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

Report from the American Society of Clinical Oncology (ASCO) Annual Meeting (hybrid), 2<sup>nd</sup>-6<sup>th</sup> June 2023, European Hematology Association (EHA) 2023 Congress (hybrid), 8<sup>th</sup>-11<sup>th</sup> June 2023, and the 17<sup>th</sup> International Conference on Malignant Lymphoma (ICML) 2023 Congress (hybrid), 13<sup>th</sup>-17<sup>th</sup> June 2023

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### Preface

#### Dear Colleagues,

Cutting-edge updates in the diagnosis and treatment of hematological malignancies were discussed by world-leading experts at the Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago, USA, 2<sup>nd</sup>–6<sup>th</sup> June 2023, the European Hematology Association (EHA) congress in Frankfurt, Germany, 8<sup>th</sup>–11<sup>th</sup> June 2023, and the 17<sup>th</sup> International Conference on Malignant Lymphoma (ICML) in Lugano, Switzerland, 13<sup>th</sup>–17<sup>th</sup> June 2023.

Over the last decade, the treatment of chronic lymphocytic leukemia has dramatically evolved due to the introduction of targeted therapies, but questions remain. In treatment-naïve asymptomatic disease, the watch & wait concept was challenged but appears to be superior to early BTK inhibitor treatment. Chemotherapy-free fixed-duration regimens have shown clinically meaningful benefits and deep, durable responses and are an attractive alternative to continuous treatment, avoiding long-term toxicity, high-costs and potentially inevitable development of resistant clones. At the same time, the

results provide the rationale for the implementation of MRD-guided strategies to further improve patient prognosis. The next-generation BTK inhibitor zanubrutinib has become a new first-line treatment in the elderly, in patients with comorbidities, and in those with adverse genetic setup. In relapsed/refractory CLL, the feasibility of venetoclax/rituximab retreatment in the context of fixed-duration strategies has been demonstrated. Also, data show that some BTK inhibitors offer advantages over others in the presence of intolerability and *BTK* mutations.

Bispecific antibodies are on the rise in hematological malignancies, which is highlighted in this report by findings obtained in the setting of follicular lymphoma and diffuse large B-cell lymphoma. Nevertheless, BTK inhibition remains a mainstay of treatment in hematological diseases such as marginal zone lymphoma and Waldenström macroglobulinemia. In elderly patients with diffuse large B-cell lymphoma, the antibody-drug conjugate polatuzumab vedotin has vielded encouraging efficacy combined with chemotherapy. Moreover, promising findings have been observed with novel agents targeting BTK and Bcl-2 in various B-cell malignancies.

Once again, experts shared groundbreaking results in the field of hematolog-



ical oncology by presenting impressive long-term follow-up data as well as innovative treatment strategies at this year's ASCO, EHA and ICML meeting. Leaving Chicago, Frankfurt and/or Lugano, we all feel excited and inspired to share our newly acquired knowledge not only with you, as a reader of this special issue, but also with our patients since science creates knowledge and saves lives.

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## Current insights into BTK inhibition and other targeted approaches in chronic lymphocytic leukemia

#### TREATMENT-NAÏVE DISEASE

### Ibrutinib vs. watch & wait in asymptomatic patients

In the setting of early-stage, asymptomatic chronic lymphocytic leukemia (CLL), the concept of watch & wait in the era of targeted agents was challenged by the placebo-controlled, double-blind, phase III CLL12 study. This trial assessed the use of ibrutinib 420 mg OD (n = 182) vs. placebo (n = 181) until symptomatic disease progression in treatment-naïve patients with asymptomatic CLL Binet stage A who had an increased risk due to factors such as del(17p), IGHV mutation status, or age. A group of 152 CLL patients without increased risk constituted the watch & wait cohort. The primary endpoint analysis has demonstrated superior event-free survival (EFS) until sympto-

matic disease progression or death from any cause for the ibrutinib-treated patients [1]. At a median observation time of 69.3 months, Langerbeins et al. presented the final analysis of the CLL12 study at EHA 2023 [2].

The superiority of ibrutinib regarding EFS was confirmed with the prolonged follow-up: while median EFS had not been reached with ibrutinib, it was 51.6 months with placebo (HR, 0.276; p < 0.001;



Figure 1: CLL12 study: long-term event-free survival with ibrutinib vs. placebo in asymptomatic patients

Figure 1). Likewise, median progressionfree survival (PFS) had not been reached in the experimental arm and was 14.0 months in the control arm (HR, 0.174; p < 0.001). The overall response rate (ORR) was 72.5% vs. 5%. Only 15.9% of ibrutinib-treated patients received subsequent therapy (vs. 43.6%), and time to next treatment (TTNT) was significantly longer (not reached vs. 68.5 months; HR, 0.244; p<0.001). For PFS2 that was assessed from the start of subsequent treatment, the analysis revealed no advantage of ibrutinib (16.6 vs. 35.1 months; HR, 1.471). Median overall survival (OS) had not been reached in either treatment arm (HR, 0.791; p=0.562). Similarly, OS, as measured from CLL diagnosis to death, did not differ across the arms; here, the analysis also included the watch-and-wait cohort.

With respect to adverse events (AEs) of clinical interest, ibrutinib-treated patients experienced bleeding and cardiac arrhythmias in 36.5% and 22.4%, respectively. Fatal AEs of interest occurred in 2.4% in the experimental arm. Second malignancies were reported in 12.9% for ibrutinib vs. 21.4% for placebo, with grade 5 events observed in 1.2% vs. 3%. In the watch & wait group, second malignancies emerged in 9.9% and were the only AEs documented.

The authors noted in their summary that ibrutinib is associated with relevant cardiovascular toxicity and increased susceptibility to bleeding. While EFS, PFS and TTNT were significantly longer in ibrutinib-treated patients, this did not translate into an OS advantage compared to the placebo group where median OS was excellent. Therefore, watch & wait should remain the standard of care in asymptomatic CLL patients with high-risk features even in the era of targeted drugs.

#### CAPTIVATE: 4-year results from the FD cohort

First-line treatment with ibrutinib plus venetoclax was assessed in the international phase II CAPTIVATE study that contained two cohorts investigating MRD-guided randomized treatment discontinuation (MRD cohort) and fixedduration treatment (FD cohort). Patients in the FD cohort received ibrutinib 420 mg OD for a total of 15 months including lead-in in addition to venetoclax 400 mg OD for 12 months. After the end of the fixed-duration period, patients could receive retreatment upon progression with single-agent ibrutinib or ibrutinib plus venetoclax as per investigator's discretion. The primary analysis has shown an ORR of 96%, a best undetectable minimal residual disease (uMRD) rate of 77 %, and a 24-month PFS rate of 95 % [3]. Ghia et al. presented 4-year follow-up data from the FD cohort (n = 159) after a median time on study of 49.8 months that included 36.0 months after the completion of FD therapy [4].

Ibrutinib/venetoclax continued to provide clinically meaningful benefits and deep, durable responses. Thirty-six months after the end of treatment (EOT), 44% of patients still showed complete response (CR). Median duration of response had not been reached, which also applied to median duration of CR. Patients with del(17p)/*TP53* mutation and

unmutated IGHV showed a somewhat faster decline in CR over time, with 36-month rates of 30% and 43%, respectively. The 4-year PFS rate was high at 79% in the entire group. For patients with del(17p)/TP53 mutation and unmutated IGHV, this was 63% and 73%, respectively. In the overall population, 21% of patients had uMRD in the peripheral blood 36 months after EOT. The analysis according to MRD status demonstrated that the 48-month PFS rate was significantly higher in patients with uMRD than in those with detectable MRD 3 months after EOT (90% vs. 66%). Ninety-eight percent of all treated patients were alive at 4 years. Median TTNT had not been reached, and 84% had not started their next treatment.

Nineteen patients who had progressed after completing the fixed-duration regimen in either the FD or the MRD cohort placebo arm initiated retreatment with single-agent ibrutinib, which yielded promising responses. One of 17 responseevaluable patients achieved CR, and 13 obtained partial remission. In the retreated group, no AEs occurred that prompted dose reduction or discontinuation. The overall safety profile was manageable and unchanged from that previously reported. In their summary, the authors pointed out that ibrutinib/venetoclax represents an effective all-oral, oncedaily, chemotherapy-free fixed-duration regimen for untreated patients with CLL/ small lymphocytic lymphoma (SLL).

### Six-year update of CLL14: venetoclax/obinutuzumab

Fixed-duration treatment with venetoclax plus obinutuzumab was assessed by the randomized, open-label, phase III CLL14 study conducted in patients with previously untreated CLL who had coexisting medical conditions (CIRS > 6 and/ or creatinine clearance <70 mL/min). In the experimental arm (n=216), venetoclax/obinutuzumab was administered for 6 cycles, which was followed by venetoclax monotherapy for another 6 cycles. Patients in the control arm (n=216) received chlorambucil plus obinutuzumab for 6 cycles followed by chlorambucil for 6 cycles. The primary analysis revealed a significant PFS benefit for venetoclax/ obinutuzumab vs. chlorambucil/obinutuzumab, with 24-month rates of 88.2 % vs. 64.1% (HR, 0.35; p<0.001) [5].

At EHA 2023, Al-Sawaf et al. reported an update of the CLL14 trial after a median of 76.4 months, with all patients being off study treatment for >5 years [6]. Median PFS was 76.2 vs. 36.4 months for venetoclax/obinutuzumab vs. chlorambucil/obinutuzumab, which translated into a 60% risk reduction (HR, 0.40; p < 0.0001). The 6-year PFS rates were 53.1% vs. 21.7%. High-risk characteristics including TP53 deletion/mutation and unmutated IGHV correlated with shorter PFS in both study arms. Nevertheless, patients with high-risk features fared considerably better when treated in the experimental arm, thus gaining several years of treatment-free disease control (Table). Within the venetoclaxtreated group, the multivariate model identified lymph node size  $\geq 5$  cm, unmutated IGHV and TP53 deletion/mutation as independent negative prognostic factors for PFS.

Median TTNT had not been reached with venetoclax/obinutuzumab and was 52.9 months with chlorambucil/obinutuzumab (HR, 0.44; p < 0.0001). At the time of the analysis, more than 60% of patients treated with venetoclax/obinutuzumab had not required any second-line treatment. Median OS had not been reached yet in either arm; at 6 years, the OS rates were 78.7% vs. 69.2% (HR, 0.69; p = 0.052). CLL-related mortality was lower with venetoclax/obinutuzumab (18.8% vs. 37.1%).

Longitudinal MRD assessments showed MRD <  $10^{-4}$  rates of 7.9% vs. 1.9% five years after EOT. The data confirmed the prognostic significance of the EOT MRD status: the depth of remission at a cutoff of  $10^{-4}$  correlated with OS (p < 0.001) and PFS. This provides the rationale for the implementation of MRDguided strategies to further improve patient prognosis. The safety update yielded virtually no post-treatment toxicity in either arm. Second primary malignancies occurred in 14.2% vs. 8.4%, without any statistically significant difference in cumulative incidence across the arms.

### SEQUOIA: zanubrutinib in elderly patients

The next-generation BTK inhibitor zanubrutinib was tested in the randomized, controlled, phase III SEQUOIA trial in treatment-naïve CLL/SLL patients who were  $\geq$  65 years or  $\geq$  18 years of age and unsuitable for treatment with chemo-

immunotherapy. In Cohort 1 of the study, patients without del(17p) were treated with either zanubrutinib 160 mg BID until progression (n = 241) or bendamustine plus rituximab (BR) for 6 cycles (n = 238), while the patients in Cohort 2 had del(17p) and received zanubrutinib monotherapy (n = 111). After a median follow-up of 26.2 months, the study met its primary endpoint, with superior PFS results for zanubrutinib in Cohort 1 and similar outcomes in Cohort 2 [7]. Updated findings were reported by Shadman et al. at ICML 2023 after 18 months of additional follow-up [8].

In Cohort 1, the risk of progression or death was reduced by 70 % with zanubrutinib compared to BR (median PFS, not reached vs. 42.2 months; HR, 0.30; p < 0.0001). At 42 months, 82.4 % vs. 50.0 % of patients were alive and progressionfree. The rate of complete remissions/CR with incomplete hematologic recovery (CRi) was 17.4% in the experimental arm, indicating deepening of response as it represented an increase versus the rate achieved at the primary analysis. Zanubrutinib therapy, as compared to BR, induced significant PFS benefits in patients with both mutated IGHV (not reached vs. 49.4 months; HR, 0.35; p=0.00033) and unmutated IGHV (not reached vs. 33.7 months; HR, 0.23; p < 0.0001). For OS, the 42-month rates were 89.4% vs. 88.3% (HR, 0.87).

Similar results were observed for zanubrutinib in the patients with del(17p) included in Cohort 2. The 42-month rates for PFS and OS were 79.4% and 89.5%, respectively. Again, at 14.5%, the CR/CRi rate was improved compared to the primary analysis. Zanubrutinib was well tolerated, and the AEs reported were in keeping with the known safety profile of BTK inhibitors. The rates of atrial fibrillation or flutter remained low over time. Taken together, the extended follow-up of the SEQUOIA study demonstrated sustained benefits of zanubrutinib, supporting the first-line use of this agent in the elderly, in patients with comorbidities, and in those with del(17p).

#### MRD findings for zanubrutinib/ obinutuzumab/venetoclax

In the phase II setting, the combination of zanubrutinib with obinutuzumab/vene-toclax (BOVen) for 8–24 months was evaluated in 52 patients with previously untreated CLL/SLL. The primary endpoint of the study was defined by uMRD <  $10^{-4}$  in the peripheral blood on two consecutive occasions, which was confirmed by bone marrow assessment. These patients discontinued treatment. BOVen appeared well-tolerated and led to high uMRD rates according to the primary analysis [9]. Updated findings were reported at ICML 2023 by Soumerai et al. [10].

After a median follow-up of 40 months, uMRD as best/EOT response was found in the peripheral blood in 96% and in both blood and marrow in 92%. All patients discontinued the treatment after a median of 10 months including the 2-month lead-in. Median PFS had not been reached yet at the time of the analysis. No additional safety signals were reported during the long-term observation period. In patients with uMRD in the bone marrow (n = 46), median MRD-free survival with the BOVen regimen was 29.8 months.

#### TABLE

Progression-free survival for venetoclax/obinutuzumab and chlorambucil/obinutuzumab by TP53 and IGHV mutational status

	Venetoclax/obinutuzumab		Chlorambucil/obinutuzumab	
	TP53 wildtype	TP53 <i>del/mut</i>	TP53 wildtype	TP53 del/mut
Median PFS, months	76.6	51.9	38.9	20.8
	HR, 2.29 p = 0.001		HR, 1.66 p = 0.03	
	IGHV mutated	IGHV umutated	IGHV mutated	IGHV unmutated
Median PFS, months	Not reached	64.8	62.2	26.9
	HR, 0.38 p < 0.001		HR, 0.33 p < 0.001	

 $\Delta$ MRD400, which represents a  $\geq$  400fold reduction in peripheral blood MRD baseline levels until day 1 of cycle 5, was achieved by 60% of patients. All of them developed early uMRD in the bone marrow after a median of 6 months. In the group of patients who did not achieve  $\Delta$ MRD400, the time to uMRD in the bone marrow was 11 months; only 21 % developed uMRD within 8 months. Interestingly,  $\Delta$ MRD400 did not appear to concur with traditional risk factors such as TP53 or IGHV mutational status. With longer follow-up, AMRD400 correlated with longer MRD-free survival despite shorter time on therapy (Figure 2). A phase II trial is exploring ∆MRD400-directed firstline treatment with BOVen for 24 vs. 10 months based on the hypothesis that longer duration of therapy in patients who failed to achieve ΔMRD400 will further improve uMRD duration.

#### RELAPSED/REFRACTORY DISEASE

#### Venetoclax/rituximab: 7-year data from MURANO

Fixed-duration treatment in the relapsed/ refractory setting was evaluated in the global, randomized, open-label phase III MURANO trial. Patients in the experimental arm received venetoclax 400 mg OD for 2 years plus rituximab for 6 months, while the control arm was treated with BR for 6 months. Venetoclax/ rituximab, as compared to BR, gave rise to significantly improved PFS, with 2-year PFS rates of 84.9% vs. 36.3% (HR, 0.17; p < 0.001) [11]. At EHA 2023, Kater et al. reported the final long-term analysis [12].

After a follow-up of 7 years, venetoclax/rituximab induced sustained improvements of the survival endpoints compared to BR. Median PFS was 54.7 vs. 17.0 months (HR, 0.23; p<0.0001), while median OS had not been reached in the experimental arm and was 87.8 months in the control arm (HR, 0.53; p < 0.0002). At 7 years, 69.6% vs. 51.0% of patients were alive, and 23.0% vs. 0% were progression-free. Moreover, the experimental treatment gave rise to significantly prolonged TTNT (63.0 vs. 24.0 months; HR, 0.30; p<0.0001). No new safety signals have been identified since the 5-year analysis [13].

The MRD status at EOT was evaluable in 118 patients. Most of those who received the full 2 years of venetoclax/rituximab treatment achieved uMRD at EOT (n=83). MRD conversion with subsequent disease progression did not occur until approximately 4 years after EOT in this cohort, with a median time to conversion of 19.4 months and a median time from conversion to progression of 28.3 months. In the group that completed 2 years of venetoclax without disease progression, uMRD was predictive of prolonged PFS: median PFS since EOT was more than 11 times longer among those with uMRD than in the cohort with high MRD (52.5 vs. 4.6 months; HR, 17.22; p<0.0001). For OS since EOT, the same analysis revealed a trend. Fourteen patients showed sustained uMRD after EOT at the most recent follow-up. This group was enriched for the favorable baseline characteristics TP53 wildtype and mutated IGHV.

A substudy of the MURANO trial explored retreatment following disease





progression. Twenty-five patients most of whom had high-risk features were retreated with fixed-duration venetoclax/ rituximab after a median of 2.3 years from the final study drug dose. In this group, the best ORR was as high as 72.0%, including a CR rate of 24 %. Median PFS was 23.3 months, and median OS had not been reached. uMRD at the end of venetoclax/rituximab retreatment resulted in 32% but was not sustained in the long run. The authors concluded that venetoclax/rituximab retreatment remains a viable option for patients with relapsed/ refractory CLL. Overall, the long-term data from MURANO continue to support the use of fixed-duration venetoclax/ rituximab and demonstrate the feasibility of venetoclax retreatment in the context of fixed-duration strategies.

#### Vision: time-limited venetoclax and ibrutinib

The aim of the Vision/HO141 trial is the assessment of MRD-guided treatment in allcomer patients with relapsed/refractory CLL. After induction therapy with ibrutinib/venetoclax for 15 cycles (n=225), patients who achieved at least partial response and uMRD at cycle 15 (n = 72; 32%) were randomized to either ibrutinib maintenance until progression (arm A; n=24) or observation (arm B; n=48). Patients in arm B who developed CLL progression or became MRD-positive (>10-2) received retreatment with ibrutinib until progression and venetoclax for 12 months. Those who remained MRD-positive after the 15-cycle induction period were not randomized and went on to receive ibrutinib until progression (n=153). The primary analysis has shown a favorable benefit-risk profile of MRD-based cessation and reinduction; the primary endpoint of PFS at 12 months after stopping treatment in arm B was met (98%) [14]. Kater et al. reported the longterm outcome and MRD kinetics after a median follow-up of 50.8 months at EHA 2023 [15].

At 51 months, the PFS rates were 92% for arm A that received ibrutinib maintenance, 81% for arm B that was treated based on MRD, and 75% for the non-randomized cohort. TTNT rates for these groups were 92%, 96% and 88%, respectively. Likewise, arms A and B fared better than the non-randomized cohort with respect to OS, with 51-month rates of 96%, 92%, and 84%, respectively.



Figure 3: Changes in MRD responses over time after 15 cycles of induction with venetoclax/ibrutinib

At 51 months, uMRD was present in 33% and 21% in arms A and B, respectively (Figure 3), and in 22% in the nonrandomized cohort. In arm B, 40% of initially MRD-negative patients experienced MRD conversion (>10<sup>-2</sup>) after a median of 24 months since the start of observation. These patients showed an enrichment for TP53 aberrations and genomic complexity (i.e.,  $\geq 3$  aberrations). Retreatment with 12 cycles of ibrutinib/venetoclax led to second uMRD responses in 47%, while progression was only observed in one patient (5%). The authors concluded that treatment cessation with MRD-guided reinitiation is a feasible approach in patients with relapsed/refractory CLL who have achieved uMRD after 15 cycles of induction treatment.

#### Zanubrutinib in patients intolerant to BTK inhibitors

Zanubrutinib has been designed to maximize BTK occupancy and minimize off-target kinase binding and associated AEs [16]. Patients with B-cell malignancies who are intolerant of other BTK inhibitors are being treated with zanubrutinib in the ongoing, single-arm, phase II BGB-3111-215 study. Cohort 1 is intolerant of ibrutinib (n=44), while Cohort 2 shows intolerance of acalabrutinib (n=9)or both ibrutinib and acalabrutinib (n=8). Previously published results have demonstrated that zanubrutinib is effective and well tolerated in this setting [17]. At ICML 2023, Shadman et al. reported preliminary longer-term findings in patients with CLL/SLL after a median follow-up of 28.2 and 10.1 months in Cohorts 1 and 2, respectively [18]. In both cohorts, >65% of patients remained on treatment. The median zanubrutinib treatment duration was 27.1 and 8.1 months, respectively.

With zanubrutinib, 68.4 % of ibrutinibintolerance AEs and 71.4 % of acalabrutinib-intolerance AEs did not recur. No intolerance AE recurred with increased severity; among those that did recur, 73.3 % of ibrutinib-intolerance AEs and 33.3 % of acalabrutinib-intolerance AEs recurred at lower grades. The most common grade  $\geq$ 3 treatment-emergent AE (TEAE) on zanubrutinib was neutropenia (11.5 %). TEAEs leading to dose interruption and reduction occurred in 49.2 % and 24.6 %, respectively.

In terms of efficacy, the analysis revealed an ORR of 71.9% and a disease control rate of 94.7% across both cohorts. At 12 months, 88.3% of patients were progression-free. In their summary, the authors concluded that ibrutinib- and acalabrutinib-intolerant patients are likely to benefit from a switch to zanubrutinib, which appears to be a viable option in this setting.

### HRQoL data from the ALPINE study

Zanubrutinib 160 mg BID (n=327) was compared to ibrutinib 420 mg OD (n=325) until progression in patients with relapsed/refractory CLL/SLL in the randomized, open-label phase III ALPINE study. At the time of the final PFS analysis, zanubrutinib was significantly superior to ibrutinib regarding PFS (HR, 0.65; p=0.0024) and ORR (86.2% vs. 75.7%; p=0.0007) [19]. Eichhorst et al. presented data on health-related quality of life (HRQoL), which was a secondary objective of the study, at EHA 2023 [20]. Patientreported outcomes were assessed using the EORTC QLQ-C30 questionnaire and the EuroQoL visual analog scale (EQ-VAS).

Global health status as well as physical and role functioning improved in both arms from baseline to both cycle 7 and 13. All improvements were clinically meaningful for the zanubrutinib arm, although no clinically meaningful differences resulted across the two arms by cycle 13. Regarding the symptom scales, both arms showed decreases in fatigue and pain (Figure 4). Zanubrutinib gave rise to clinically meaningful improvements for both of these symptoms at cycles 7 and 13. For diarrhea, zanubrutinib-treated patients experienced more pronounced improvement, although this difference did not reach the predefined clinically relevant threshold. The mean change from baseline in the EQ-VAS demonstrated a similar pattern of improvement with both agents up to cycle 13.

Overall, the data suggested that treatment with zanubrutinib improved HRQoL over time, although the differences were not significant given the generally good HRQoL at baseline in both arms. Long-term follow-up and additional analyses linking patient-reported endpoints to clinical outcomes will further determine the effect of zanubrutinib on HRQoL.

### Findings in the Chinese subgroup of ALPINE

Patients included in the ALPINE study were stratified by geographical region. Qiu et al. reported a descriptive analysis of the prespecified subgroup from China that included 90 patients 47 of whom were treated with zanubrutinib [21]. At a



Figure 4: Mean changes in EORTC QLQ-C30 symptom scales from baseline at cycle 7 with zanubrutinib vs. ibrutinib

median follow-up of 25.3 months, zanubrutinib, as compared to ibrutinib, significantly improved PFS, with 18-month rates of 88.9% vs. 71.6% (HR, 0.24; p = 0.002). In the high-risk group featuring del(17p)/TP53 mutation, the patients in the experimental arm derived a 49% risk reduction (18-month PFS rates, 80.0 % vs. 64.3 %; HR, 0.51). ORR also favored zanubrutinib (87.2% vs. 76.7%). The efficacy results were consistent with those from the global population. Zanubrutinib showed a favorable safety profile, with lower treatment discontinuation rates compared to ibrutinib (14.9% vs. 41.9%), as well as lower rates of grade  $\geq 3$  AEs (64.4% vs. 72.1%) and serious AEs (35.6% vs. 51.2%).

### Resistance mechanisms to pirtobrutinib

Patients receiving covalent BTK inhibitors (cBTKi) frequently discontinue treatment due to progression or intolerance [22-24]. BTK cysteine 481 substitution has been found to contribute to acquired cBTKi resistance in the context of treatment with ibrutinib, acalabrutinib and zanubrutinib [25, 26]. Non-covalent BTK inhibitors use a different BTK-binding mechanism that might provide benefit in cBTKi-resistant patients [27]. The noncovalent BTK inhibitor pirtobrutinib has been shown to inhibit both wildtype and C481-mutant BTK with equal low nM potency [28, 29]. Brown et al. investigated the genomic evolution and resistance to pirtobrutinib in cBTKi-pretreated CLL patients enrolled in the phase I/II BRUIN study (n=279) [30]. Next-generation sequencing results for paired baseline

and progression samples were available from 49 patients who progressed on pirtobrutinib.

The most common mutations at baseline were found in BTK (51%), TP53 (49%), ATM (27%), NOTCH1 (20%), SF3B1 (18%), and PLCG2 (10%). A total of 31 BTK mutations in 25 patients were detected at baseline, including C481S (n=23), C481R (n=4), C481Y (n=2), C481F (n=1), and T474I (n=1). At the time of progression on pirtobrutinib, acquired mutations tended to be non-C481 BTK mutations, with the gatekeeper T474 and kinase-impaired L528 mutations representing the greatest proportion (Figure 5). Approximately half of progressing patients had not acquired BTK mutations or any mutations at all, which suggests alternate resistance mechanisms.

In 24%, acquired non-C481 mutations observed at disease progression had pre-existed at low variant allele frequencies of 1-3% at baseline; this is indicative



Figure 5: Pattern of acquired resistance mutations to pirtobrutinib

of emergence on prior cBTKi treatment. C481 clones decreased or disappeared in 92 % of patients. Pirtobrutinib displayed efficacy regardless of the type of prior cBTKi as well as baseline and acquired *BTK* mutations, with ORRs ranging from 83 % to 92 % across several groups with different acquired *BTK* mutations.

#### Treatment persistence and surrogate trial endpoints

Persistence with oral therapy is a wellrecognized factor for the efficacy of treatment [31-33]. Real-world insights regarding persistence with oral BTK inhibitors and the impact of comorbidities on this factor in Swedish patients with CLL/SLL were presented at EHA by Nevalainen et al. [34]. The analysis was based on pseudonymized data collected in the National Prescribed Drugs Register and the National Patient Register from January 2017 to December 2021.

The researchers identified patients with CLL (n=1,425) and SLL (n=115) who had received new prescriptions of oral CLL drugs for continuous use. Prescription data related to ibrutinib, acalabrutinib, idelalisib, and venetoclax. Among these, ibrutinib was prescribed for the majority of cases (87%), with a median treatment time of 1.4 years. Venetoclax was the second most commonly prescribed drug, followed by acalabrutinib and idelalisib. The most common change in treatment was from ibrutinib to venetoclax, the second most common from ibrutinib to acalabrutinib.

With respect to drug persistence, the analysis revealed 36-month rates of 50% and ≤ 10% for ibrutinib and idelalisib, respectively. The 50% persistence for idelalisib was reached at approximately 10 months. For acalabrutinib, the follow-up was very short; at 9 months, the persistence rate was 92%. Comorbidities that mostly included infections and cardiovascular disease were present in 62% of patients at the time of or after their first prescription. While the presence of both infections and cardiovascular disease significantly increased the likelihood of ibrutinib discontinuation, venetoclax discontinuation was more likely in the context of infections but not in the context of cardiovascular disease. For acalabrutinib and idelalisib, no statistically significant difference was seen among any of the comorbidity groups. The authors concluded that for CLL patients treated with an oral drug for continuous use, persistence with therapy may reflect adherence and possibly function as a proxy for PFS.

Bahar et al. conducted a systematic literature review of 69 randomized controlled trials to evaluate the validity of ORR as a surrogate endpoint for PFS and OS, and PFS as a surrogate endpoint for OS in CLL, in light of the need to identify surrogate outcomes that can be measured earlier in clinical trials than the true endpoints [35]. Indeed, the scientists

found robust evidence that ORR serves as a surrogate for PFS in CLL, especially when evaluating the treatment effect of BTK inhibitors. Some evidence was obtained for an association between PFS and OS, while no clear evidence of ORR as a surrogate for OS emerged.

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### Follicular lymphoma: study results with bispecific antibodies and BTK inhibitors

#### Mosunetuzumab: CR at EOT

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL) subtype [1]. In general, it remains incurable with standard therapies, and most patients experience multiple relapses over time. Therefore, there remains a great need for innovative new regimens such as the first-in-class CD20xCD3 T-cell-engaging bispecific antibody mosunetuzumab that is being tested in a pivotal phase II trial in patients with relapsed/refractory grade 1-3a FL after  $\geq 2$  lines of therapy (including an anti-CD20 antibody and an alkylating agent). Mosunetuzumab Q3W is administered intravenously for a fixed period: patients achieving complete remission (CR) after 8 cycles discontinue their treatment at that time, while those with partial remission or disease stabilization can receive another 9 cycles for a total of 17 cycles. Indeed, mosunetuzumab has been shown to induce a high CR rate and durable responses [2]. Cytokine release syndrome (CRS) was reported as the most common AE, although this was predominantly grade 1 or 2.

At ICML 2023, Sehn et al. presented an update after a median follow-up of 28.3 months for 90 patients, with a focus on individuals who achieved CR by the end of treatment (EOT) [3]. Most patients (82%) received 8 or fewer cycles. Fifty-four (60%) obtained CR as best response; at EOT, CR was present in 49 individuals (54%). Among the remaining five patients, one with CR developed disease progression in cycle 8, while the other four achieved CR only after EOT due to delayed bone marrow confirmation.

The 49 patients in a confirmed CR at the EOT had durable responses. Median duration of response (DOR) had not been reached yet in this group at data cutoff. At 24 months, 100% of patients were alive, 65% retained CR, and 77% were progression-free. The time to first CR did not affect the outcomes, as patients with early CR (by month 3) and late CR (after month 3) showed similar results for DOR, progression-free survival (PFS), and overall survival (OS; **Table**). In contrast, patients with partial remission as best response fared considerably worse regarding these endpoints.

An exploratory analysis revealed no correlation between total metabolic tumor volume (TMTV) at baseline and best overall response. Importantly, many patients who achieved CR had a high TMTV at baseline. Moreover, the researchers sought to determine factors conferring an increased likelihood of grade  $\geq 2$  CRS. These data suggested more frequent grade  $\geq 2$  CRS rates in patients with bone or bone marrow disease at baseline compared to those without (33.3 % vs. 13.8 %).

### First pivotal results for odronextamab

Novelli et al. reported first interim results from the open-label, pivotal phase II ELM-2 study investigating the CD20xCD3 bispecific antibody odronextamab [4]. ELM-2 contains five disease-specific cohorts for different types of relapsed/refractory B-NHL. The FL cohort includes patients with grade 1-3a FL who are refractory to or relapsed after  $\geq$  2 prior lines of therapy including an anti-CD20 antibody and an alkylator. Odronextamab 160 mg is administered intravenously Q2W after step-up dosing in cycle 1 and 3 doses on days 1, 8 and 15 in cycles 2–4, with 21 days per cycle. The step-up regimen had to be optimized in the course of the study to further mitigate the CRS risk; approximately half of the study population received the 1/20/80 mg regimen, while the other half was treated with the 0.7/4/20 mg regimen. The latter included 0.7 mg on days 1/2, 4 mg on days 8/9, and 20 mg on days 15/16 of cycle 1. In cycles 2–4, 80 mg were administered on days 1, 8 and 15. Objective response rate (ORR) by independent central review is defined as the primary endpoint.

In this heavily pretreated population (n=131), 30.5% of patients had previously undergone autologous stem cell transplantation, 43.5% were double refractory to an anti-CD20 antibody and an alkylator, and almost half had experienced progression within 24 months of starting first-line treatment (POD24). In spite of these high-risk characteristics, the ORR was 81.8%, with 75.2% of patients achieving CR. High response rates were observed across high-risk subgroups; also, ORR and CR rates were similar regardless of the type of step-up regimen administered in cycle 1. Also, responses appeared durable, with median duration of CR of 20.5 months and a median PFS of 20.2 months. Median OS

#### TABLE

Time-to-event outcomes with mosunetuzumab for early or late complete remission, or partial remission as best response

	Early complete remission (n = 33)	Late complete remission (n = 21)	Partial remission as best response (n = 16)
Median duration of response, months (95 % CI)	NE (23.2-NE)	NE (22.8-NE)	4.0 (2.5-6.7)
24-month DOR rate, % (95 % CI)	67.8 (43.5-92.0)	66.1 (39.3-93.0)	NE
Median progression-free survival, months (95 % Cl)	NE (26.3-NE)	NE (24.0-NE)	5.4 (4.1-11.8)
24-month PFS rate, % (95 % CI)	79.2 (64.1-94.2)	65.1 (37.7-92.5)	NE
Median overall survival,	NE (NE-NE)	NE (32.3-NE)	NE (NE-NE)
24-month OS rate, % (95 % Cl)	100 (100-100)	100 (100-100)	78.8 (56.9-100)

NE, not estimable

had not been reached yet at the time of the analysis. The 18-month PFS and OS rates were 55.3 % and 76.3 %, respectively.

With the optimized step-up regimen, odronextamab had a generally manageable safety profile. CRS events as the most common treatment-related AEs occurred in 55.7% but were predominantly lowgrade and mainly emerged during cycle 1. No immune effector cell-associated neurotoxicity syndrome or tumor lysis syndrome emerged in the group treated with the optimized step-up strategy. Three treatmentrelated grade 5 AEs were reported. The incidence of AEs leading to treatment discontinuation was low at 7.6%.

In their summary, the authors pointed out that these first results from the pivotal phase II trial of odronextamab demonstrate a new benchmark for efficacy in heavily pretreated, relapsed/refractory FL. Randomized, controlled phase III studies will be initiated in earlier lines of treatment.

### Epcoritamab according to POD24 status

The CD3xCD20 bispecific antibody epcoritamab, which is administered subcutaneously, is being assessed in addition to rituximab and lenalidomide (R<sup>2</sup>) in the ongoing phase Ib/2 EPCORE NHL-2 trial. Patients with relapsed/refractory CD20positive FL grade 1-3a and stage II-IV disease are receiving two different schedules of epcoritamab 48 mg (arms 2a and 2b) for up to 2 years in combination with R<sup>2</sup> in cycles 1-12. The first pooled analysis of arms 2a and 2b was presented at the ASCO 2023 Congress by Merryman et al. [5]. Many of the 111 enrolled patients had high-risk features, such as POD24 (n = 42), primary refractory disease (n=38), refractoriness to prior anti-CD20 therapy (n = 48), double refractory disease (n=37), and FLIPI 3-5 (n=64). Only 21 patients did not fall into any of these categories. In patients experiencing POD24, no standard of care has been established to date, as current therapeutic options provide suboptimal clinical results [6-8].

Within the efficacy-evaluable cohort (n=104), the ORR was 98%, and 87% of patients achieved a complete metabolic response (CMR). These response rates were higher than the ORR and CMR obtained with the immediate prior line of therapy (85% and 58%, respectively). Moreover, the analysis revealed consist-



Figure 1: Complete and partial metabolic responses with epcoritamab plus R<sup>2</sup> in various subgroups

ently high CMR and partial metabolic response rates across all high-risk subgroups including those with POD24 (**Figure 1**). Median duration of CR and median PFS had not been reached in the overall and POD24 populations.

Epcoritamab plus R<sup>2</sup> displayed a manageable safety profile that was consistent with previous reports. CRS events occurred in a predictable manner, were primarily low-grade, and all of them resolved. No clinical tumor lysis syndrome events were observed. Combination regimens containing epcoritamab are being assessed in the randomized, phase III EP-CORE FL-1 study (NCT05409066) and in a POD24 cohort in the EPCORE NHL-2 trial (NCT04663347).

#### ROSEWOOD: zanubrutinib + obinutuzumab

The second-generation BTK inhibitor zanubrutinib is being tested in the randomized phase II ROSEWOOD trial. Patients with grade 1-3a relapsed/refractory FL after  $\geq 2$  lines of treatment including an anti-CD20 antibody and an alkylating agent were randomized to receive zanubrutinib plus obinutuzumab (n=145) versus single-agent obinutuzumab (n=72)until disease progression. The trial previously met its primary endpoint of ORR by independent review (68.3% vs. 45.8%; p=0.0017) [9]. Updated findings presented at ICML 2023 after a median follow-up of 20.2 months showed significant benefits of the combined treatment in terms of ORR (69.0 % vs. 45.8 %; p=0.0012) and CR (39.3 % vs.19.4 %; p=0.0035) [10]. Median DOR had not been reached in the experimental arm and was 14.0 months in the control arm. Likewise, median duration of CR had not been reached and was 26.5 months, respectively. At 18 months, 69.3 % vs. 41.9 % of patients had responded, and 87.4 % vs. 51.1 % had a CR. The combination showed consistent ORR benefit across all prespecified subgroups. Furthermore, significant superiority of zanubrutinib plus obinutuzumab was demonstrated for PFS (28.0 vs. 10.4 months; HR, 0.50; p=0.0007) and time to next anti-lymphoma treatment (not reached vs. 12.2 months; HR, 0.34; p<0.0001; **Figure 2**). Regarding OS, the analysis demonstrated a trend favoring the combination (not reached vs. 34.6 months; HR, 0.62; p=0.0845).

No unexpected safety findings emerged with the prolonged follow-up. Diarrhea and fatigue were the most common AEs in the experimental arm, while pyrexia and infusion-related reactions occurred more frequently with obinutuzumab alone. Among grade ≥3 non-hematologic treatment-emergent AEs, pneumonia was reported most commonly (9.8% vs. 4.2%). Median treatment exposure for zanubrutinib plus obinutuzumab was twice that for obinutuzumab monotherapy (12.2 vs. 6.5 months). After adjustment for exposure, the incidence rates of treatment-emergent AEs of special interest were similar for both arms with the exception of any-grade hemorrhage (2.4 vs. 1.3 persons/100 person-months).

According to the authors, zanubrutinib plus obinutuzumab might represent a potential novel combination therapy for patients with relapsed/refractory FL. The global, randomized, open-label, phase III MAHOGANY study is currently investigating zanubrutinib plus obinutuzumab *versus* lenalidomide plus rituximab in patients with relapsed/refractory grade 1-3a FL after  $\geq 1$  prior treatment line that included an anti-CD20 agent



Figure 2: Time to next anti-lymphoma treatment for zanubrutinib plus obinutuzumab vs. obinutuzumab alone

(NCT05100862) [11]. MAHOGANY contains two independent cohorts for patients with relapsed/refractory FL and marginal zone lymphoma.

### First-line rituximab with or without ibrutinib

The randomized, double-blind phase II SAKK35/14 trial explored chemotherapyfree frontline treatment with ibrutinib 560 mg OD (n = 94) or placebo (n = 98) for 24 months in addition to 16 administrations of rituximab in patients with advanced FL who required therapy. Need of treatment was defined as  $\geq 1$  of several criteria including B symptoms, clinically significant progression over  $\geq 6$  months, and bulky disease  $\geq 6$  cm in long diameter, among others.

CR at 24 months according to independent review constituted the primary objective. After a median follow-up of 42 months, this endpoint was not met (40% vs. 36%; OR, 0.80; p=0.233) [12]. However, ibrutinib plus rituximab performed significantly better than rituximab alone with regard to the ORR rate at 24 weeks (73% vs. 59%; p = 0.046). In the ibrutinib arm, there were trends toward improved PFS (3-year rates, 45% vs. 37%; p = 0.056) and time to next treatment (not reached vs. 41.2 months; p=0.099). At 3 years, 96% of patients were alive in both arms.

As expected, the combined regimen conferred increased toxicity. Among grade  $\geq$  3 AEs, neutropenia (14% vs. 8%), hypertension (5% each) and skin rash (10% vs. 5%) were most common. According to the authors, the improvements in secondary endpoints observed with ibrutinib plus rituximab indicate a potential clinical benefit that could be further explored. Moreover, the very good OS in both arms supports the current use of rituximab as a therapeutic partner in clinical trials of novel combinations.

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## Outcome improvements in relapsed and untreated marginal zone lymphoma

#### **Final analysis of MAGNOLIA**

Systemic treatment for patients with advanced marginal zone lymphoma (MZL) is often based on regimens used in follicular lymphoma, although new agents and combinations are called for. As MZL depends on B-cell receptor signaling, treatment with BTK inhibitors is being investigated in clinical trials. The multicenter, open-label, single-arm, phase II MAGNOLIA study was initiated to assess the potent and highly specific next-generation BTK inhibitor zanubrutinib 160 mg BID as monotherapy in patients with relapsed/refractory MZL after ≥1 CD20directed regimen. Overall response rate (ORR) by independent review constituted the primary endpoint, which was met at the primary analysis after a median follow-up of 15.7 months [1]. At EHA 2023, Opat et al. presented the final analysis of MAGNOLIA after a median follow-up of 28 months [2]. A total of 68 patients had been enrolled 34 of whom were still receiving zanubrutinib.

The ORR by independent review was 68%, with 26% of patients experiencing complete response (CR). All MZL sub-types (i.e., extranodal, nodal, splenic) showed high ORRs, with the highest ORR observed in patients with nodal MZL and the highest CR in those with extranodal MZL (**Figure 1**). Responses resulted in all key subgroups including difficult-to-treat cohorts. At 24 months, 86% of pa-

tients were alive, and 71% were progression-free. For duration of response, the 24-month rate was 73%. Durable disease control was achieved in all three MZL subtypes.

Zanubrutinib was generally well tolerated. Treatment-emergent adverse events (TEAEs) of clinical interest mainly included infections (56%) and hemorrhage (41 %), with grade  $\geq 3$  rates of 22 % and 1.5%, respectively. Cardiac TEAEs were rare; all-grade hypertension, atrial fibrillation/flutter and ventricular extrasystoles occurred in 4%, 3%, and 1.5%, respectively. The incidence of cardiac TEAEs was comparable to that observed in a pooled safety analysis of 10 clinical studies of zanubrutinib, and was lower than the rates reported for ibrutinib [3]. Overall, these data support the use of zanubrutinib in patients with relapsed/ refractory MZL.

### Comparisons of zanubrutinib with ibrutinib and rituximab

In the absence of head-to-head randomized controlled trials, matching-adjusted indirect comparisons were performed to estimate the comparative efficacy of zanubrutinib vs. ibrutinib and rituximab in the setting of relapsed/refractory MZL. The researchers obtained data for zanubrutinib from the MAGNO-LIA trial [1] and the phase I/II BGB-3111-AU-003 study [4]. Regarding ibruti-



Figure 1: Best overall responses achieved with zanubrutinib by MZL subtype. PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response nib and rituximab, the analyses were based on data from the phase II PCYC-1121 trial [5, 6] and the phase III CHRONOS-3 trial, respectively [7]. Propensity score models were employed to match baseline characteristics, and prognostic factors were ranked by clinical experts. Variables balanced in the basecase model included number of prior lines of treatment, MZL subtype, response to prior therapy, and age. Additional variables such as bulky disease, prior anti-CD20 therapy and bone marrow involvement were considered in the sensitivity analysis conducted for zanubrutinib vs. ibrutinib; for zanubrutinib vs. rituximab, this was not possible due to a lack of reporting of additional factors from CHRONOS-3. Nevertheless, the impact of each covariate was explored via a leave-one-out analysis for both comparisons. Logistic regression models for binary outcomes and Cox proportional hazard models for time-to-event outcomes were used to estimate relative treatment effects.

The matching-adjusted indirect comparison for zanubrutinib vs. ibrutinib showed that zanubrutinib gave rise to a significant reduction in the risk of progression (adjusted HR, 0.38; p=0.001) and a significantly higher ORR (OR, 2.37 according to the base-case model with all covariates; p<0.01) [8]. Overall survival (OS) was comparable between the two treatments, which matches expectations for indolent lymphomas (adjusted HR, 0.68; p=0.295), although point estimates favored zanubrutinib. The sensitivity analysis accounting for additional prognostic factors suggested that zanubrutinib and ibrutinib were comparable across all outcomes, owing in part to the low effective sample size for zanubrutinib in the expanded models, although point estimates were in favor of zanubrutinib.

Likewise, compared to rituximab, zanubrutinib therapy significantly reduced the risk of progression (adjusted HR, 0.29; p=0.003) [9] and conferred significantly higher probability of response (OR, 5.09 according to the basecase model with all covariates; p < 0.01). OS was again comparable for the two drugs, while point estimates were in favor of zanubrutinib.

### MALIBU: ibrutinib plus rituximab

In the untreated setting, the phase II IELSG47/MALIBU trial is aiming to assess the combination of ibrutinib and rituximab in patients with extranodal MZL. Moreover, a limited number of nonextranodal cases was included for a preliminary exploration of the safety and activity of ibrutinib plus rituximab in these subtypes, where data are lacking to date. The splenic and nodal MZL cohorts contained 30 and 15 patients, respectively. Thieblemont et al. presented the findings for these subgroups at ICML 2023 after a median follow-up of 23 months [10]. This is the first report for rituximab plus ibrutinib in the first-line setting of MZL. Rituximab was administered for a total of 8 infusions together with ibrutinib 560 mg OD for 2 years. The CR rate at 12 months and the progression-free survival (PFS) rate at 5 years constituted the two primary endpoints of the study.

At 12 months, the patients with splenic and nodal MZL showed CR rates of 42% and 80%, respectively. In the whole group, this amounted to a CR rate of 53%. The ORR in the entire cohort was 97%, with rates of 100% and 90% for splenic and nodal MZL, respectively. Best objec-



Figure 2: Duration of response observed with ibrutinib plus rituximab in patients with splenic and nodal marginal zone lymphoma

tive response rates did not differ from the remission rates achieved at 12 months. Median duration of response had not been reached in the group with splenic MZL and was 22.3 months for the patients with nodal MZL **(Figure 2)**. Similarly, the PFS results differed greatly across the cohorts. Patients with splenic MZL had a 2-year PFS rate of 86%, whereas this was 59% for nodal MZL. OS was identical and excellent in both groups.

The toxicity profile of the combination appeared acceptable, with no obvious differences between splenic and nodal MZL. In all patients, the most common AEs included musculoskeletal pain (all grades, 28.9%), injection site reactions (28.9%) and fatigue (17.8%). Drug-re-

lated AEs of specific interest were mainly neutropenia, diarrhea and cardiac events (i.e., hypertension, atrial fibrillation/flutter, ventricular extrasystoles). Two cases of grade ≥3 cardiac toxicity were reported. Lower-grade hemorrhage occurred in 3 patients in the overall group, while no grade  $\geq 3$  events emerged with respect to hemorrhage or infections. Dose reductions were predominantly due to ibrutinib-related AEs such as neutropenia, cardiac disorders, and musculoskeletal pain. In their summary, the authors pointed out that rituximab plus ibrutinib showed promising activity in both splenic and nodal MZL, although some differences were noted in terms of efficacy outcomes.

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### Waldenström macroglobulinemia: findings from ASPEN and BRUIN

#### ASPEN: HRQoL for zanubrutinib vs. ibrutinib

In the management of patients with Waldenström macroglobulinemia (WM), BTK inhibitors have changed the therapeutic landscape and are considered preferred treatment options for the first and later lines [1]. Compared to the first-in-class agent ibrutinib, the potent and irreversible BTK inhibitor zanubrutinib offers improved BTK selectivity that minimizes offtarget effects and toxicities [2]. Zanubrutinib 160 mg BID was compared with ibrutinib 420 mg OD until progression in the open-label, randomized, phase III AS-PEN trial in patients with relapsed/refractory or treatment-naïve WM harboring activating MYD88 mutations. Analyses have previously demonstrated deep and durable responses with zanubrutinib compared to ibrutinib, as well as an improved safety/tolerability profile [3, 4].

The investigators assessed health-related quality of life (HRQoL) exploratory endpoints via patient-reported outcome data based on the EORTC QLQ-C30 and the EQ-5D-5L visual analog scale. At EHA 2023, Tedeschi et al. reported the results for both the intent-to-treat (ITT) population and patients achieving very good partial response (VGPR) by cycle 25 [5]. The ITT population consisted of 102 vs. 99 patients treated with zanubrutinib vs. ibrutinib, while in the group with VGPR, 31 (38.2%) and 17 (25.3%) had received zanubrutinib and ibrutinib, respectively. Median time to VGPR was shorter with zanubrutinib (8.3 vs. 16.6 months). No patient in either arm achieved complete remission.

Both in the ITT population and the patients with VGPR by cycle 25, zanubrutinib therapy gave rise to clinically meaningful differences for diarrhea and nausea/vomiting at cycle 4 as the symptom scores remained stable in the experimental arm but showed initial worsening in the ibrutinib arm (Figure). Regarding other endpoints, the differences were not significant, with both arms showing improvements. In the



Figure 1: Least-squares mean change from baseline in the fatigue symptom score with zanubrutinib vs. ibrutinib (population with very good partial response by cycle 25)

group of patients with VGPR, the zanubrutinib-treated cohort generally experienced greater functional and symptomatic improvements than the ibrutinib group. Differences for physical functioning and fatigue were clinically meaningful at cycles 7 and 25.

According to the authors, the improved HRQoL seen at cycle 25 in the zanubrutinib-treated VGPR group is consistent with the shorter median time to VGPR and suggests that when the disease is controlled to a similar extent, patients on zanubrutinib fare better in terms of overall HRQoL than those on ibrutinib. Moreover, the EQ-5D-5L visual analog scale analysis showed that improvements from baseline were consistently greater in the zanubrutinib arm both in the ITT and VGPR populations. Overall, these findings support the use of zanubrutinib as an effective BTK inhibitor therapy option in patients with WM.

#### Pirtobrutinib: BRUIN study

Progression and intolerance frequently necessitate discontinuation of covalent BTK inhibitor therapy with ibrutinib, leaving the patients with an unfavorable prognosis [6-9]. The highly selective, noncovalent (reversible) BTK inhibitor pirtobrutinib has been designed to inhibit both wildtype and C481-mutant BTK with equal low nM potency and has favorable oral pharmacology that enables continuous BTK inhibition throughout the dosing interval regardless of the intrinsic BTK turnover rate, thus likely defying resistance mechanisms to BTK inhibition [10, 11].

The phase I/II BRUIN study is evaluating pirtobrutinib in various B-cell malignancies including WM (n=80); this cohort contains 63 patients pretreated with covalent BTK inhibitors (cBTKi) as well as 17 cBTKi-naïve individuals. The median number of prior lines of systemic therapy in these two groups is 3 and 2, respectively. Chemotherapy has been administered in 83% and 100%, respectively, and anti-CD20 antibody treatment in 92% and 94%, respectively. Scarfò et al. presented efficacy and safety results at EHA 2023 [12].

The major response rates for cBTKipretreated and cBTKi-naïve patients were 66.7% and 88.2%, respectively. Although no complete remissions emerged, the cBTKi-pretreated group achieved a notable VGPR rate of 23.8%. In this cohort, median overall survival had not been reached yet, and progression-free survival was 19.4 months. At 18 months, 57.1 % of patients were alive and progression-free. Patients who were cBTKi-naïve achieved a VGPR rate of 29.4 %.

In the safety population of the BRUIN study (n = 773), treatment-related adverse events mainly included bruising (all grades, 15.1%), neutropenia (14.7%) and

contusion (12.8%), with few grade  $\geq 3$ events. The safety profiles in the overall and WM populations were generally consistent. cBTKi-associated side effects such as hemorrhage, hypertension and atrial fibrillation/flutter were infrequent. Discontinuations and dose reductions

due to treatment-related adverse events occurred in 2.6% and 4.5% of all patients, respectively. As the authors noted, pirtobrutinib showed promising efficacy in this heavily pretreated relapsed/refractory WM patients and continued to be well-tolerated.

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### **DLBCL: treatment of elderly patients and relapsed disease**

#### **POLAR BEAR:** novel regimen from the age of 75

Overall survival has improved considerably in the setting of diffuse large B-cell lymphoma (DLBCL). However, patients above the age of 80 years are an exception in terms of survival prolongation and therefore face an unmet clinical need [1]. At the same time, this is a group that constitutes an increasing proportion of DLBCL patients. The current treatment standard in elderly patients with DLBCL is rituximab plus miniCHOP (R-miniCHOP) [2]. Innovative approaches include the combination of rituximab with the antibody-drug conjugate polatuzumab vedotin and the modified chemotherapy regimen miniCHP that is administered without vincristine (R-pola-miniCHP). The ongoing randomized phase III POLAR BEAR trial is comparing 6 courses of R-pola-miniCHP with 6 courses of R-miniCHOP in patients aged  $\geq$  80 years or frail patients aged 75-80 years with DLBCL, which also includes transformation from indolent lymphoma, or other types of high-risk B-cell lymphoma. Progression-free survival (PFS) has been defined as the primary endpoint.

The safety data presented at EHA 2023 related to 140 patients the majority of whom had DLBCL (87.5% and 92.4% in the R-pola-miniCHP and R-miniCHOP arms, respectively) [3]. Adverse events (AEs) in both arms were mainly categorized as "other", as these could not be classified further; here, grade 1 and 2 events occurred more commonly with R-pola-miniCHP than with R-miniCHOP. Infections and gastrointestinal AEs ranked second and third, respectively. The majority of all AEs were grade 1 or 2, and the safety profiles were largely comparable across the two study arms. Grade  $\geq$  3 anemia was more common in the experimental arm (14% vs. 2.8%), as

was gastrointestinal toxicity of all grades (55% vs. 31%) and of grade  $\geq$ 3 (30% vs. 17%). Infections occurred somewhat more frequently with R-pola-miniCHP (57% vs. 45%), while the grade  $\geq$  3 infection rates did not differ across the arms (16 % vs. 14 %). In contrast, cardiovascular AEs were observed more commonly with the comparator regimen (23% vs. 30%). The rates for grade 1 peripheral neuropathy were similar for both regimens (13% vs. 9.9%). Gastrointestinal toxicity mostly consisted of diarrhea, which predominantly occurred early on during the treatment (Figure 1).

After a median follow-up of 1.1 years, median PFS had not been reached in the



Figure 1: Grade 2-5 gastrointestinal toxicity in the POLAR BEAR trial

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pooled population. At 2 years, the PFS rate was 65%. Further analyses assessed potential associations between PFS and age (<80 years, 80-85 years, >85 years) as well as the degree of comorbidity (CIRS-G < 10, CIRS-G  $\geq$  10) but found no impact of these factors on PFS. The authors concluded that both R-pola-miniCHP and R-miniCHOP are tolerable in elderly patients with DLBCL, with encouraging early pooled efficacy data for the novel combination.

#### Odronextamab in the relapsed/ refractory setting

Approximately one third of DLBCL patients ultimately develop relapsed/refractory disease, which remains a major cause of mortality [4]. This raises a significant unmet need for effective off-theshelf therapies, especially in patients who have no access to or are ineligible for treatment options such as CAR T-cell therapy or high-dose therapy/stem cell transplantation. The CD20xCD3 bispecific antibody odronextamab is investigated as single agent in patients with relapsed/refractory B-cell non-Hodgkin lymphoma in the pivotal open-label, multicohort, phase II ELM-2 trial. First interim results for the DLBCL cohort (n = 140) were reported at EHA 2023 by Walewski et al. [5].

The patients have received  $\geq 2$  lines of pretreatment including an anti-CD20 antibody and an alkylator. In 90.7%, the disease is refractory to any prior line of therapy, and 65.7% of patients show double refractoriness to an alkylator/anti-CD20 antibody treatment in any line. Odronextamab is administered i. v. with step-up in cycle 1 followed by 160 mg on days 1,8 and 15 in cycles 2-4 and 320 mg Q2W from cycle 5 onwards until progression. During the study, the step-up in cycle 1 was modified from a 1/20 mg regimen to a 0.7/4/20 mg regimen to further mitigate the risk of cytokine release syndrome (CRS). The objective response rate (ORR) by independent central review is defined as the primary endpoint.

Clinically relevant antitumor activity of odronextamab was observed in this heavily pretreated, highly refractory population. The ORR was 49.2%, and complete responses (CRs) occurred in 30.8%. Responses were durable, with an 18-month PFS rate of 26.0% and median duration of CR of 17.9 months. Consistent ORR and CR rates resulted at 12 weeks irrespective of the type of step-up regimen in cycle 1. Patients with prior CAR T-cell therapy who had enrolled in the phase I dose expansion cohort were analyzed separately (n=31). Similar to the overall population, they showed ORR and CR rates of 48.4% and 32.3%, respectively. Median duration of CR had not been reached in this group at the time of the analysis.

Odronextamab generally exhibited a manageable safety profile with the optimized 0.7/4/20 mg step-up regimen that reduced the rate of grade 3 CRS events to 1.4%. Approximately half of patients developed CRS that was mostly grade 1. No grade 4 or 5 CRS events were noted. Moreover, no cases of tumor lysis syndrome, infusion-related reactions or grade  $\geq 3$  immune effector cell-associated neurotoxicity syndrome emerged with the optimized step-up treatment. Any-grade infections were reported in 58.9%; the majority of these were grade 1 or 2 (32.9%), although grade 5 events occurred in 9.6%. Discontinuation was due to treatment-related AEs in 7.9%. Randomized controlled phase III trials will be initiated to further investigate odronextamab in earlier lines of treatment.

### Zanubrutinib plus lenalidomide: phase I data

The BTK inhibitor zanubrutinib in addition to lenalidomide is tested in Chinese patients with relapsed/refractory DLBCL after  $\geq 1$  prior treatment line and ineligibility for stem cell transplantation (if not received previously) in the ongoing openlabel phase I BGB-3111-110 study. Zanubrutinib 160 mg BID and lenalidomide 25 mg OD on days 1-21 per 28-day cycle were identified as the recommended part 2 dose (RP2D) in the dose escalation part [6]. At ASCO 2023, Zhang et al. presented the results of the interim analysis for a total of 46 patients included in the dose escalation and dose expansion parts of the study [7]. Thirty of them had received the RP2D. ORR constitutes the primary endpoint of the dose expansion phase.

The ORR was 45.7% overall, with CRs observed in 23.9%; at the RP2D, these rates were 56.7% and 30.0%, respectively **(Figure 2)**. Patients with the non-GCB subtype experienced higher CR rates than those with the GCB subtype in both the total group (28.1% and 16.7%, respectively) and the RP2D cohort (34.8% and 16.7%, respectively). The ORRs ranged from 46.9% to 60.9% across these groups.



Figure 2: Responses to zanubrutinib plus lenalidomide in the RP2D and total cohorts

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; DIS, discontinued prior to first treatment; RP2D, recommended part 2 dose

In the overall population, median duration of response had not been reached yet, and the 6-month event-free rate was 63.5%. Median PFS was 5.5 months, with a 9-month event-free rate of 31.1%.

Grade ≥3 treatment-emergent AEs occurred in 60.9% of patients. Most commonly, they consisted of hematologic toxicities such as neutrophil count decreases that were generally manageable across all dose levels. In the RP2D group, one patient (3.3%) had febrile neutropenia but recovered within 2 days. Treatmentemergent AEs that prompted discontinuation were observed in 8.7%. No fatal treatment-related events occurred. In their conclusion, the authors noted that zanubrutinib plus lenalidomide demonstrated an acceptable safety profile and promising efficacy. Further evaluation of this combination in a larger sample is planned.

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## Updates on BTK- and Bcl-2–targeted treatment in various B-cell malignancies

#### Ibrutinib plus CIT: SELENE trial

Survival outcomes typically deteriorate with repeated lines of chemoimmunotherapy (CIT) in patients with relapsed/ refractory non-Hodgkin lymphoma. The randomized, double-blind phase III SE-LENE trial was conducted to determine whether the addition of the BTK inhibitor ibrutinib to CIT in patients with relapsed/ refractory follicular lymphoma (FL) or marginal zone lymphoma (MZL) improves progression-free survival (PFS). CIT consisted of either bendamustine/ rituximab (BR) or R-CHOP. In the control arm, placebo was administered in addition to these regimens. Each arm contained 200 patients pretreated with  $\geq 1$ anti-CD20 CIT strategy. The majority had FL (86.1% in both arms), and 90% received BR as the backbone CIT. Nastoupil et al. presented the results of SELENE at ICML 2023 [1].

Ibrutinib plus CIT did improve PFS compared to CIT alone, although the primary study endpoint was not met (40.5 vs. 23.8 months; HR, 0.81; p=0.0922). In each arm, 28 patients had MZL; this group fared better with both regimens than the overall population. Median PFS by investigator had not been reached with ibrutinib plus CIT and was 91.6 months with placebo plus CIT in the MZL cohort (HR, 0.52; p=0.1118). The overall response rates (ORRs) did not differ across the study arms in the ITT population (91.6 % vs. 90.5 %), with complete responses observed in 55.0% vs. 50.2%. Similar ORRs and complete response rates were found in the MZL subgroup. Median duration of response in the overall population was longer with ibrutinib plus CIT than with CIT alone (44.3 vs. 21.7 months; Figure 1). Median OS had not been reached with either treatment. At 7 years, the OS rates did not differ across the arms (67.4% vs. 68.3%), with similar rates for the MZL cohort (76.6% vs. 68.5 %; HR, 0.69; p=0.4964).

The overall safety profile of ibrutinib plus CIT was consistent with the known profiles of the individual agents. Grade  $\geq 3$ 



Figure 1: Duration of response with ibrutinib vs. placebo plus chemoimmunotherapy

thrombocytopenia and anemia occurred more frequently with the ibrutinib-based therapy than with CIT alone (10.0% vs. 5.0% and 11.4% vs. 4.0%, respectively). Treatment-emergent AEs (TEAEs) leading to dose reduction were more common in the experimental arm (20.4% vs. 10.6%), as were TEAEs leading to discontinuation (30.8% vs. 18.6%). The authors concluded that the administration of ibrutinib resulted in additive toxicity but did not impact OS. Further analyses are required to define specific FL/MZL subgroups that might benefit from extended treatment with ibrutinib following CIT.

#### Zanubrutinib: pooled safety data

Continuous therapy with ibrutinib and acalabrutinib is effective in B-cell malignancies, although many patients discontinue treatment with these BTK inhibitors due to intolerance potentially caused by off-target kinase binding [2]. The nextgeneration BTK inhibitor zanubrutinib has been designed to maximize tolerability by minimizing off-target kinase binding [3]. Pooled safety analyses reported at ICML 2023 showed that zanubrutinib is well tolerated in patients with B-cell malignancies including chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), MZL, Waldenström macroglobulinemia (WM), FL, and other entities [4]. Data from 1,550 patients treated with zanubrutinib und 422 treated with ibrutinib were included.

Zanubrutinib-related TEAEs were generally mild to moderate; the most common grade ≥3 TEAEs were pneumonia (8.4%) and hypertension (8.1%). Compared with ibrutinib, exposure-adjusted incidence rates of AEs of special interest were numerically lower in head-tohead comparisons of the ASPEN/ALPINE study populations, with the exception of neutropenia. Exposure-adjusted incidence rates were significantly lower with zanubrutinib for atrial fibrillation and infections (p < 0.0001 and p = 0.0098, respectively). Hypertension tended to increase over time with ibrutinib, whereas it remained relatively stable with zanubrutinib. The prevalence of atrial fibrillation remained lower with zanubrutinib than with ibrutinib. Mortality due to cardiac events was lower with zanubrutinib (0.2% vs. 1.7%). Overall, these analyses support zanubrutinib as an appropriate long-term treatment option for patients with B-cell malignancies.

### Improved tolerability after BTKi and in the real world

Updated results from the phase II BGB-3111-215 study that investigated

zanubrutinib in patients with CLL/SLL, MCL, MZL or WM who were intolerant of ibrutinib (n=57) or acalabrutinib  $\pm$  ibrutinib (n=25) were reported by Shadman et al. at a median follow-up of 25.2 months [5]. According to this analysis, 67.7 % of ibrutinib-intolerance events and 73.0% of acalabrutinib-intolerance events did not recur on treatment with zanubrutinib. Among the events that did recur, none showed a higher grade; indeed, 75.0% and 40.0% in the two groups were classified as lower grade. Regarding the efficacy of zanubrutinib, the data showed that  $\geq$  95 % of the 76 efficacy-evaluable patients across cohorts obtained disease control, with  $\geq 65\%$ achieving partial remission, thereby maintaining or improving response compared to their previous treatment (Table). The safety profile observed during the longer follow-up was consistent with that previously reported for zanubrutinib. As the authors concluded, these longer-term outcomes suggest that patients who are intolerant of other BTK inhibitors can achieve clinical benefit by switching to zanubrutinib. Study enrollment and follow-up are ongoing.

These insights are in keeping with a retrospective observational real-world analysis assessing treatment patterns in patients with relapsed/refractory MCL who started BTK inhibitor therapy between January 2019 and November 2021 in 18 community oncology practices in the United States [6]. Among 402 patients, 44 received zanubrutinib, 161 acalabrutinib and 197 ibrutinib. Although

the zanubrutinib group had a relatively shorter mean follow-up than acalabrutinib and ibrutinib (493 vs. 701 and 746 days, respectively) given its later approval date, the zanubrutinib group showed significantly longer median duration of treatment (292 vs. 259 and 149 days, respectively; p < 0.01). Starting from >60 days, the adherence rates were generally higher for zanubrutinib than for the other two drugs. The discontinuation rate was lowest with zanubrutinib (43.2% vs. 51.6% and 45.2%, respectively). Further analyses on long-term utilization and outcomes are required upon data maturation.

#### Once-daily vs. twice-daily use

Zanubrutinib is administered at doses of 320 mg OD or 160 mg BID for the treatment of relapsed/refractory MCL, WM, MZL, and CLL/SLL. While both OD and BID doses were assessed in select phase I and II trials, only the BID dose has been used in pivotal clinical studies. Tam et al. reported a comparative summary of clinical data and exposure-response analyses between the two schedules across various B-cell malignancies at EHA 2023 [7]. A total of 216 patients from five studies examining zanubrutinib as monotherapy and in combination with obinutuzumab were identified.

The analysis showed that both 320 mg OD and 160 mg BID are safe and effective, with ORRs ranging from 54.2% to 100%. Also, comparable safety profiles were observed with both dosing schedules. Simi-

or acalabrutinib ± ibrutinib						
	lbrutinib intolerance (n = 56)	Acalabrutinib ± ibrutinib intolerance (n = 20)	Total (n = 76)			
Disease control rate, n (%)	54 (96.4)	19 (95.0)	73 (96.1)			
Overall response rate, n (%)	41 (73.2)	13 (65.0)	54 (71.1)			
Complete response	1 (1.8)	0 (0)	1 (1.3)			
Partial response	40 (71.4)	13 (65.0)	53 (69.7)			
Stable disease	13 (23.2)	6 (30.0)	19 (25.0)			
Progressive disease	1 (1.8)	1 (5.0)	2 (2.6)			
Time to best overall response, months	5.7	3.0	5.6			
Time to first overall response, months	3.0	2.9	3.0			

lar rates resulted with respect to grade  $\geq 3$  hemorrhage, grade  $\geq 3$  hypertension and grade  $\geq 3$  atrial fibrillation/flutter, as well as AEs leading to treatment discontinuation. No evident exposure-response relationships were noted between pharmacokinetic parameters (AUC,  $C_{max}$ ,  $C_{min}$ ) and efficacy endpoints or AEs of special interest across indications.

#### BTK protein degrader BGB-16673

Very little is known about resistance to BTK degraders such as the orally available chimeric degradation-activating compound BGB-16673 that is being investigated in two clinical phase I trials (NCT05006716 and NCT05294731). Feng et al. conducted N-ethyl-N-nitrosourea mutagenesis screening to characterize the profile and tendency of BGB-16673 to cause on-target BTK resistance mutations as compared with the non-covalent BTK inhibitor pirtobrutinib [8]. According to this analysis, BGB-16673 gave rise to fewer resistant clones and showed lower BTK mutation frequency than pirtobrutinib, demonstrating a unique ontarget resistance mutation profile. Also, BGB-16673 overcame all BTK resistance mutations from both covalent and noncovalent BTK inhibitor trials except A428D that was resistant to all BTK inhibitors (Figure 2). The new compound degraded BTK in the presence of the clinically relevant resistance mutations V416L, M437R, T474I, C481S, C481F, C481Y, and L528W. As the authors noted, BGB-16673 is a promising novel BTK degrader that could benefit patients who develop BTK inhibitor on-target resistance mutations.

These findings are supported by an analysis conducted based on cell lines and mouse xenograft models [9]. Here, BGB-16673 exhibited high potency on clinically relevant BTK mutants resistant to pirtobrutinib and the covalent BTK inhibitor ibrutinib in cancer cells. The BTK degrader drove complete tumor regression of the lymphoma xenograft models expressing wildtype or *BTK* mutations that were resistant to the BTK inhibitors. Responses to BGB-16673 lasted longer than those to ibrutinib and pirtobrutinib. Compared to these agents, long-term survival improved with BGB-16673, and metastatic tumor infiltration in spleens was diminished.

### Efficacy outcomes with zanubrutinib in patients intolerant to ibrutinib or acelabrutinib + ibrutinib

TABI F



Figure 2: Degradation of BTK mutants by the BTK protein degrader BGB-16673

#### **Optimized BcI-2 inhibition**

Bcl-2 inhibition with venetoclax has been established in the treatment of CLL/SLL, although the clinical utility of this drug can be limited by AEs and the development of resistance [10, 11]. BGB-11417, a potent and highly selective Bcl-2 inhibitor, has been designed with the potential to achieve deeper target inhibition and clinical responses [12, 13]. The ongoing phase I BGB-11417-102 study is evaluating BGB-11417 at doses of 80 mg, 160 mg, 320 mg and 640 mg OD in adults with relapsed/refractory B-cell malignancies. Cohort A includes patients with FL, MZL, DLBCL or transformed non-Hodgkin lymphoma, while Cohort B contains patients with CLL/SLL with low tumor burden. Daily and weekly ramp-up schedules were used in Cohorts A and B, respectively, to decrease the risk of tumor lysis syndrome. Li et al. presented the results for 34 and 23 evaluable patients

in Cohorts A and B, respectively, at ASCO 2023 [14].

BGB-11417 monotherapy, at all tested doses up to 640 mg, was well tolerated without dose-dependent increases in toxicity. Most TEAEs were grade 1 or 2. In 28.1 %, TEAEs necessitated dose modifications. The most common grade  $\geq 3$ TEAE was neutropenia (33.3%), followed by decreases in white blood cell counts (21.1%) and thrombocytopenia (19.3%). Dose-limiting toxicities were reported in three patients. No clinical tumor lysis syndrome events occurred.

In Cohort A, six patients (17.6%) achieved complete or partial responses. Complete remission was observed in two patients both of whom had DLBCL and were treated in the 640 mg cohort. In contrast, responses in Cohort B were observed already at lower dose levels, with 56.5% showing complete or partial response from 80 mg upwards. Most of these patients remained on study at the time of the analysis (87.0%), while this proportion was smaller in Cohort A (64.7%). Among nine MRD-evaluable patients in Cohort B, three had undetectable MRD. Further expansion data are being generated.

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### Expert interviews





**Paolo Strati** overviews how patient outcomes can be optimized with current therapies in relapsed or refractory diffuse large B-cell lymphoma in later lines and outlines which innovative approaches might become available in the long run for the treatment of R/R DLBCL. Finally, he explains what can be achieved today in patients with follicular lymphoma and high tumor burden and depicts his personal highlights from this year's EHA congress.

Philipp Staber explains the role of functional drug testing in the treatment of patients with hematologic diseases, shares the rationale of the EXALT-2 trial as well as his thoughts on future developments in the field of precision medicine. Finally, he gives insights in the current research topics of the EHA SWG-Precision Hematology and their goal for the next five years. Follow us on LinkedIn to get all our memo inOncology updates directly! Watch this space for our community channel for discussions and exchange with other oncologists and haematologists - coming soon!

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### **Forthcoming Special Issue**

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



## iwCLL 2023 Annual Meeting

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Alessandra Tedeschi gives insights into the health-related quality of life data from the ASPEN study conducted in patients with Waldenström macroglobulinemia, discusses the notable results from the extended followup of the SEQUOIA study in patients with treatment-naïve chronic lymphocytic leukemia as well as the clinical activity of zanubrutinib in the setting of R/R marginal zone lymphoma while finally depicting her personal highlights from this year's EHA congress.



Anna Schuh talks about genetic aberrations in subclones in terms of the molecular dynamics of relapse in patients with CLL, the benefits of liquid biopsies as well as the current role and future application of wholegenome sequencing in precision hematology while ultimately depicting her personal highlights from this year's EHA congress.

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