2022 after a median follow-up of 12.5 months [4]. The trial included patients with relapsed/refractory grade I-IIIA FL after ≥ 2 lines of therapy including an anti-CD20 antibody and an appropriate alkylator-based combination therapy. While 145 individuals received zanubrutinib plus obinutuzumab, 72 were treated with single-agent obinutuzumab; these were allowed to cross over to the combination in case of confirmed disease progression or lack of response at 12 months.

The study met its primary endpoint, which was overall response superiority of the combination vs. obinutuzumab by independent review (68.3 % vs. 45.8 %; p = 0.0017). Notably, the rate of complete remissions for patients in the experimental arm was nearly double that of patients in the control arm (37.2 % vs. 19.4 %; p = 0.0083). Almost all pre-defined subgroups derived overall response rate (ORR) advantages from zanubrutinib/obinutuzumab vs. obinutuzumab alone. Twenty-nine patients crossed over from the control arm to the experimental arm; in this group, the subsequent ORR amounted to 24.1 % according to investigator assessment, with only 2 patients (6.9 %) obtaining complete response.

The combination conferred a 49 % reduction in the risk of progression or death compared to the monotherapy, with median progression-free survival of 27.4 vs. 11.2 months (HR, 0.51; p = 0.0040). Median duration of response had not been reached yet in either arm; at 18 months, 70.9 % vs. 54.6 % of patients responded. Time to next anti-lymphoma treatment was significantly prolonged with zanubrutinib/obinutuzumab (not reached vs. 12.1 months; HR, 0.37; p < 0.0001; **Figure 1**). Although ROSEWOOD was not powered to detect an overall survival difference between the regimens, the findings favored the combination over the single-agent treatment, with a 56 % reduction in mortality risk (HR, 0.44).

The safety profile of zanubrutinib/obinutuzumab was generally comparable to that of obinutuzumab monotherapy. Decreases in thrombocyte and neutrophil counts occurred most commonly, and among treatment-emergent adverse events of special interest (AESIs), infections prevailed. In their summary, the authors concluded that zanubrutinib plus obinutuzumab has a favorable benefit-risk profile and represents a potential combination therapy for patients with relapsed/refractory FL.

Intermittent dosing of zandelisib

Specific pharmacologic properties such as extensive tissue distribution and prolonged tumor residence compared to plasma permit the administration of the potent and selective oral PI3Kδ inhibitor zandelisib on an intermittent dosing schedule [5]. This schedule was introduced to allow regulatory T cell repopulation and to mitigate immune-medi-

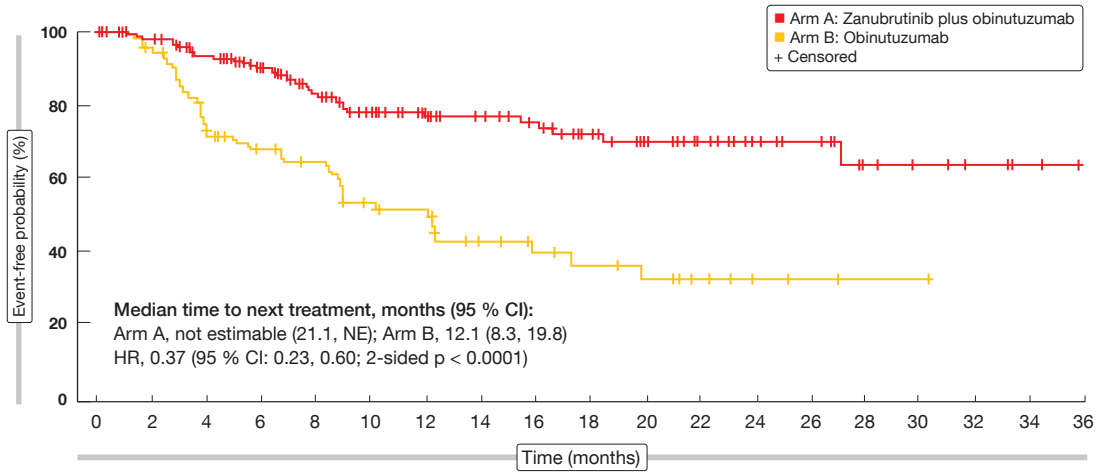


Figure 1: Superior time to next anti-lymphoma treatment with zanubrutinib/obinutuzumab vs. obinutuzumab monotherapy in the ROSEWOOD trial

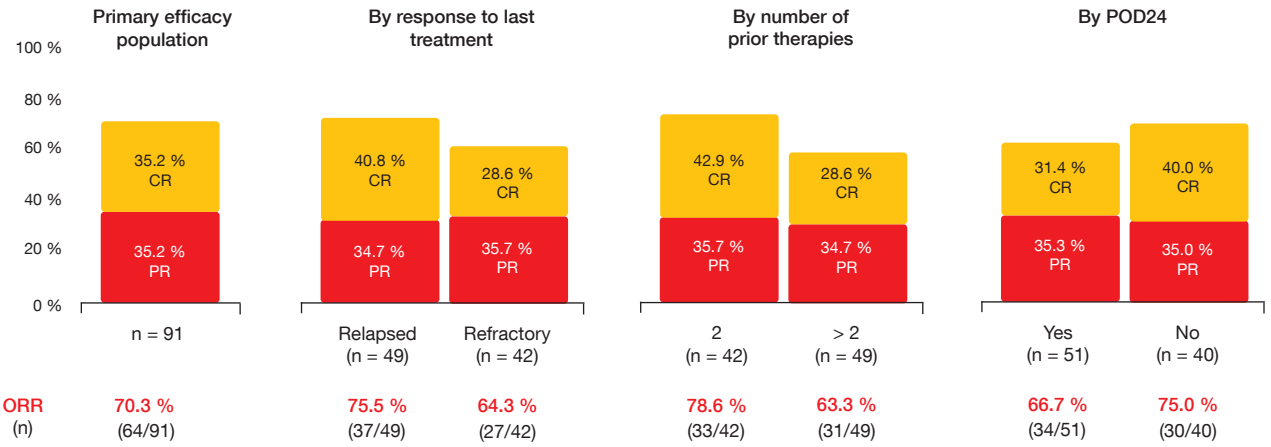


Figure 2: TIDAL study: overall response rates obtained with intermittent dosing of zandelisib in the overall population and in several subgroups

ated AESIs without loss of disease control. A phase Ib study assessing intermittent dosing on days 1-7 of 28-day cycles revealed high ORRs with zandelisib monotherapy (77.8 %) and the combinations of zandelisib with rituximab (94.7 %) or zanubrutinib (82.1 %) in the setting of relapsed/refractory FL [6]. The regimens were generally well tolerated, with low rates of AESIs and discontinuations due to treatment-related AEs.

These findings support the ongoing open-label, global, phase II TIDAL study that is investigating single-agent zandelisib 1 week on/3 weeks off from cycle 3 after daily dosing for 2 cycles. The study population consists of patients with grade I-IIIA FL who have developed progression after ≥ 2 treatment lines including an anti-CD20 antibody and an alkylating agent. Initially, TIDAL had been a randomized trial containing a continuous dosing arm, which was closed after maturing data from the phase Ib study demonstrated improved results of the intermittent treatment. At EHA 2022, the primary analysis of TIDAL was reported [7]. The safety population comprised 121 patients, while the primary efficacy population was made up by the first 91 patients treated with intermittent dosing. ORR in the primary efficacy population constituted the primary outcome.

Substantial responses with low rates of grade 3 AESIs

In this heavily pretreated patient group, zandelisib gave rise to an ORR of 70.3 %, including 35.2 % of complete remissions. Responses occurred early on; 87.5 % of all remissions were noted at the end of cycle 2, and 75.0 % of complete remissions had emerged until the end of cycle 4. Disease control was achieved in 85 %. ORRs did not differ according to response to the last treatment, number of prior therapies, or presence of progression of disease within 2 years **(Figure 2)**.

Intermittent treatment with zandelisib displayed a favorable toxicity profile. The most common AEs included diarrhea (all grades, 33 %), neutropenia (26 %), and nausea (19 %). Approximately half of patients with neutropenia experienced grade 4 events, although they responded to growth factor support. Discontinuations due to treatment-related AEs were observed in less than 10 %, and the analysis demonstrated low rates of grade 3 AESIs such as diarrhea (4.9 %), rash (3.3 %), stomatitis (2.5 %), and colitis (1.7 %). The cumulative incidence of grade 3 AESIs did not exceed 20 %, with the vast majority occurring during the first 3 cycles.

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

Parsaclisib plus obinutuzumab/bendamustine: CITADEL-102

Monotherapy with the oral, potent, highly selective next-generation PI3Kδ inhibitor parsaclisib has demonstrated rapid and durable responses in the phase II CITADEL-203 trial in the setting of relapsed/refractory FL [8]. The open-label, phase I, dose-finding CITADEL-102 study assessed parsaclisib in addition to the proven combination of obinutuzumab and bendamustine in patients with relapsed/refractory FL after pretreatment with rituximab-containing regimens. Overall, 26 patients at 15 sites in Europe and the US participated in the safety run-in and dose expansion periods.

The data suggested that parsaclisib plus obinutuzumab/bendamustine has a manageable safety profile [9]. No dose de-escalation was required, and the maximum tolerated dose of parsaclisib was not exceeded. Among any-grade AEs, pyrexia (53.8 %), neutropenia (50.0 %), and diarrhea (46.2 %) occurred most frequently. The most common grade 3/4 AE was neutropenia (34.6 %), followed by febrile neutropenia (23.1 %). Treatment-emergent AEs leading to parsaclisib treatment discontinuation and dose reductions were noted in 30.8 % and 23.1 %, respectively. Most AEs proved manageable with dose delays or reductions.

Almost all patients experienced substantial reductions from baseline in target lesions size. The ORR observed in

CITADEL-102 was 76.9 %, with complete responses/complete metabolic responses in 65.4 %. Median progression-free survival, median overall survival, and median duration of response had not been reached yet. In their assessment of the study findings, the authors concluded that parsaclisib plus obinutuzumab/bendamustine showed promising efficacy in rituximab-pretreated FL patients and warrants further investigation. ■

REFERENCES

1 Carbone A et al., Follicular lymphoma. Nat Rev Dis Primers 2019; 5(1): 83
2 Rivas-Delgado A et al., Response duration and survival shorten after each relapse in patients with follicular lymphoma treated in the rituximab era. Br J Haematol 2019; 184(5): 753-759
3 Tam CS et al., Zanubrutinib (BGB-3111) plus obinutuzumab in patients with chronic lymphocytic leukemia and follicular lymphoma. Blood Adv 2020; 4(19): 4802-4811
4 Zinzani PL et al., Zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy in patients with relapsed or refractory follicular lymphoma: primary analysis of the phase 2 randomized ROSEWOOD trial. EHA 2022, S205
5 Moreno O et al., Safety, pharmacokinetics, and pharmacodynamics of ME-401, an oral, potent, and selective inhibitor of phosphatidylinositol 3-kinase P110δ, following single ascending dose administration to healthy volunteers. Clin Ther 2018; 40(11): 1855-1867
6 Soumerai JD et al., Zandelisib on intermittent dosing as single agent or in combination with rituximab or zanubrutinib in relapsed/refractory follicular lymphoma: results from a multi-arm phase 1B study. EHA 2022, P1114
7 Zelenetz AD et al., Efficacy and safety of zandelisib administered by intermittent dosing in patients with relapsed or refractory follicular lymphoma: primary analysis of the global phase 2 study TIDAL. EHA 2022, S208
8 Lynch RC et al., Efficacy and safety of parsaclisib in patients with relapsed or refractory follicular lymphoma: primary analysis from a phase 2 study (CITADEL-203). Blood 2021; 138(Suppl 1): 813
9 Hamadani M et al., A phase 1 study evaluating safety and efficacy of parsaclisib in combination with obinutuzumab + bendamustine in patients with relapsed or refractory follicular lymphoma (CITADEL-102). EHA 2022, P1104

New options in untreated and pretreated mantle cell lymphoma

SHINE trial: first-line regimen for older patients

Patients of an advanced age with previously untreated mantle cell lymphoma (MCL) usually receive chemoimmunotherapy regimens such as bendamustine/rituximab (BR), R-CHOP or bortezomib/rituximab/cyclophosphamide/doxorubicin/prednisone (VR-CAP), with BR having become the most commonly used first-line strategy [1]. Two independent observational studies have shown significantly improved progression-free survival (PFS) for BR followed by rituximab maintenance [1, 2]. Also, ibrutinib, which has transformed the treatment of patients with relapsed/refractory MCL, has been tested successfully in the first-line phase IB setting in combination with BR [3].

Based on this information, the randomized, double-blind, phase III SHINE study was designed to assess ibrutinib until disease progression in addition to BR induction for 6 cycles in patients with previously untreated, stage II-IV MCL who were ≥ 65 years of age. Those who obtained complete or partial response after BR induction went on to receive rituximab maintenance every 8 weeks for 12 cycles. The control arm was treated with BR induction and rituximab maintenance plus placebo. At 183 study sites in 28 countries, a total of 523 patients were randomized in a 1:1 manner. The PFS in the ITT population constituted the primary endpoint.

SHINE was the first phase III study to show that ibrutinib plus chemoimmunotherapy is highly effective in patients with newly diagnosed MCL. According to the results presented at EHA 2022 by Wang et al., the primary endpoint was met after a median follow-up of 84.7 months, with a statistically significant and clinically meaningful 2.3-year advantage and a 25 % reduction in the risk of progression or death (80.6 vs. 52.9 months; HR, 0.75; p = 0.011; **Figure**) [4]. The PFS benefit emerged early on in the first year and persisted over time. Almost all subgroups treated with ibrutinib plus chemoimmunotherapy benefited to a greater extent in terms of PFS. However, no advantage was noted in the group with high risk according to the Mantle Cell Lymphoma International Prognostic Index (MIPI).

Additional outcomes

The overall response rates (ORRs) were comparable across the arms (89.7 % vs. 88.5 %), although complete remissions occurred numerically more frequently with the ibrutinib-based regimen (65.5 % vs. 57.6 %; p = 0.057). Time to next treatment was significantly longer in the experimental arm (not reached vs. 92.0 months; HR, 0.48). Markedly fewer ibrutinib-treated patients required subsequent second-line antilymphoma treatment (19.9 % vs. 40.5 %), with 11.5 % vs. 38.7 % receiving BTK inhibition. Median overall survival had not been reached yet in either arm. At 84 months, 55 % vs. 57 % of patients were alive.

The adverse events (AEs) noted in the experimental arm were consistent with the known profiles of ibrutinib and BR. Neutropenia represented the most common treatment-emergent adverse event (TEAE) in the entire study population. Rash, diarrhea, thrombocytopenia, anemia and pneumonia were seen more frequently with the ibrutinib-based treatment. Regarding TEAEs of special clinical interest, any bleeding occurred predominantly in the ibrutinib arm (42.9 % vs. 21.5 %), whereas the rates for major bleeding did not differ (5.8 % vs. 4.2 %). Atrial fibrillation was reported more commonly with ibrutinib plus chemo-

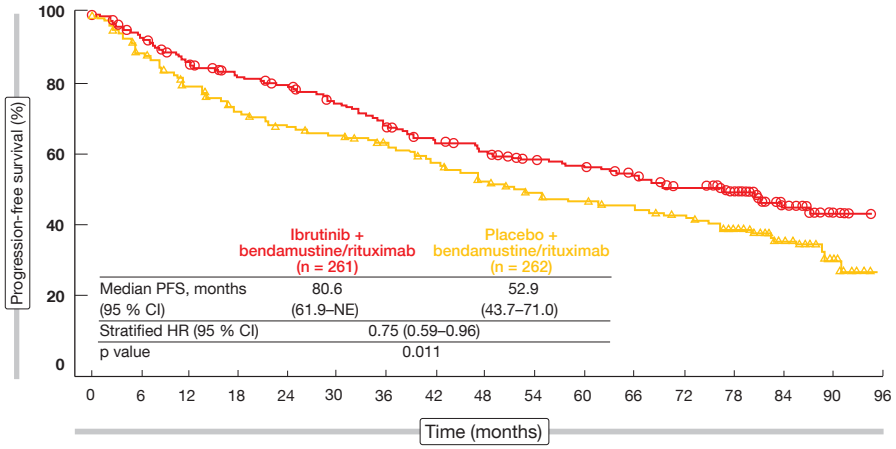


Figure: Improved progression-free survival with ibrutinib plus chemoimmunotherapy vs. placebo plus chemoimmunotherapy in the SHINE study

immunotherapy (13.9 % vs. 6.5 %), while no differences became apparent for hypertension or arthralgia. Bleeding and atrial fibrillation were generally not treatment-limiting. During the entire study period, second primary malignancies including skin cancers emerged in 21 % vs. 19 %. Death due to TEAEs occurred in 10.7 % vs. 6.1 %. An exploratory analysis of cause-specific survival including only deaths due to disease progression and TEAEs yielded an HR of 0.88 in favor of ibrutinib plus chemoimmunotherapy.

In their summary, the authors emphasized that the median PFS of 6.7 years observed in SHINE is the longest PFS ever published in this population. The study has set a new benchmark for the first-line treatment of older patients with MCL or those unsuitable for autologous stem cell transplantation.

Promising results for pirtobrutinib after BTK inhibition

Patients with MCL who progress following treatment with covalent BTK inhibition show poor overall survival [5-7]. The potent and selective non-covalent BTK inhibitor pirtobrutinib is being investigated in patients with MCL in the phase I/II BRUIN study. Eyre et al. reported updated results from the safety population (n = 134) and the efficacy population (n = 111) that included 100 BTK-inhibitor–pretreated and 11 BTK-inhibitor–naïve patients [8].

Overall, 51 % and 82 % of pretreated and naïve patients, respectively, responded to the pirtobrutinib therapy **(Table)**. Complete remissions were obtained in 25 % and 18 %, respectively. Efficacy of the treatment was also seen in patients with prior stem cell transplantation (n = 28; ORR, 64 %) and prior CAR-T therapy (n = 6; ORR, 50 %). After a median follow-up of 8.2 months for responders, 60 % of responses were ongoing.

Moreover, pirtobrutinib showed favorable safety and tolerability, with low rates across the range of side effects. Fatigue was the most common TEAE (23 %), followed by diarrhea (19 %), neutropenia (18 %), and contusion (17 %). Grade 3/4 events were rare. TEAEs of special interest included bruising (22 %), rash (11 %), arthralgia (11 %), hemorrhage (8 %), hypertension (7 %), and atrial fibrillation/flutter (2 %). These were mainly grade 1/2 events. No dose-limited toxicities were reported, and the maximum tolerated dose was not reached. Only 1 % of patients permanently discontinued pirtobrutinib therapy due to treatment-related adverse events.

As the authors noted, pirtobrutinib demonstrated promising efficacy in MCL patients previously treated with BTK inhibitors. The ongoing, randomized, global, phase III BRUIN MCL-321 trial is comparing pirtobrutinib with investigator's choice of covalent BTK inhibitors in BTK-inhibitor–naïve patients with relapsed MCL (NCT04662255). ■

TABLE
Response rates achieved with pirtobrutinib in BTK-inhibitor–pretreated and BTK-inhibitor–naïve MCL patients

	BTK-inhibitor–pretreated patients (n = 100)	BTK-inhibitor–naïve patients (n = 11)
Overall response rate, %	51	82
Best response		
Complete response, n (%)	25 (25)	2 (18)
Partial response, n (%)	26 (26)	7 (64)
Disease stabilization, n (%)	16 (16)	1 (9)

REFERENCES

1 Martin P et al., Real-world treatment patterns and outcomes of 3,455 previously untreated mantle cell lymphoma patients in U.S. routine clinical practice. J Clin Oncol 2021; 39(suppl 15): 7504
2 Hill BT et al., Maintenance rituximab is associated with improved overall survival in mantle cell lymphoma patients responding to induction therapy with bendamustine + rituximab. Hematol Oncol 2019; 37(S2): 405-407
3 Maddocks K et al., A phase 1/1b study of rituximab, bendamustine, and ibrutinib in patients with untreated and relapsed/refractory non-Hodgkin lymphoma. Blood 2015; 125(2): 242-248
4 Wang ML et al., Primary results from the phase 3 SHINE study of ibrutinib in combination with bendamustine-rituximab and R maintenance as a first-line treatment for older patients with mantle cell lymphoma. EHA 2022, S209
5 Cheah CY et al., Patients with mantle cell lymphoma failing ibrutinib are unlikely to respond to salvage chemotherapy and have poor outcomes. Ann Oncol 2015; 26(6): 1175-1179
6 Martin P et al., Postibrutinib outcomes in patients with mantle cell lymphoma. Blood 2016; 127(12): 1559-1563
7 Rai S et al., MCL-041: Outcomes for recurrent mantle cell lymphoma post-BTK inhibitor therapy in Japan: An administrative database study. Clin Lymphoma Myeloma Leuk 2021; 21(Suppl 1): S407-S408
8 Eyre et al., Pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in previously treated mantle cell lymphoma: updated results from the phase 1/2 BRUIN study. EHA 2022, P1101

Tackling acute myeloid leukemia via diverse pathways

Mutations of *FLT3* are found in approximately 30 % of patients with newly diagnosed acute myeloid leukemia (AML), with the internal tandem duplication (ITD) representing the most common type [1-4]. *FLT3*-ITD^{high} is associated with high leukemia burden and poor prognosis [2, 5, 6].

Quizartinib has been developed as a potent and selective, second-generation type II FLT3 inhibitor [7]. The pivotal QuANTUM-First study evaluating quizartinib in the phase III setting is the first randomized trial to assess the efficacy and safety of a specific FLT3 inhibitor in patients with *FLT3*-ITD–positive AML up to the age of 75 years and up to 3 years of continuation therapy.

QuANTUM-First: OS difference of almost 17 months

Newly diagnosed patients aged 18-75 years with ≥ 3 % *FLT3*-ITD allelic frequency participated in the international QuANTUM-First trial. They started 7+3 chemotherapy during *FLT3*-ITD screening and were randomized on day 7. Patients in the experimental arm (n = 268) received quizartinib on days 8-21 in addition to standard induction chemotherapy (cytarabine plus daunorubicin or idarubicin for up to 2 cycles) and, after achievement of complete response (CR) or CR with incomplete hematologic recovery (CRi), quizartinib plus consolidation (i.e., high-dose cytarabine for up to 4 cycles and/or allogeneic hematopoietic stem cell transplantation). Subsequently, those in remission at the end of consolidation including allo-HSCT could continue with up to 36 cycles of quizartinib QD. Patients in the control arm (n = 271) were treated with placebo plus identical induction and consolidation strategies followed by placebo QD for up to 36 months. Overall survival (OS) constituted the primary endpoint. The disease characteristics in the two arms were as expected for a population with *FLT3*-ITD–positive AML and a high burden of aggressive disease.

According to the analysis presented by Erba et al. at EHA 2022, the trial met its primary endpoint [8]. Median OS was more than doubled with the quizartinib-based treatment compared to standard induction and consolidation therapy alone (31.9 vs. 15.1 months; HR, 0.776; p = 0.0324; **Figure 1**). In the experimental and control arms, 144 and 128 patients, respectively, received allo-HSCT during the study. A sensitivity analysis in which all treated patients were censored at the time of transplant yielded an HR of 0.752 for OS, which was consistent with the primary analysis. By means of a descriptive, post-hoc analysis, OS was examined in the subgroups of patients who achieved CR during the induction phase and continued treatment with or without allo-HSCT in first remission. Here, both groups derived 40 % risk reductions when treated with quizartinib (HRs vs. placebo, 0.591 and 0.607, respectively).

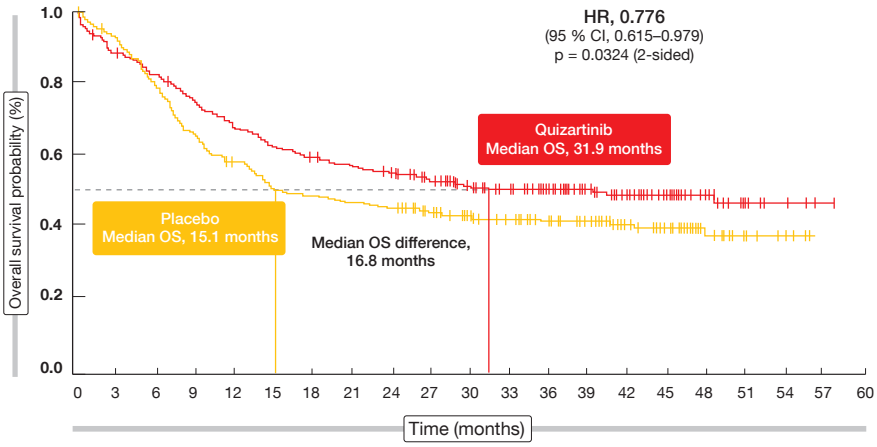


Figure 1: Superior overall survival with the addition of quizartinib to standard induction and consolidation therapy in the QuANTUM-First trial

Improvements across a range of endpoints

The OS benefit was underpinned by clinically meaningful improvements in duration of CR, which was 3 times longer in the experimental arm (38.6 vs. 12.4 months), and findings in patients who achieved CR. In this group, median relapse-free survival was 39.3 vs. 13.6 months (HR, 0.613), and the cumulative incidence of relapse was lower, with 24-month rates of 31.2 % vs. 43.3 %. The CR rates themselves did not differ across the arms (54.9 % vs. 55.4 %). Also, the primary analysis for event-free survival (EFS), which required CR by day 42 of the last induction cycle, did not yield a statistically significant difference. However, prespecified sensitivity analyses of EFS (and the original definition of EFS per protocol) showed superiority of the quizartinib-based therapy regarding achievement of CR by the end of induction (HR, 0.818) as well as CR with incomplete neutrophil or platelet count recovery by the end of induction (HR, 0.729).

The safety of quizartinib combined with intensive chemotherapy and as monotherapy was generally manageable. In the experimental arm, treatment-emergent adverse events (TEAEs) led to discontinuation in 20.4 % (vs. 8.6 %) and dose reduction in 18.9 % (vs. 6.3 %). TEAEs with fatal outcome occurred in 11.3 % vs. 9.7 %. These events were mainly due to infection that emerged predominantly during the induction and consolidation phases. Infections and cytopenias represented the most common serious AEs and TEAEs associated with study drug discontinuation. Although neutropenia was observed more frequently with the quizartinib-based therapy (20.4 % vs. 10.1 %), rates for febrile neutropenia were comparable (all grades, 44.2 % vs. 42.2 %; grade ≥ 3, 43.4 % vs. 41.0 %). Non-hematologic AEs with the combined treatment included mainly pyrexia, diarrhea, hypokalemia, and nausea. QT prolonga-

tion occurred more commonly in the quizartinib arm, although most cases were mild to moderate, and proved manageable. The authors pointed out that the data obtained in the QuANTUM-First trial have the potential to change the standard of care for the treatment of adult patients with newly diagnosed *FLT3*-ITD–positive AML.

Unfit patients with *TP53*-mutated AML: magrolimab

The first-in-class anti-CD47 antibody magrolimab is a macrophage immune checkpoint inhibitor that works by blocking the inhibitory ("don't eat me") signal between CD47 and SIRPα, which is overexpressed in multiple cancers, including AML, and leads to macrophage immune evasion [9, 10]. Thus, magrolimab prompts macrophage activation, which enables tumor cell elimination. The rationale for the combination of this agent with the hypomethylating drug azacitidine results from the fact that azacitidine induces prophagocytic "eat me" signals, such as calreticulin, on cancer cells [11]. These signals were shown to synergize with the CD47 blockade in AML xenograft models, giving rise to enhanced phagocytosis.

Daver et al. reported phase IB results for 72 previously untreated AML patients with *TP53*-positive disease who received magrolimab plus azacitidine in the 5F9005 study [12]. Magrolimab was administered as a 1 mg/kg priming dose i. v. on days 1 and 4, followed by ramp-up to 30 mg/kg maintenance once or twice weekly. Azacitidine therapy entailed subcutaneous or intravenous doses of 75 mg/m^2 on days 1-7 of each cycle. The study population was ineligible for intensive induction chemotherapy with cytarabine and anthracycline. Almost 80 % were ≥ 65 years old. Adverse cytogenetic risk factors and underlying myelodysplasia were present in 79.2 % and 47.2 %, respectively. Median *TP53* variant allele frequency (VAF) was 38.

Encouraging remissions and OS

Magrolimab plus azacitidine demonstrated an acceptable safety profile and promising efficacy consistent with the synergy observed in the preclinical setting. The most commonly reported AEs included constipation, diarrhea, febrile neutropenia, and nausea. Grade 3 anemia was seen in 26.4 %, with grade 4 events in 2.8 % regardless of attribution. All-grade infusion-related reactions occurred in 22.2 %, while grade ≥ 3 reactions were rare at 1.4 %. Notably, no patient required dose reductions, and dose delays were reported in 45.8 %. TEAEs led to discontinuation of magrolimab and azacitidine in 30.6 % and 29.2 %, respectively. Eighteen percent of patients died within 60 days of the first study drug dose. However, the authors pointed out that early mortality is inherently high in the setting of *TP53*-mutated AML, with studies into azacitidine/decitabine and venetoclax reporting 20-25 % early mortality in this specific molecular subset of patients, a large proportion of this being due to refractory disease and more profound cytopenias.

Magrolimab plus azacitidine induced encouraging response rates. Almost 50 % of patients responded and 33.3 % developed CR, with half of these achieving MRD negativity. CR/CRi resulted in 41.7 %. Median duration of response was encouraging for *TP53*-mutated patients at 8.7 months, and median progression-free survival amounted to 7.3 months. Whole exome sequencing plus best overall response data were available for 13 patients. In this group, *TP53* VAF decreased in most individuals; 7 of 9 longitudinally evaluable responders obtained *TP53* VAF < 0.07 by the end of cycle 4 of combination therapy. Moreover, the analysis showed promising OS for *TP53*-mutated AML, with a median of 10.8 months. Among patients who were transfusion-dependent at baseline, 29.7 % and 45.8 % converted to red blood cell and platelet transfusion independence, respectively.

Patients who were able to progress to allo-HSCT experienced particularly favorable outcomes. Median OS after allo-HSCT had not been reached yet (vs. 8.4 months without allo-HSCT), and 83 % of the transplanted individuals were alive at 1 year (vs. 36 %; **Figure 2**). According to the authors, performing transplantation as soon as possible after achieving at least remission in the bone marrow appears to be the preferable treatment path on the road to long-term survival. Magrolimab plus azacitidine as frontline strategy is currently being assessed in patients with *TP53*-mutated AML in the phase III ENHANCE-2 trial (NCT04778397).

STIMULUS-AML1: sabatolimab plus venetoclax/azacitidine

Another novel target is TIM-3, an immune-myeloid regulator that is expressed on both immune cells and leukemic stem cells in myeloid malignancies [13]. The anti-TIM-3 antibody sabatolimab has a potential dual mechanism to combat AML and myelodysplastic syndrome (MDS) by boosting the ability of the immune system to eliminate leukemic stem cells and blasts, and by directly targeting TIM-3–positive leukemic stem cells [14, 15]. The combination of sabatolimab with hypomethylating agents has shown durable responses in patients with higher-risk AML and MDS in a phase IB study [14].

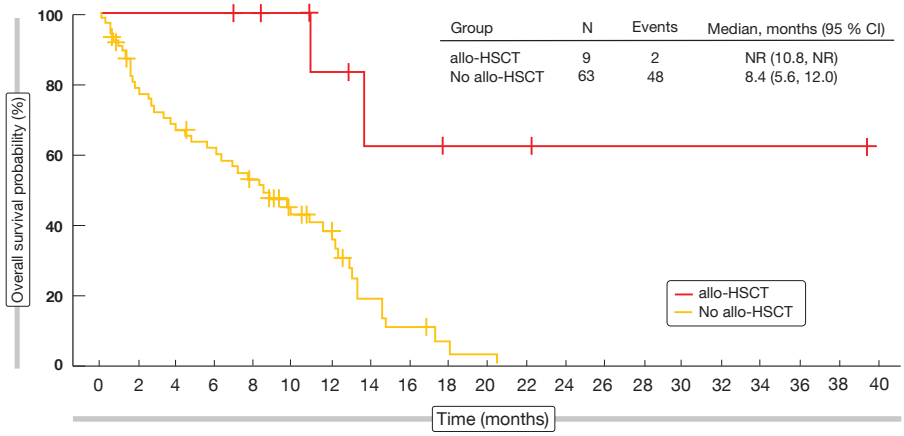
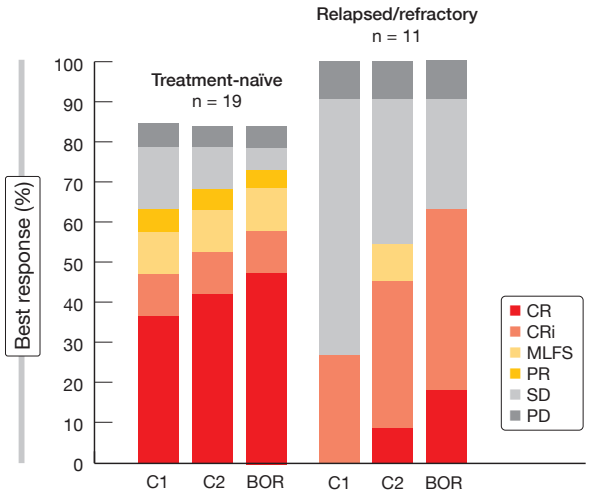


Figure 2: Survival advantage after magrolimab followed by allogeneic stem cell transplant (allo-HSCT) vs. patients who were ineligible for allo-HSCT



CR, complete response; CRi, CR with incomplete hematologic recovery; MLFS, morphological leukemia-free state; PR, partial response; SD, stabile disease; PD, progressive disease

Figure 3: Best overall response (BOR) and responses by cycle 1 and 2 with BGB-11417 plus azacitidine in patients with treatment-naïve and relapsed/refractory AML

Sabatolimab plus azacitidine and venetoclax is being investigated in the single-arm, phase II STIMULUS-AML1 trial in patients with newly diagnosed AML who are not fit for intensive chemotherapy. Cohorts 1 and 2 received sabatolimab 400 mg and 800 mg Q4W, respectively, in addition to azacitidine and venetoclax. After the 800 mg dose had proven safe, the trial progressed to the expansion part testing the combination treatment based on the higher sabatolimab dose. At EHA 2022, preliminary findings from the completed dose-escalation part of the study (n = 18) were presented [16].

According to this, the overall safety and tolerability of the regimen were comparable to the previously reported safety profile of venetoclax and azacitidine, and there were no notable differences across the 400 mg and 800 mg dose levels. Among AEs suspected to be treatment-related, grade 3/4 neutropenia was observed most frequently, followed by grade 3/4 thrombocytopenia, grade 1/2 constipation, and anemia that was mainly grade 3/4. Three patients discontinued sabatolimab therapy due to treatment-related events. AEs leading to venetoclax and azacitidine treatment discontinuation emerged in two cases each. No dose reduction of sabatolimab was required, and only one dose-limiting toxicity (i.e., troponin T elevation suggesting asymptomatic myocarditis) occurred.

The sabatolimab-based therapy conferred preliminary clinical responses. In Cohort 1, 1 patient developed CR, while 3 had CRi, and 1 experienced disease stabilization. Among the 13 patients included in Cohort 2, 3 experienced CR, 5 CRi, and 1 morphological leukemia-free state (MLFS). Stable disease was reported in 2 patients. At present, accrual in the expansion cohort is ongoing.

BGB-11417 combined with azacitidine

Venetoclax-based therapies have improved outcomes in patients with AML who are ineligible for induction chemotherapy, although concerns regarding disease resistance and toxicities remain [17]. BGB-11417 is a potent and highly selective investigational BCL2 inhibitor that has shown superior antitumor activity compared with venetoclax in the preclinical setting and a tolerable safety profile at doses of up to 640 mg in a phase I monotherapy study [18, 19]. The ongoing, phase IB/II dose-finding and dose-expansion study BGB-11417-103 is evaluating the safety and efficacy of BGB-11417 plus azacitidine in the setting of AML. In the dose-escalation part, 3 dose levels of BGB-11417 (40 mg, 80 mg, 160 mg) were tested for 10 days after a 4-day ramp-up in cycle 1; in addition, the 160 mg dose is being assessed for 28 days.

Shortt et al. reported preliminary data obtained with the 10-day doses in 19 treatment-naïve AML patients unfit for intensive chemotherapy and in 12 patients with relapsed/refractory AML who had not received prior BCL2 inhibitor or azacitidine treatment [20]. Across the 3 dose levels, BGB-11417 was well tolerated and active in combination with azacitidine. Dose-limiting toxicities occurred in 2 patients, and 4 patients discontinued study treatment due to AEs. At 55 %, neutropenia represented the most common grade ≥ 3 AE, followed by thrombocytopenia (48 %) and anemia (42 %). Neutropenia proved manageable with growth factor support and dose modifications.

Overall responses, which were a composite of CR, CRi, MLFS and partial response, resulted in 74 % and 64 % of treatment-naïve and relapsed/refractory patients, respectively **(Figure 3)**. Within these groups, 58 % and 55 % of patients, respectively, met the criteria for CR plus CR with partial hematological recovery. Most CRs were achieved by the end of cycle 1. Nearly 40 % of 13 patients with CR/CRi who had evaluable flow cytometry results obtained MRD negativity. Enrollment in the safety expansion is ongoing, and evaluation of the 28-day dosing regimen is planned. ■

REFERENCES

1 O'Donnell MR et al., Acute myeloid leukemia, version 3.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2017; 15(7): 926-57
2 Levis M, FLT3 mutations in acute myeloid leukemia: what is the best approach in 2013? Hematol Am Soc Hematol Educ Program 2013; 2013: 220-226
3 Kottaridis PD et al., Flt3 mutations and leukaemia. Br J Haematol 2003; 122(4): 523-538
4 Nagel G et al., Epidemiological, genetic, and clinical characterization by age of newly diagnosed acute myeloid leukemia based on an academic population-based registry study (AMLSG BiO). Ann Hematol 2017; 96(12): 1993-2003
5 Ding L et al., Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. Nature 2012; 481(7382): 506-510
6 Grimwade D, Mrozek K. Diagnostic and prognostic value of cytogenetics in acute myeloid leukemia. Hematol Oncol Clin North Am 2011; 25(6): 1135-1161, vii

7 Zarrinkar P et al., AC220 is a uniquely potent and selective inhibitor of FLT3 for the treatment of acute myeloid leukemia. Blood 2009; 114(14): 2984-2992
8 Erba HP et al., Quizartinib prolonged survival vs placebo plus intensive induction and consolidation therapy followed by single-agent continuation in patients ages 18-75 years with newly diagnosed *FLT3*-ITD+ AML. EHA 2022, S100
9 Liu J et al., Pre-clinical development of a humanized anti-CD47 antibody with anti-cancer therapeutic potential. PLoS One 2015; 10(9): e0137345
10 Chao MP et al., Therapeutic targeting of the macrophage immune checkpoint CD47 in myeloid malignancies. Front Oncol 2020; 9: 1380
11 Feng D et al., Combination treatment with 5F9 and azacitidine enhances phagocytic elimination of acute myeloid leukemia. Blood 2018; 132(1 Suppl): 2729
12 Daver NG et al., Tolerability and efficacy of the first-in-class anti-CD47 antibody magrolimab combined with azacitidine in frontline patients with TP53-mutated acute myeloid leukemia: phase 1b results. EHA 2022, S132
13 Das M et al., Tim-3 and its role in regulating anti-tumor immunity. Immunol Rev 2017; 276(1): 97-111
14 Brunner AM et al., Efficacy and safety of sabatolimab (MBG453) in combination with hypomethylating agents in patients with very high/high-risk myelodysplastic syndrome and acute myeloid leukemia: final analysis from a phase Ib study. ASH 2021, abstract 244
15 Acharya N et al., Tim-3 finds its place in the cancer immunotherapy landscape. J Immunother Cancer 2020; 8(1): e00091
16 Zeidan AM et al., First results of a phase II study (STIMULUS-AML 1) investigating sabatolimab + azacitidine + venetoclax in patients with newly diagnosed acute myeloid leukemia. EHA 2022, P582
17 DiNardo CD et al., Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med 2020; 383(7): 617-629
18 Hu N et al., Preclinical characterization of BGB-11417, a potent and selective Bcl-2 inhibitor with superior antitumor activities in haematological tumor models. Cancer Res 2020; 80(suppl 16): 3077
19 Opat S et al., A phase 1 study with the novel B-cell lymphoma inhibitor BGB-11417 as monotherapy or in combination with zanubrutinib in patients with B-cell malignancies: preliminary data. EHA 2022, P687
20 Shortt J et al., Preliminary safety and efficacy of BGB-1147, a potent and selective B-cell lymphoma 2 inhibitor in patients with acute myeloid leukemia, EHA 2022, P590

Expert interviews at EHA 2022

Naval Daver overviews the most promising new agents in the treatment of AML, how existing drugs can blend into new regimens and how the prognosis of patients with AML will evolve in the years to come. Finally, he talks about risk factors for ICI-related pneumonitis development and if pneumonitis increases mortality in AML patients.

Jorge Castillo explains the most meaningful diagnostic criteria for WM, give insights into the "real-world" treatment of WM with zanubrutinib, bortezomib and other treatment strategies and how to sequence therapies in WM. He explains promising modes of action of new agents in the treatment of WM and depicts his personal highlights from this year's EHA congress.

Wojciech Jurczak outlines what can be achieved with the current standard treatments in the setting of follicular lymphoma, which findings have been observed for PI3K inhibitor therapy in the TIDAL study and were we are today with respect to CAR-T cell therapy for patients with follicular lymphoma.

Shirley D´Sa discusses how the treatment and especially the prognosis of patients with WM evolved over the last decades, which approaches can be used to successfully treat patients with MYD88^{WT}WM, how the interaction between WM cells and the bone marrow microenvironment can be used to develop new ways to overcome treatment resistance and finally explains how often the Binge-Neel Syndrome happens, how its diagnosed and how it should be treated.

Constantine Tam highlights the most relevant findings presented at EHA 2022 as well as promising modes of action of new agents in the treatment of indolent lymphomas. He explains how resistance to BTK inhibitors can be addressed in B-cell malignancies while giving an outlook on a BTK protein degrader and finally summarizes the long-term results obtained with zanubrutinib compared to ibrutinib in the ASPEN trial in patients with WM.

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