Springer Medizin

www.memoinoncology.com

03/23

memo – inHaematology SPECIAL ISSUE

Congress Report iwCLL 2023

A GLOBAL CONGRESS DIGEST ON CHRONIC LYMPHOCYTIC LEUKEMIA

Report from International Workshop on Chronic Lymphocytic Leukemia (XX iwCLL 2023), 6th–9th October, 2023, Boston, USA

IMPRESSUM/PUBLISHER

Media owner and publisher: Springer-Verlag GmbH, AT, 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.springer.at, www.SpringerMedizin.at. **Owner and Copyright:** © 2023 Springer-Verlag GmbH Austria, part of Springer Nature. **Managing Directors:** Joachim Krieger, Juliane Ritt, Dr. Alois Sillaber. **Medical Writer:** Judith Moser, MD. **Publishing Editor:** Anna Fenzl, PhD. **Layout:** Katharina Bruckner. **Published in Vienna. Produced in Linz. Printer:** Global-Print, Wien, Austria.

Table of Contents

Editorial Board:

Publishing editor: Anna Fenzl, PhD

Lecture Board for this issue: Nitin Jain, MD; Nadine Kutsch, MD; Kiyomi Mashima, MD, PhD; William F. Mawalla, MD; Constantine Tam, MD; Rachel Thijssen, PhD; Adrian Wiestner, MD, PhD.

Medical Writer for this issue: Judith Moser, MD

BeiGene

Supported by BeiGene in the form of an unrestricted grant

Preface

Dear Colleagues,
The 20th International Workshop on chronic lymphocytic leukemia (iwCLL) was held in Boston, USA, and virtually from 6th–9th October 2023. This conference featured 11 sessions committed to discussing the management of patients with CLL world-wide and to creating progress regarding patient outcomes.

In the treatment of CLL, targeted drugs are continuously gaining ground. Continuous use of Bruton tyrosine kinase inhibitors (BTKi) including ibrutinib, acalabrutinib, and zanubrutinib has significantly improved treatment standards. While these drugs are highly effective, especially in high-risk CLL, they usually do not eliminate leukemia entirely.

Thus, in the first chapter of this memo inHaematology special issue, the pros and cons of various first-line treatment options are outlined. Differences in toxicity profiles among BTK inhibitors allow for the tailoring of treatment and switching in case of intolerance. Recent studies have also been investigating the combination of BTK and BCL-2 inhibitors; this approach offers potential benefits regarding the emergence of resistance and tolerability. Additionally, the merits of time-limited doublet and triplet therapies in CLL are elaborated. Promising results from studies have been obtained on combinations involving ibrutinib, acalabrutinib or zanubrutinib with venetoclax and obinutuzumab, with second-generation BTK inhibitors giving rise to numerically higher uMRD rates compared to ibrutinib.

In chapter 2, long-term follow-up data on fixed-duration venetoclax plus rituximab (MURANO trial) and obinutuzumab plus acalabrutinib and venetoclax (CLL2-BAAG trial) in the relapsed/refractory setting are summarized, as well as study results on zanubrutinib plus obinutuzumab and venetoclax in previously untreated CLL patients (BOVen trial) and first-line zanubrutinib monotherapy in CLL patients unsuitable for chemoimmunotherapy (SEQUOIA trial). Health-related quality-of-life data from the ALPINE study and pooled safety data on zanubrutinib vs. ibrutinib are discussed.

Furthermore, this report delves into the complex world of resistance mechanisms to targeted inhibitors in the treatment of CLL, shedding light on subclonal mutations, primary resistance, and the role of critical signaling pathways. The emerging strategies of non-covalent BTK inhibition, BTK degradation, and alternative treatments like zanubrutinib for patients intolerant to other BTK inhibitors are outlined, providing valuable insights for clinicians and researchers.

Next, this report focuses on real-world CLL treatment insights from around the globe, such as evolving treatment trends in the USA, the efficacy of BTK inhibitors in China and the impact of hypertension on patient outcomes in Denmark.


© author's own

Last but not least, survey findings identifying gaps regarding unmet needs between low-/middle-income countries and high-income countries are discussed. As a remarkable example, the achievements of the iwCLL capacity-building program in Tanzania are highlighted.

The iwCLL 2023 once again provided an outstanding platform to display the dynamic advancements in global CLL care. In accordance with the iwCLL vision of a world where every CLL patient can be cured, I hope you enjoy reading this special issue!

Kiyomi Mashima MD, PhD
Medical Oncology, CLL Center, Dana-Farber Cancer Institute, Boston, MA, USA
Department of Medicine, Harvard Medical School, Boston, MA, USA

Continuous BTK inhibition and combination regimens: present and future

Agents of outstanding efficacy

Inhibitors of Bruton tyrosine kinase (BTK) have changed the standards of care in the setting of chronic lymphocytic leukemia (CLL). However, they do not eliminate leukemia, and undetectable residual disease is only very rarely achieved. Continuous treatment is therefore the standard approach, with the covalent BTK inhibitors ibrutinib, acalabrutinib and zanubrutinib being in widespread use as front-line single agents. Also, responses to BTK inhibition tend to deepen over time [1].

Kerry A. Rogers, MD, James Cancer Hospital and Solove Research Institute, Columbus, Ohio, USA, pointed out that these are highly effective therapies, even in the high-risk setting. The NCCN guidelines for CLL/SLL list acalabrutinib ± obinutuzumab and zanubrutinib as preferred first-line options, along with venetoclax/obinutuzumab, for patients with and without del(17p)/*TP53* mutations [2]. The outstanding efficacy of BTK inhibitors is demonstrated by tri-

TABLE
Pros and cons of various first-line treatment options

	Continuous BTK inhibitors	Venetoclax/obinutuzumab	Venetoclax/BTK inhibitors
Pros	+ Easy to start and take + Highly effective in *TP53*-disrupted disease	+ 1-year treatment duration + No cardiovascular side effects	+ Fixed duration + All-oral treatment
Cons	+ Indefinite duration + Cardiovascular and bleeding adverse events	+ Difficult to start (tumor lysis syndrome risk) + Unsuitable for patients with renal disease or unable to tolerate hydration + Anti-CD20 antibody has risks	+ Difficult to start (tumor lysis syndrome risk) + Unsuitable for patients with renal disease or unable to tolerate hydration

als such as the randomized E1912 study in which ibrutinib/rituximab outperformed the most effective chemoimmunotherapy regarding overall survival, reducing mortality by more than 50 % (HR, 0.47; p = 0.018) [3]. In the RESONATE-2 trial, ibrutinib monotherapy, as compared to chlorambucil, gave rise to a sustained significant progression-free survival (PFS) advantage, with 7-year PFS rates of 59 % vs. 9 % [1].

Outcome improvement in patients with *TP53* aberration

Importantly, BTK inhibitor treatment confers significant benefits in *TP53*-disrupted CLL. In the Alliance A041202 trial, ibrutinib ± rituximab induced superior PFS compared to bendamustine/rituximab (BR), which was independent of the presence of *TP53* abnormalities [4]. Fixed-duration treatment with venetoclax/obinutuzumab, on the other hand, did not abrogate the adverse effect of *TP53* aberrations, as was shown by the CLL14 study [5]. Dr. Rogers pointed out that these findings support continuous BTK inhibitor therapy as the preferred option for patients with *TP53*-disrupted CLL. Nevertheless, according to real-world data, the presence of del(17p) still affects the overall survival obtained with first-line ibrutinib, although these outcomes are certainly improved compared to the previous treatment standard of chemoimmunotherapy [6].

Another advantage of BTK inhibitors results from the possibility of combinations with anti-CD20 monoclonal antibodies. While BTK inhibition is continuous, anti-CD20 therapy is commonly restricted to 6 cycles. The choice of agents appears to make a difference. Rituximab plus ibrutinib did not improve PFS over ibrutinib alone in the Alliance A041202 trial [4], whereas obinutuzumab plus acalabrutinib was shown to increase PFS compared to acalabrutinib monotherapy in the ELEVATE-TN study (HR, 0.51; p = 0.0259) [7]. Moreover, the addition of obinutuzumab to acalabrutinib improved the undetectable MRD (uMRD) rate vs. acalabrutinib alone (42 % vs. 2 %), which raises the question of treatment discontinuation. However, as Dr. Rogers noted, further research is called for in this respect.

Specific toxicity profiles

Randomized comparisons across covalent BTK inhibitors in pretreated patients have revealed diverse results. While the ELEVATE-RR study did not show a significant PFS difference between ibrutinib and acalabrutinib [8], zanubrutinib prolonged PFS vs. ibrutinib in the ALPINE trial (HR, 0.65) [9]. In both ELEVATE-RR and ALPINE, the rates of atrial fibrillation/flutter were higher with ibrutinib than with the next-generation BTK inhibitors acalabrutinib and zanubrutinib. Hypertension occurred less commonly with acalabrutinib vs. ibrutinib. However, not all adverse events (AEs) are reduced with the newer drugs; for bleeding events, the reduction is unclear, and specific AEs such as headache for acalabrutinib and neutropenia for zanubrutinib have been reported. Nevertheless, the availability of several agents allows for some tailoring of treatment and for switching in the setting of intolerance, thus enabling some patients to continue BTK inhibitor therapy after the emergence of unacceptable AEs.

In addition, BTK inhibitors represent a convenient therapy for both patients and physicians. Oral daily regimens are easy to administer and can be used in a wide variety of settings. While venetoclax confers a considerable risk of tumor lysis syndrome, the initiation of BTK inhibition requires only limited monitoring (**Table**). Generally, BTK inhibitors are well-tolerated drugs, and many patients are hardly impaired with regard to their daily activities. Current questions in the setting of BTK inhibition relate to the ideal timing of discontinuation of continuous monotherapy and the definition of differences between covalent BTK inhibitors in terms of efficacy, toxicity, and resistance. Another issue is optimal sequencing of the next CLL treatment(s) in case of progression.

BTK/BCL-2 inhibitor combinations

Nitin Jain, MD, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, presented clinical trials exploring BTK-inhibitor–based doublets and triplets in previously untreated patients with CLL. The all-oral combination of BTK and BCL-2 inhibitors potentially offers benefits as different mechanisms of action might prevent the emergence of resistance. Moreover, it can be safely administered due to different toxicity profiles. To date, combined BTK/BCL-2 inhibitor treatment has been approved in the European Union, but not in the USA.

A phase II study evaluated 24 cycles of combined ibrutinib and venetoclax after 3 cycles of ibrutinib monotherapy. Both drugs were discontinued in patients who achieved MRD negativity at the end of this period, while those with MRD-positive disease received 12 additional combined cycles. At four years, all patients including high-risk individuals obtained uMRD as best response in 72 %, and the PFS rate was 94.5 % [10]. The PFS curves of patients with *TP53*-aberrant status and unmutated IGHV overlapped with those of patients without these high-risk features.

The largest combination study was the phase II CAPTIVATE trial that contained an MRD cohort (n = 164) and a fixed-duration cohort (n = 159). Each cohort received 12 cycles of ibrutinib

and venetoclax. In the MRD cohort, this was followed by MRD-guided randomization. According to the most recent update, the fixed-duration cohort experienced a 4-year PFS rate of 79 % [11]. The phase III GLOW study led to the approval of ibrutinib plus venetoclax in many countries. Older patients and/or patients with comorbidities were randomized to either ibrutinib/venetoclax or chlorambucil/obinutuzumab. With respect to PFS, ibrutinib/venetoclax gave rise to a 78 % risk reduction (HR, 0.216; p < 0.001; **Figure**) [12].

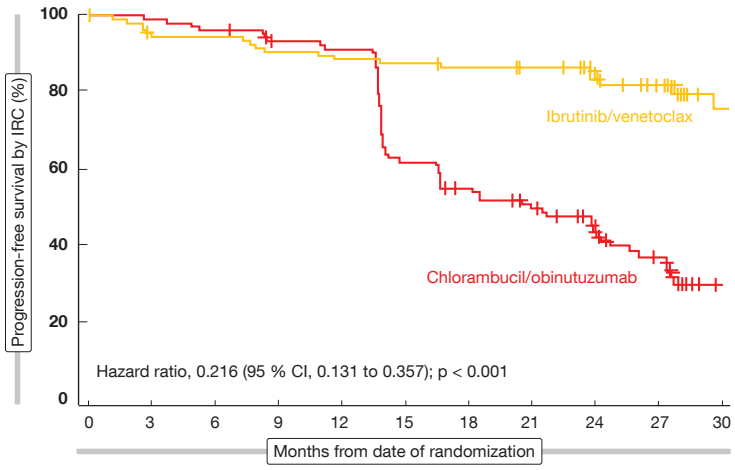


Figure: GLOW study: progression-free survival with ibrutinib plus venetoclax vs. chlorambucil plus obinutuzumab

First-line triplets

Dr. Jain emphasized the time-limited nature of doublet and triplet therapies. This has some advantages such as decreased risk of resistance mutations and improved cost-effectiveness. Also, if patients progress after first-line combination regimens, unpublished data indicate that retreatment works.

In the first-line setting, several studies have investigated ibrutinib, acalabrutinib or zanubrutinib in addition to a backbone consisting of venetoclax and obinutuzumab (Ven + G). The CLL2-GIVe trial focused on ibrutinib plus Ven + G in patients with del(17p)/*TP53*-mutated CLL. In this population, the results were encouraging, with a 3-year PFS rate of 79.9 %, although the PFS curve suggested some late relapses [13]. Notable differences were observed regarding the type of aberration: while patients with *TP53* mutation alone did not develop any relapses for more than three years, those with del(17p) with or without *TP53* mutation fared considerably worse. Another study conducted in the high-risk setting tested the combination of acalabrutinib plus Ven + G. At cycle 16, high uMRD rates resulted across the total population and the patients with *TP53* aberrations [14]. Similarly, the long-term follow-up of a phase II study has shown uMRD rates of 96 % and 92 % in the peripheral blood and bone marrow with zanubrutinib plus Ven + G [15].

As Dr. Jain pointed out, uMRD rates are numerically higher with second-generation BTK inhibitors than with ibrutinib, although this observation needs to be confirmed in a larger context. Ongoing phase III studies that are currently evaluating doublet and triplet regimens in the first-line setting will be reported over the next few years. Combination data for acalabrutinib plus venetoclax ± obinutuzumab and zanubrutinib plus venetoclax are awaited. Also, new BCL-2 inhibitors such as sonrotoclax and lisaftoclax are under development and will be assessed as part of combination strategies. ■

Source: Session "Optimizing initial therapy of CLL", iwCLL 2023, 8th October 2023, Boston, USA

REFERENCES

1 Barr BM et al., Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. Blood Adv 2022; 6(11): 3440-3450
2 NCCN Guidelines Chronic Lymphocytic leukemia/Small Lymphocytic Lymphoma, version 3.2023
3 Shanafelt TD et al., Long-term outcomes for ibrutinib-rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. Blood 2022; 140(2): 112-120
4 Woyach J et al., Long-term results of Alliance A041202 show continued advantage of ibrutinib-based regimens compared with bendamustine plus rituximab (BR) chemoimmunotherapy. ASH 2021, abstract 639
5 Al-Sawaf O et al., Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: Extended off-treatment follow-up from the randomized CLL14 study. J Clin Oncol 2021; 39(36): 4049-4060
6 Mato AR et al., A clinical practice comparison of patients with chronic lymphocytic leukemia with and without deletion 17p receiving first-line treatment with ibrutinib. Haematologica 2022; 107(11): 2630-2640
7 Sharman JP et al., Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. Leukemia 2022; 36(4): 1171-1175
8 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
9 Brown JR et al., Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med 2022; 388(4): 319-332
10 Jain N et al., Combined ibrutinib and venetoclax for first-line treatment of patients with chronic lymphocytic leukemia: 4-year follow-up data. ASH 2022, abstract 95
11 Barr PM et al., Fixed-duration ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): 4-y follow-up from the FD cohort of the phase 2 CAPTIVATE study. J Clin Oncol 41, 2023 (suppl 16; abstr 7535)
12 Kater AP et al., Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. NEJM Evid 2022; 1(7) DOI: 10.1056/EVIDoa2200006
13 Huber H et al., Final analysis of the CLL2-GIVe trial: obinutuzumab, ibrutinib, and venetoclax for untreated CLL with del(17p)/TP53 mut. Blood 2023; 142(11): 961-972
14 Ryan CE et al., Updated results from a multicenter, phase 2 study of acalabrutinib, venetoclax, obinutuzumab (AVO) in a population of previously untreated patients with CLL enriched for high-risk disease. Blood 2022; 140(Suppl 1): 837-838
15 Soumerai JD et al., Long-term follow-up of multicenter phase II trial of zanubrutinib, obinutuzumab, and venetoclax (BOVen) in previously untreated patients with CLL/SLL. Hematol Oncol 2023; 41(S2): 233-235

Long-term results and other findings from clinical trials

MURANO: 7-year data and retreatment substudy

Fixed-duration venetoclax plus rituximab (VenR; n = 194) was tested against bendamustine plus rituximab (BR) for six months (n = 195) in the global, open-label, randomized phase III MURANO study that enrolled patients with relapsed/refractory CLL. In the experimental arm, 6 cycles of rituximab were administered, and venetoclax monotherapy was taken for a total of 24 months. Indeed, VenR gave rise to improvements in progression-free survival (PFS; 53.6 vs. 17.0 months; $p < 0.0001$) and overall survival (OS), with 5-year OS rates of 82.1 % vs. 62.2 % ($p < 0.0001$) [1].

According to the final analyses after a median follow-up of approximately seven years, the benefits of VenR over BR were sustained [2]. Median PFS was 54.7 vs. 17.0 months (HR, 0.23; $p < 0.0001$), with the 7-year PFS rates being 23.0 % and not estimable, respectively. Median OS had still not been achieved 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. Time to the next anti-leukemic treatment was longer for VenR (63.0 vs 24.0 months; HR, 0.30). Most patients who received the full two years of VenR treatment had undetectable MRD (uMRD) at the end of therapy (EOT). Patients with uMRD showed significantly longer PFS from EOT than those with low MRD positivity (HR, 3.46; $p < 0.0001$) and high MRD positivity (HR, 17.22; $p < 0.0001$; **Figure 1**). For OS, these differences were not significant. Favorable baseline characteristics such as *TP53* wild-type and IGHV mutation were over-represented in the group with enduring uMRD. If MRD conversion with subsequent disease progression occurred, it did not do so until approximately four years after EOT. No new safety signals had been identified since the 5-year data cutoff.

An amendment has been added to the initial study design that allows for retreatment of patients with disease progression on VenR in a substudy.

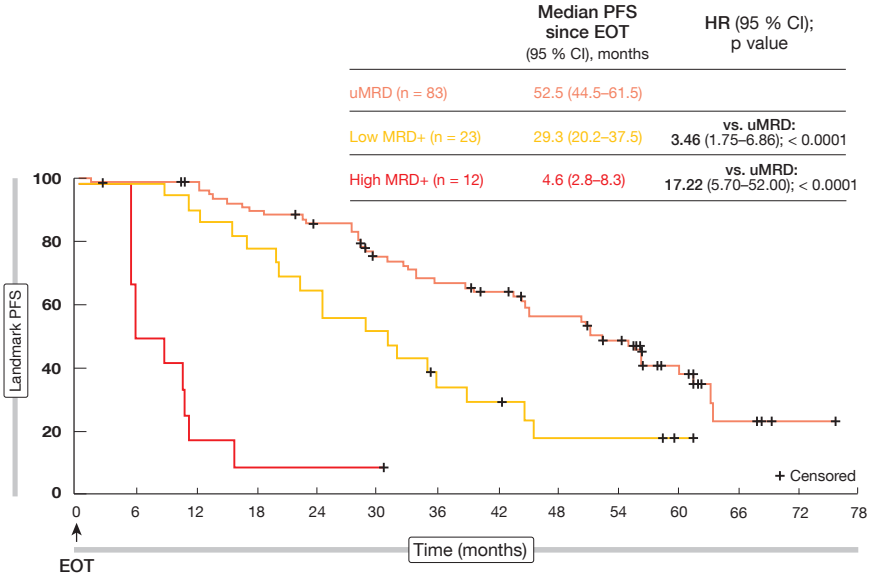


Figure 1: PFS according to MRD status in patients who completed two years of venetoclax treatment without disease progression

Twenty-five of the 34 patients with disease progression who entered this substudy were retreated with VenR. Median time from the final drug dose in the main study to retreatment was 2.3 years. Most of these patients were classified as having high risk. In this population, median PFS from retreatment was 23.3 months, the best overall response rate was 72.0 %, the complete response (CR) rate was 24 %, and median OS had not been reached yet. Moreover, uMRD was still attainable in this high-risk patient group. Eight VenR-retreated patients achieved uMRD, although this was not sustained until the end of retreatment in any of these cases. The authors concluded that retreatment with VenR is a viable option for pretreated patients. Overall, these very mature data from the MURANO study continue to support the use of fixed-duration VenR in patients with relapsed/refractory CLL.

CLL2-BAAG

The phase II CLL2-BAAG trial was designed to investigate the combination of obinutuzumab, acalabrutinib and venetoclax in patients with relapsed/refractory CLL. After optional debulking with bendamustine, obinutuzumab was started in the first cycle, acalabrutinib in the second and venetoclax in the third. From cycle 4 onward, the patients received the triplet. Maintenance followed after the final restaging at cycle 6, and the treatment was continued until CR and uMRD were achieved. Forty-five patients were treated with the induction regimen, and 43 went on to receive maintenance. Among these, 25 patients were able to discontinue treatment after reaching CR and uMRD. Nine individuals completed the full 24 months of maintenance treatment. The group was enriched for risk factors such as unmutated IGHV, *TP53* aberration, and complex karyotype. According to the primary endpoint analysis, all patients responded; after induction, 13 had already achieved CR [3]. Thirty-four patients (76 %) obtained uMRD.

Cramer et al. provided an update of the study after all patients had discontinued treatment [4]. These data confirmed that bendamustine, followed by obinutuzumab, acalabrutinib and venetoclax does not lead to cumulative or unexpected toxicity. Infections and cytopenias were the most common adverse events (AEs). Responses improved

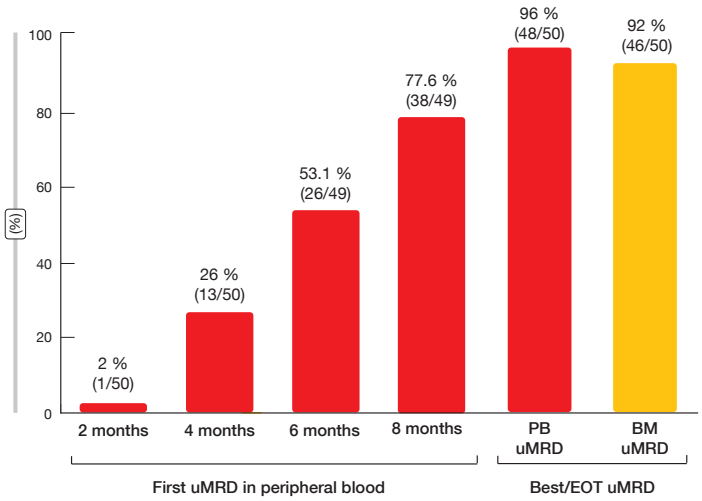


Figure 2: MRD responses with zanubrutinib plus obinutuzumab and venetoclax

with continued maintenance. CR was achieved in 44 %, and the best uMRD rate was 93 %. The group of 25 patients who were able to stop treatment earlier due to obtaining CR and uMRD remained in uMRD for an extended period after EOT. At 30 months, the OS and PFS rates were 100 % and 88.2 %, respectively. To date, six cases of MRD conversion have emerged. Within the cohort of 21 patients who had been pretreated with targeted therapy including venetoclax (n = 10) before study inclusion, the results did not differ regarding the uMRD or PFS rates. However, this regimen is not ready for use in clinical routine practice, and further randomized trials exploring the triple combination are called for.

Update of the BOVen trial

In previously untreated patients with CLL/SLL, a multicenter, single-arm, phase II study has been initiated to assess MRD-driven duration of combined treatment with zanubrutinib, obinutuzumab, and venetoclax (i.e., the BOVen regimen). Indeed, the trial met its primary endpoint, with 89 % of patients reaching uMRD in both peripheral blood and bone marrow despite a median treatment duration of only 10 months that was due to the uMRD-driven treatment discontinuation design [5].

Study findings presented at iwCLL 2023 after an extended follow-up confirmed that the BOVen regimen led to frequent uMRD in the blood and bone marrow (96 % and 92 %, respectively; **Figure 2**) [6]. PFS was durable, with median PFS not having been reached in the total population (n = 50). Median MRD-free survival was 29.8 months after EOT in the group that showed uMRD in the bone marrow (n = 46). ΔMRD400, which was defined as a decrease in MRD in the peripheral blood at day 1 of cycle 5 (i.e., one month after reaching the target venetoclax dose), was demonstrated to be associated with longer MRD-free survival. In patients who achieved ΔMRD400 in addition to uMRD in the peripheral blood at EOT (n = 21), median MRD-free survival had not been reached, while this was 18.1 months in the group with uMRD at EOT but without ΔMRD400 (n = 13; p = 0.003). This benefit was achieved despite significantly shorter time on therapy in the group meeting the ΔMRD400 definition (8 vs. 13 months; p < 0.001). A phase II trial of BOVen investigating ΔMRD400-directed therapy in treatment-naïve patients with CLL/SLL is being planned based on the hypothesis that longer treatment duration for patients who fail to achieve ΔMRD400 will further improve uMRD duration.

Another trial in progress is BruVenG that is testing the addition of 6 cycles of obinutuzumab to zanubrutinib and venetoclax as consolidation in patients with detectable MRD after initial treatment with zanubrutinib/venetoclax [7]. The primary objectives are the MRD negativity rate after the induction phase and the MRD negativity rate after the end of triplet therapy. Patients who achieved MRD negativity on the initial doublet therapy are being observed.

SEQUOIA: first-line zanubrutinib

The SEQUOIA study was initiated to explore the efficacy and safety of first-line zanubrutinib in CLL patients who are unsuitable for chemoimmunotherapy. Cohort 1 had no del(17p) and received either zanubrutinib (n = 241) or BR for 6 cycles (n = 238). Cohort 2 contained patients with del(17p) who were treated with zanubrutinib only (n = 111). At the interim analysis conducted after a median follow-up of 26.2 months, zanubrutinib showed superior PFS compared to BR (HR, 0.42; p < 0.0001), with similar results in the group with del(17p) [8]. At iwCLL 2023, Brown et al. reported updated findings after approximately 18 months of additional follow-up [9].

In cohort 1, median PFS had not been reached and was 42.2 months for zanubrutinib and BR, respectively (HR, 0.30; p < 0.0001). The estimated 42-month PFS rates were 82.4 % vs. 50.0 %. Significant PFS improvements on zanubrutinib treatment were noted for both patients with mutated IGHV (p = 0.00033) and unmutated IGHV (p < 0.0001). Median OS had not been reached in either group; the estimated 42-month OS rates were 89.4 % and 88.3 %, respectively. CR and CR with incomplete hematologic recovery (CRi) rates amounted to 17.4 % vs. 21.8 %. In cohort 2, median OS and PFS had not been reached, with estimated 42-month rates of 79.4 % and 89.5 %, respectively, and the CR/CRi rate was 14.5 %.

Zanubrutinib was well tolerated over the extended treatment period, and the AEs were in keeping with the known profile of BTK inhibitors. Atrial fibrillation events remained low over time, ranging from 1.3 % to 6.3 %. Overall, the results support the use of first-line zanubrutinib for elderly patients with CLL/SLL and those with del(17p).

HRQoL in ALPINE

In the relapsed/refractory setting, the randomized, open-label, phase III ALPINE trial was conducted to compare zanubrutinib (n = 327) with ibrutinib (n = 325). The final PFS analysis after a median follow-up of 29.6 months demonstrated superiority of zanubrutinib (HR, 0.65; p = 0.0024), which also applied to the overall response rate

(86.2 % vs. 75.7 %; p = 0.0007) [10]. Health-related quality of life (HRQoL) was defined as a secondary endpoint of the ALPINE study and was reported at iwCLL 2023 [11].

According to this analysis, both agents gave rise to sustained improvements in global health scores and functioning scales from baseline to both cycle 7 and cycle 13. All improvements were clinically meaningful for the zanubrutinib arm. Given the generally good HRQoL at baseline in both arms, these differences were not significant. Decreases in fatigue and pain were observed for both zanubrutinib- and ibrutinib-treated patients, with the zanubrutinib arm experiencing clinically meaningful improvements in both symptoms at both cycles. More pronounced improvement was obtained for diarrhea with zanubrutinib, although this did not reach the predefined clinically meaningful threshold. The mean change from baseline in the EQ-VAS scores demonstrated a similar pattern of improvement with both therapies up to cycle 13. Long-term follow-up and additional analyses linking patient-reported outcome endpoints to clinical outcomes will further determine the effect of zanubrutinib on HRQoL.

Pooled safety data on zanubrutinib vs. ibrutinib

As is known, the use of the first-generation BTK inhibitor ibrutinib can be limited by AEs including cardiovascular and gastrointestinal toxicities that are attributed to off-target kinase inhibition [12-15]. The next-generation BTK inhibitor zanubrutinib has been designed to improve tolerability by maximizing BTK occupancy and minimizing off-target effects [16]. A previous pooled analysis of 779 patients from six clinical trials has demonstrated a consistent and generally well tolerated safety profile of zanubrutinib [17]. Brown et al. presented an updated pooled analysis comprising 1,550 patients with CLL/SLL and other B-cell malignancies from ten clinical studies at iwCLL 2023 [18]. These included the ASPEN and ALPINE trials that compared zanubrutinib head-to-head with ibrutinib. Median exposure was 34.4 months among all patients who received zanubrutinib, with 45.0 % being on treatment for ≥ 36 months.

Among non-hematologic treatment-emergent AEs (TEAEs) of zanubrutinib, upper respiratory tract infections and diarrhea were most common. No grade ≥ 3 TEAEs occurred in > 10 % of patients. In the pooled zanubrutinib population, deaths attributed to TEAEs occurred in 7.3 %; most (3.7 %) were due to infections, including COVID-19–related TEAEs. Cardiac-related TEAEs leading to death occurred less commonly with zanubrutinib than with ibrutinib (0.2 % vs 1.7 %) in the head-to-head trial populations.

The prevalence of AEs of special interest (AESIs) tended to remain stable with zanubrutinib or to decrease over time. For atrial fibrillation, the rates were persistently lower than with ibrutinib (**Figure 3**). Exposure-adjusted incidence rates (EAIRs) of AESIs, including infections, were numerically lower with zanubrutinib than with ibrutinib in the ASPEN/ALPINE study populations, with the exception of neutropenia. Regarding hypertension, EAIRs were low and consistent for zanubrutinib across the studies except for ALPINE that was an outlier from the rates observed in other studies of zanubrutinib [10, 19]. Despite the higher hypertension rate in ALPINE, the EAIR for atrial fibrillation was significantly lower with zanubrutinib than with ibrutinib (p < 0.0001), which also

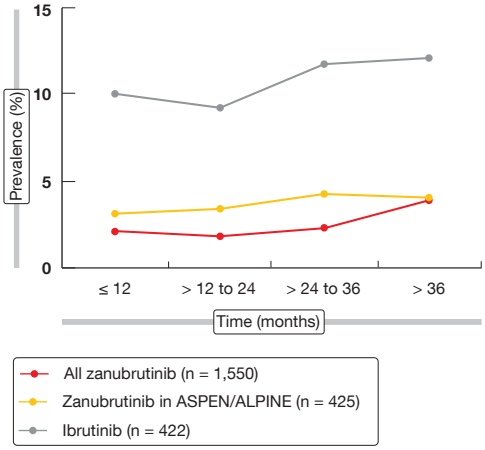


Figure 3: Prevalence of atrial fibrillation/flutter over time with zanubrutinib vs. ibrutinib

REFERENCES

1 Seymour JF et al., Enduring undetectable MRD and updated outcomes in relapsed/refractory CLL after fixed-duration venetoclax-rituximab. Blood 2022; 140(8): 839-850
2 Kater AP et al., Final 7-year follow-up and retreatment substudy analysis of MURANO: venetoclax-rituximab-treated patients with relapsed/refractory chronic lymphocytic leukemia. iwCLL 2023, poster 2002
3 Cramer P et al., Obinutuzumab, acalabrutinib, and venetoclax, after an optional debulking with bendamustine in relapsed or refractory chronic lymphocytic leukemia (CLL2-BAAG): a multicentre, open-label, phase 2 trial. Lancet Haematol 2022; 9(10): e745-e755
4 Cramer P et al., Bendamustine, followed by obinutuzumab, acalabrutinib and venetoclax in patients with relapsed/refractory chronic lymphocytic leukemia: updated results of the CLL2-BAAG trial of the German CLL Study Group. iwCLL 2023, session "Future directions for the treatment of relapsed/refractory CLL", 8th October 2023, Boston, USA
5 Soumerai JD et al., Zanubrutinib, obinutuzumab, and venetoclax with minimal residual disease-driven discontinuation in previously untreated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: a multicentre, single-arm, phase 2 trial. Lancet Haematol 2021; 8(12): E879-E890
6 Soumerai J et al., Long-term follow-up of multicenter phase II trial of zanubrutinib, obinutuzumab, and venetoclax (BOVen) in previously untreated patients with chronic lymphocytic leukemia: impact of early MRD kinetics on post-treatment outcomes. iwCLL 2023, poster 2016
7 Allan JN et al., Zanubrutinib and venetoclax as initial therapy for CLL with obinutuzumab triplet consolidation in patients with detectable minimal residual disease (BruVenG): trial in progress. iwCLL 2023, poster 3002
8 Tam CS et al., Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. Lancet Oncol 2022; 23(8): 1031-1043
9 Brown JR et al., Zanubrutinib vs bendamustine + rituximab in patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma: extended follow-up of the SEQUOIA study. iwCLL 2023, poster 2010
10 Brown JR et al., Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med 2023; 388(4): 319-332
11 Brown JR et al., Zanubrutinib vs ibrutinib in relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma: impact on health-related quality of life. iwCLL 2023, poster 2013
12 Coutre SE et al., Long-term safety of single-agent ibrutinib in patients with chronic lymphocytic leukemia in 3 pivotal studies. Blood Adv 2019; 3(12): 1799-1807
13 O'Brien S et al., Safety analysis of four randomized controlled studies of ibrutinib in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma or mantle cell lymphoma. Clin Lymphoma Myeloma Leuk 2018; 18(10): 648-657
14 Jain P et al., Ibrutinib with rituximab in first-line treatment of older patients with mantle cell lymphoma. J Clin Oncol 2021; 40(2): 202-212
15 Buske C et al., Ibrutinib plus rituximab versus placebo plus rituximab for Waldenström's macroglobulinemia: Final analysis from the randomized phase III iNNOVATE study. J Clin Oncol 2022; 40(1): 52-62
16 Guo Y et al., Discovery of zanubrutinib (BGB-3111), a novel, potent, and selective covalent inhibitor of Bruton's tyrosine kinase. J Med Chem 2019; 62(17): 7923-7940
17 Tam CS et al., Pooled safety analysis of zanubrutinib monotherapy in patients with B-cell malignancies. Blood Adv 2022; 6(4): 1296-1308

applied to infections (p = 0.0098). These findings support zanubrutinib as an appropriate long-term treatment option for patients with B-cell malignancies.

Immune cell number changes in long-term treatment

Changes in T cells have been observed during long-term treatment with ibrutinib in CLL patients [20], although it is unclear to which extent these are induced by the inhibition of interleukin-2–inducible T cell kinase (ITK) rather than by the reduction of the tumor burden. Andersson et al. explored the impact of zanubrutinib treatment on T cell and natural killer (NK) cells in 16 patients with CLL who received long-term zanubrutinib therapy compared to ibrutinib. Eight of them had been included in the SEQUOIA trial and were treatment-naïve, while the other eight had been enrolled in the ALPINE study that assessed zanubrutinib in relapsed/refractory disease. After 24 months of follow-up, six patients in each study were still on treatment and had achieved partial response. All patients stayed on full-dose zanubrutinib during the whole treatment period.

According to the results presented at iwCLL 2023, changes in the T and NK cell profiles occurred in both treatment-naïve and relapsed/refractory patients and were similar to what had previously been observed in ibrutinib-treated patients [21]. Decreases were noted for CD19+ and CD8+ cells, as well as regulatory T cells and effector memory CD4+ and CD8+ cells, among others. Naïve CD4+ and CD8+ T-cells remained unchanged. NK cells decreased from week 16 and normalized at week 12 in relapsed/refractory patients while remaining stable in treatment-naïve patients. Taken together, these changes appear to be related to the reduction of the tumor burden rather than to ITK inhibition. ■

REFERENCES

18 Brown JR et al., Characterization of the safety/tolerability profile of zanubrutinib and comparison with the profile of ibrutinib in patients with B-cell malignancies: post hoc analysis of a large clinical trial safety database. iwCLL 2023, poster 2014

19 Ma H et al., Rate of cardiac disorders in patients with B-cell malignancies who undergo treatment with Zanubrutinib. British Society for Haematology Annual Meeting 2023, abstract BSH23-OR19

20 Mulder TA et al., Ibrutinib has time-dependent on- and off-target effects on plasma biomarkers and immune cells in chronic lymphocytic leukemia. Hemasphere 2021; 5(5): e564

21 Andersson ML et al., Changes in immune cell numbers and profile during long-term zanubrutinib treatment in treatment-naïve and relapsed/refractory patients with chronic lymphocytic leukemia. iwCLL 2023, poster 2001

Overcoming resistance to targeted inhibitors

Subclonal mutations on covalent BTK inhibitor treatment

As covalent BTK inhibitors have been in use for the treatment of CLL in clinical practice for an extended period of time, different resistance mutations are being observed. Dr. Adrian Wiestner, MD, PhD, National Institutes of Health, Bethesda, USA, noted that mutations at progression are variable depending on the specific BTK inhibitor used, with the "classical" C481 mutations prevailing on ibrutinib and acalatinib treatment, while L528W mutations are mainly found in the context of zanubrutinib therapy. This variability is due to different chemical structures of BTK inhibitors that shape the BTK binding properties [1, 2].

CLL with primary resistance to ibrutinib treatment is virtually always transformed lymphoma (i.e., Richter's transformation, Hodgkin lymphoma; **Figure 1**) [3]. Progression that occurs later on typically carries *BTK* or *PLCG2* mutations. Dr. Wiestner presented unpublished findings according to which

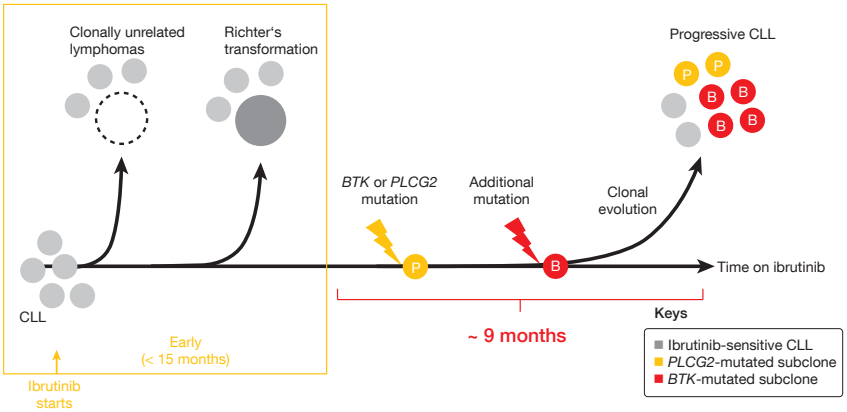


Figure 1: Clonal evolution observed in ibrutinib-treated patients with CLL

mutations are found in separate subclones and show different clonal evolution, with some undergoing linear evolution while others branch out in various subclones. The distribution of *BTK* and *PLCG2* resistance mutations was demonstrated to differ across compartments such as peripheral blood, lymph nodes and bone marrow. Critical signaling pathways that had been downregulated at the time of response were restored in patients progressing on ibrutinib, with pathway activation being normalized to pre-treatment levels.

TP53 aberrations are common in patients progressing on BTK inhibitors. However, they do not represent a resistance mechanism, and successful long-term disease control with first-line ibrutinib is possible in the setting of *TP53*-aberrant CLL [4]. Similarly, deletion 8p is common in patients progress-

ing on BTK inhibitor therapy and can already be present at baseline, but it only appears to set the stage for increased risk of the eventual acquisition of resistance mutations [5, 6]. The same applies to the immunologic marker CD49d, which is a prognostic factor for the time from diagnosis to treatment and a predictor for the efficacy of BTK inhibition [7, 8].

Non-covalent inhibition: pirtobrutinib

Data on the genomic evolution and resistance to the non-covalent BTK inhibitor pirtobrutinib were presented by Jennifer R. Brown, MD, PhD, Dana-Farber Cancer Institute and Harvard Medical School, Boston, USA. The BRUIN trial evaluated single-agent pirtobrutinib in 311 CLL patients; among these, 279 had previously received covalent BTK inhibitor treatment, and 111 showed progression on pirtobrutinib at data cutoff. For 49 of these, paired pre- and post-progression samples were available for targeted next generation sequencing (NGS).

At baseline, 51 % of patients had *BTK* mutations the vast majority of which were C481S mutations. At progression, 71 % had ≥ 1 acquired mutation. Acquired resistance to pirtobrutinib mainly converged around non-C481 *BTK* mutations, with the gatekeeper T474 mutation being most frequent. This was followed by the L528 mutation and other kinase mutations. Approximately half of patients did not acquire *BTK* mutations, and 29 % did not acquire any mutations, which suggests other mechanisms of resistance.

Decrease or clearance of C481 clones at the time of progression on pirtobrutinib were observed in 92 %, while *BTK* T474, L528, C481R/S/Y and other kinase mutations arose at or near progression. Importantly, baseline and acquired *BTK* mutations did not preclude pirtobrutinib efficacy. Overall response rates (ORRs) were high regardless of the type of acquired *BTK* mutation, ranging from 83 % to 92 %. Twenty-four percent of acquired non-C481 *BTK* mutations pre-existed already at baseline at low variant allele frequencies (VAFs) of 1–3 %. Patients with these pre-existing mutations had similar responses to pirtobrutinib, with an ORR of 75 %.

Optimizing outcomes on pirtobrutinib

Varsha Gandhi, MD, Anderson Cancer Center, Houston, Texas, reported research efforts into strategies to improve clinical results in pirtobrutinib-treated patients. At the MD Anderson Cancer Center, 14 of 23 evaluable patients with relapsed/refractory CLL who received pirtobrutinib in the BRUIN study developed progression. In this group, different types of second-site mutations prevailed. Only two individuals had *BTK* wildtype, and the C481 clone was eradicated in almost all cases. The researchers sought to identify genomic features at baseline that were associated with maintenance of the response to pirtobrutinib. According to this, risk factors for progression on pirtobrutinib included relapsed/refractory status after previous covalent BTK inhibition (rather than intolerance to these agents) and the presence of *BTK* mutations at baseline, complex karyotype and bulky lymph nodes. As Dr. Gandhi pointed out, this observation needs to be validated in the larger BRUIN cohort. Nevertheless, it implies that pirtobrutinib should preferably be used in previously untreated CLL patients.

Pharmacologic profiling was performed to develop a sequencing strategy during pirtobrutinib therapy, while the cells are sensitive to treatment, to achieve deeper responses. Mononuclear cells obtained in the course of treatment were incubated with ibrutinib, acalabrutinib, venetoclax and their combinations, and their viability was assessed. Indeed, after ≥ 10 cycles of pirtobrutinib treatment, the cells showed increased sensitivity to targeted agents alone and in combination.

Moreover, post-progression therapeutic intensification options were investigated based on pharmacological and genetic or genomic profiling. Characterization of cells showed that the chemokines CCL3 and CCL4 were increased at the time of progression, which indicated activation of the B-cell receptor pathway. Also, phosphorylation of BTK, ERK and NF-κβ increased, as did BCL-2 and MCL-1 protein levels. These pirtobrutinib-resistant cells proved sensitive to ibrutinib as well as to doublets and triplets containing BCL-2–, MCL-1– and BTK-targeted agents. This was confirmed *in vivo*. Eleven patients were sensitive to the combinations regardless of their genomic background, with the exception of *BCL-2* mutations that abrogated the treatment effect. Overall, these results hint at options for treatment sequencing, intensification and reuse of covalent BTK inhibition. Dr. Gandhi emphasized that an unmet need persists in patients with double-refractory CLL harboring second-site *BTK* and *BCL-2* mutations.

Heterogeneity of BCL-2 resistance

Insights into mechanisms of resistance to BCL-2–targeted treatment were reported by Rachel Thijssen, PhD, The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia and Amsterdam UMC, the Netherlands. CLL cells from relapsed patients have shown to be intrinsically less sensitive to venetoclax [9]. Among intrinsic mechanisms, the *BCL-2* Gly101Val mutation that reduces binding affinity of venetoclax to BCL-2 in the CLL cell was identified [10]. However, this is subclonal and is found only in a subset of patients progressing on venetoclax.

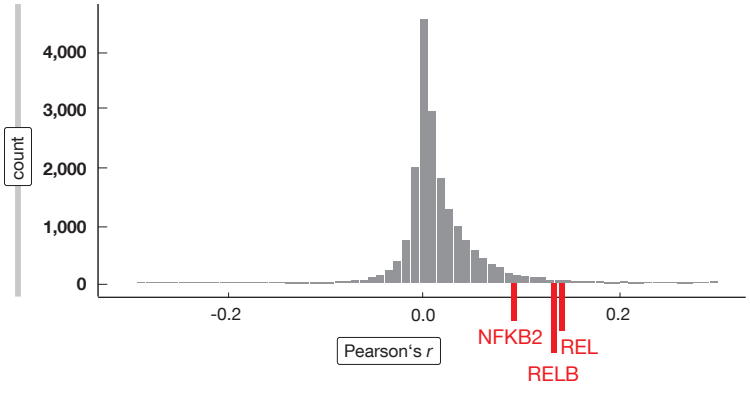


Figure 2: Correlation between *MCL-1* and other genes

The researchers applied single-cell rapid capture hybridization sequencing (scRaCH-seq), a novel multi-omics approach that allows for the assessment of transcriptomes and genotypes of single cells. According to this, CLL cells at progression have different transcriptome profiles, with various mechanisms of resistance in the same patient sample [9]. Intrinsic resistance was found to be driven by high MCL-1 and NF-κB activation with ongoing venetoclax therapy. Most of the relapse samples showed an increased expression of MCL-1, which was strongly correlated with that of REL, RELB and NFKB2 **(Figure 2)**. Moreover, a universal activation of NF-kB and increased MCL-1 expression were observed in circulating resistant tumor cells. These characteristics dissipated after venetoclax treatment had been discontinued, and according to the *ex vivo* sensitivity assay, the cells were again sensitive to the BCL-2 inhibitor.

Regarding extrinsic resistance mechanisms, a shift was seen in the expression of BCL-2 family members. CLL cells in lymph nodes had different transcriptome profiles than CLL cells in the peripheral blood. Overall, the researchers observed a high degree of interpatient and intrapatient heterogeneity at venetoclax relapse, both intrinsically and extrinsically. The significance of MCL-1 and NF-κB activation with ongoing venetoclax therapy underscores the importance of time-limited treatment. Considering the findings regarding extrinsic resistance, combinations of venetoclax with agents preventing microenvironment support appear warranted. The question of whether fixed-duration treatment with venetoclax plus BTK inhibition prevents drug resistance remains to be answered.

Mutation patterns in the real world

Real-world information is required on the patterns of mutations during BTK inhibitor treatment, especially with non-covalent agents. Kiyomi Mashima, MD, PhD, Dana-Farber Cancer Institute and Harvard Medical School, Boston, USA, presented the results of a retrospective cohort analysis of CLL patients treated with ibrutinib, acalabrutinib or pirtobrutinib at the Dana-Farber Cancer Institute between 2014 and 2022.

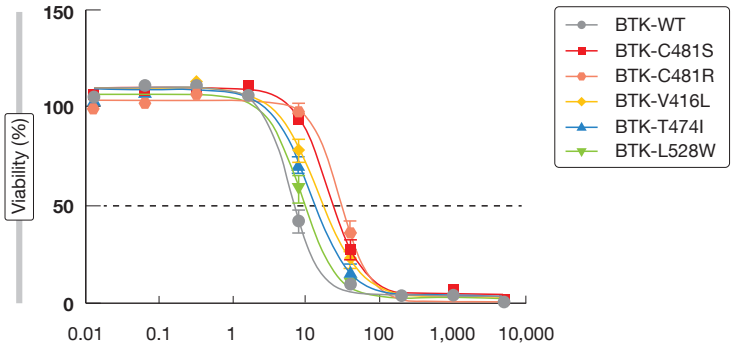


Figure 3: Activity of NX-2127 against BTK inhibitor resistance mutations

The scientists included 118 clinical sequencing reports from 85 patients who were divided into two groups, one undergoing NGS at the time of disease progression (PD; n = 36) and another without progression (non-progressors, NP) in whom NGS was performed during response (n = 49). Sixty and 58 of the sequencing reports were obtained from the PD and NP groups, respectively.

Mutations that were new or had increased VAF were significantly more common among PD vs. NP patients ($p < 0.001$). Significant differences were found for *TP53*, *BTK*, *SF3B1*, *PLCG2* and *NOTCH2*. Only patients from the NP group did not develop any mutations. The analysis revealed six different types of C481 mutations. Interestingly, L528W mutations arose on both ibrutinib (2/7) and pirtobrutinib (1/6) treatment. Four of six patients progressing on pirtobrutinib had T474 mutations.

Paired sequencing results before and during BTK inhibitor therapy were obtained. All of the patients in the PD group exhibited at least one new or increased *BTK*, *PLCG2* or *TP53* mutation. In contrast, in the NP group, none of these mutations newly appeared or increased. Four pre-existing *TP53* mutations and six pre-existing *NOTCH1* mutations decreased or completely disappeared during BTK inhibitor treatment in the NP group. Overall, the enrichment of RAS/RAF/MAPK pathway mutations in the PD group suggests that these may be related to BTK inhibitor resistance beyond *BTK*, *PLCG2* and *TP53* mutations.

What can be achieved with BTK degraders?

Kinase inhibition might not suffice to overcome resistance to BTK inhibitors as some *BTK* mutations carry a scaffold function that cannot be surmounted by tyrosine kinase inhibitors [11]. Therefore, targeted protein degradation has emerged as a strategy to circumvent acquired resistance to BTK inhibitors. Proteolysis-targeted chimeras (PROTAC) are a novel class of agents that enable catalytic ubiquitination and proteasomal degradation of different targets. Alexey V. Danilov, MD, PhD, Lymphoma Center, City of Hope, Irwindale, USA, explained that kinases such as BTK, BRAF or KRAS can be targeted, although this basically applies to any type of protein.

Multiple covalent and non-covalent BTK degraders are currently in preclinical development. An example is NRX-0492 that degrades BTK, IL2-inducible T-cell kinase (ITK) and IKAROS family zinc finger (IKZF), thus inhibiting B-cell receptor signaling [12]. Importantly, BTK degradation overcomes *BTK* resistance mutations. In a preclinical resistance model, NX-2127 reduced proliferation and induced apoptosis **(Figure 3)** while ibrutinib failed to do so [13-15]. NX-2127 and NX-5948 induce BTK degradation by recruiting cereblon that was originally recognized for its modulation of the immune system. However, only NX-2127 was shown to downregulate the transcription factors Aiolos and Ikaros, which indicates an immunomodulatory function of this compound [16]. NX-2127, but not NX-5948, enhanced synapse formation to levels comparable to those of lenalidomide. Whether this is clinically important in terms of efficacy and toxicity remains to be determined.

The BTK degraders NX-2127, NX-5948, BGB-16673, AC0676 and ABBV-101 are being tested in clinical trials. Early data from the phase I NX-2127-001 study investigating NX-2127 in patients

with relapsed/refractory CLL and B-cell malignancies have been presented at ASH 2022 [17]. All of the 23 CLL patients were heavily pretreated and were refractory to prior BTK inhibitor therapy, with most being double-refractory to both BTK and BCL-2 inhibitors. The adverse event (AE) profile was generally consistent with previous reports for BTK-targeted therapies. NX-2127 showed clinically meaningful efficacy, with an ORR of 33 % and durable responses in some patients. Importantly, responses were noted in patients double-refractory to BTK/BCL-2 inhibitors as well as in those who had progressed on a non-covalent BTK inhibitor. *In vivo* BTK degradation was significant and was essentially independent of the dose level.

Zanubrutinib in patients intolerant of other BTKi

The ongoing, single-arm, phase II BGB-3111-215 study has demonstrated efficacy and tolerability of zanubrutinib in patients with B-cell malignancies who are intolerant of ibrutinib and/or acalabrutinib [18]. Preliminary longer-term findings for patients with CLL or small lymphocytic lymphoma were presented at iwCLL 2023 by Shadman et al. [19]. Overall, 61 individuals received zanubrutinib; 44 and 17 of these were ibrutinib-intolerant and acalabrutinib-intolerant, respectively. In the latter group, eight patients were intolerant of both agents. At the time of the analysis, approximately 70 % in each cohort were still on treatment.

The data showed that AEs that had caused the patients to discontinue their previous BTK inhibitor therapy were unlikely to recur on zanubrutinib treatment. Indeed, 68.4 % of ibrutinib-intolerance AEs and 71.4 % of acalabrutinib-intolerance AEs did not recur (**Figure 4**). No intolerance AEs recurred at a higher severity. Sixty-two percent of patients with ibrutinib intolerance and 70.6 % of those

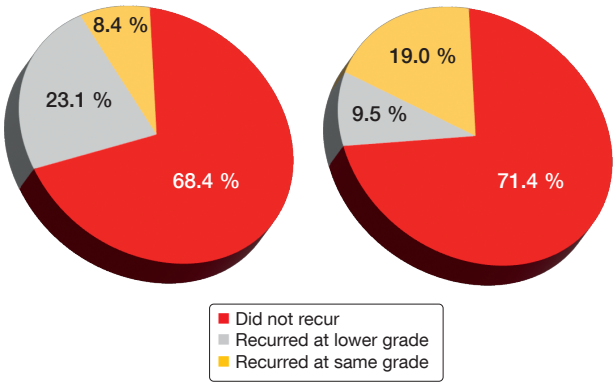


Figure 4: Recurrence of ibrutinib-intolerance events (left) and acalabrutinib-intolerance events (right) on zanubrutinib treatment

with acalabrutinib intolerance did not experience recurrence of any of their intolerance events. Grade ≥ 3 AEs emerging on zanubrutinib treatment were reported in 50.8 % of patients, with neutropenia (11.5 %), COVID-19 (6.6 %) and pneumonia (6.6 %) representing the most common events.

In terms of efficacy of zanubrutinib, the analysis showed an ORR of 71.9 % and a disease control rate of 94.7 %. At 12 months, 88.3 % of patients were progression-free. As the authors noted, the high disease control rate suggests that patients who were intolerant of ibrutinib or acalabrutinib are likely to benefit from switching to zanubrutinib. Overall, zanubrutinib appears to be a viable option for patients who are intolerant of ibrutinib or acalabrutinib.

Assessment of evolutionary characteristics

Zhu et al. used multi-omics to assess clonal evolutionary characteristics in ten retrospectively identified CLL patients who had developed zanubrutinib resistance [20]. This included two patients with Richter's transformation. Deep targeted-gene NGS covering BTK (exons 1–19) and PLCG2 (exons 1–33), as well as high sensitivity droplet digital PCR (ddPCR) were used to assess serial samples. Moreover, the scientists performed single-cell RNA sequencing of matching peripheral blood and lymph node samples in three patients who showed progressive lymphadenopathy.

BTK Cys481 and Leu528 mutations were identified as the two main *BTK* resistance mutations. ddPCR was performed in the samples of four patients with undetectable *BTK* mutation according to NGS. The Cys481Ser mutation was found in two cases, which suggested spatial clonal heterogeneity in zanubrutinib resistance. As the authors noted, deep targeted-gene NGS and ddPCR should be used comprehensively to evaluate the emergence of resistant clones in light of spatial heterogeneity and clonal evolution. Patients with Richter's transformation showed the highest upregulation of the MYC, OXPHOS and G2M pathways, as well as downregulation of BCR signaling. Furthermore, upregulation of MCL-1 in this group indicated an underlying mechanism leading to insensitivity to venetoclax treatment following zanubrutinib resistance. ■

Source: Sessions "Mechanisms of resistance" and "Future directions for the treatment of relapsed/refractory CLL", iwCLL 2023, 8th October 2023, Boston, USA

REFERENCES

1 Johnson AR et al., Battling Btk mutants with noncovalent inhibitors that overcome Cys481 and Thr474 mutations. ACS Chem Biol 2016; 11(10): 2897-2907
2 Lin DY, Andreotti AH, Structure of BTK kinase domain with the second-generation inhibitors acalabrutinib and tirabrutinib. PLoS One 2023; 18(8): e0290872
3 Ahn IE et al., Clonal evolution leading to ibrutinib resistance in chronic lymphocytic leukemia. Blood 2017; 129(11): 1469-1479
4 Ahn IE et al., Ibrutinib for chronic lymphocytic leukemia with TP53 alterations. N Engl J Med 2020; 383(5): 498-500
5 Burger JA et al., Clonal evolution in patients with chronic lymphocytic leukaemia developing resistance to BTK inhibition. Nat Comm 2016; 7: 11589
6 Kadri S et al., Clonal evolution underlying leukemia progression and Richter transformation in patients with ibrutinib-relapsed CLL. Blood Adv 2017; 1(12): 715-727
7 Bulian P et al., CD49d is the strongest flow cytometry-based predictor of overall survival in chronic lymphocytic leukemia. J Clin Oncol 2014; 32(9): 897-904
8 Alsadhan A et al., CD49d expression identifies a biologically distinct subtype of chronic lymphocytic leukemia with inferior progression-free survival on BTK inhibitor therapy. Clin Cancer Res 2023; 29(18): 3612-3621
9 Thijssen R et al., Single-cell multiomics reveal the scale of multilayered adaptations enabling

CLL relapse during venetoclax therapy. Blood 2022; 140(20): 2127-2141
10 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
11 Wang et al., Mechanisms of resistance to noncovalent Bruton's tyrosine kinase inhibitors. N Engl J Med 2022; 386(8): 735-743
12 Zhang D et al., NRX-0492 degrades wild-type and C481 mutant BTK and demonstrates in vivo activity in CLL patient-derived xenografts. Blood 2023; 141(13): 1584-1596
13 Abdel-Wahab O et al., Kinase dead BTK mutations confer resistance to covalent and noncovalent BTK inhibitors but are susceptible to clinical stage BTK degraders. ASH 2022, abstract 750
14 Noviski M et al., NX-5948 promotes selective, sub-nanomolar degradation of inhibitor-resistant BTK mutants. AACR 2023, abstract 2850
15 Noviski M et al., NX-5948 and NX-2127 potently degrade a broad array of clinically-relevant BTK mutants that display resistance to inhibitors and other BTK degraders. iwCLL 2023, poster 2020
16 Huynh T et al., NX-2127 and NX-5948, two clinical stage cereblon-recruiting BTK degraders, facilitate T-cell functionality in CLL. iwCLL 2023, poster 1050
17 Mato AR et al., NX-2127-001, a first-in-human trial of NX-2127, a Bruton's tyrosine kinase-targeted protein degrader, in patients with relapsed or refractory chronic lymphocytic leukemia and B-cell malignancies. Blood 2022; 140 (Supplement 1): 2329-2332
18 Shadman M et al., Zanubrutinib in patients with previously treated B-cell malignancies intolerant of previous Bruton tyrosine kinase inhibitors in the USA: a phase 2, open-label, single-arm study. Lancet Haematol 2023; 10(1): e35-e45
19 Shadman M et al., A phase 2 study of zanubrutinib in previously treated B-cell malignancies intolerant to ibrutinib and/or acalabrutinib: preliminary results for patients with CLL/SLL. iwCLL 2023, poster 2009
20 Zhu H et al., Integrating multi-omics to reveal the heterogeneous clonal evolutionary characteristics in CLL patients with zanubrutinib resistance. iwCLL 2023, poster 1102

CLL treatment in the real world: insights from across the globe

Second- and later-line therapies in the USA

The analysis reported by Davids et al. at iwCLL 2023 examined the characteristics, treatment patterns and outcomes of a cohort of 1,102 real-world US patients with CLL receiving two or more lines of therapy [1]. Data were obtained from the COTA real-world database. Second-line treatment was initiated between 2014 and 2021. The median patient age at diagnosis was 64 years, 61 % were males, and 88.1 % were treated in the community setting.

Second-line regimens predominantly included ibrutinib, bendamustine plus rituximab (BR), rituximab monotherapy, acalabrutinib, and investigational regimens. In the third line, patients most commonly received ibrutinib, acalabrutinib, and BR. Fourth-line regimens were mainly ibrutinib, rituximab plus venetoclax, and acalabrutinib. Between 2014 to 2022, the utilization of BTK inhibitors had increased from 39.9 % to 48.9 %; for BCL-2 inhibitors and anti-CD20 antibodies, these proportions had risen from 0.0 % to 34.0 % and from 9.2 % to 25.5 %, respectively (**Figure 1**). At the same time, the utilization of chemoimmunotherapy had decreased considerably from 37.9 % to 6.4 %.

Although targeted agents have improved patient outcomes, the findings suggested that there is still an unmet need. Second-line therapies were discontinued in 77.5 %. Toxicity was the reason for this in 29.0 %, physician preference in 9.4 %, progression in 6.4 % and death in 6.8 %. In almost half of cases, the reasons for discontinuation were classified as "other". Approximately 18 % of patients died after the initiation of second-line therapies and prior to the start of the third line; 25.5 % of all patients died prior to the initiation of the fourth line. From the start of second-line treatment, median real-world progression-free survival (PFS) was 31.4 months, and median real-world overall survival (OS) was 79.0 months. The authors noted that innovative treatment options and novel mechanisms of action are required to improve outcomes in patients with CLL.

Observations from China

In light of the scarcity of empirical evidence on the usage of BTK inhibitors in China, a retrospective cohort study in-

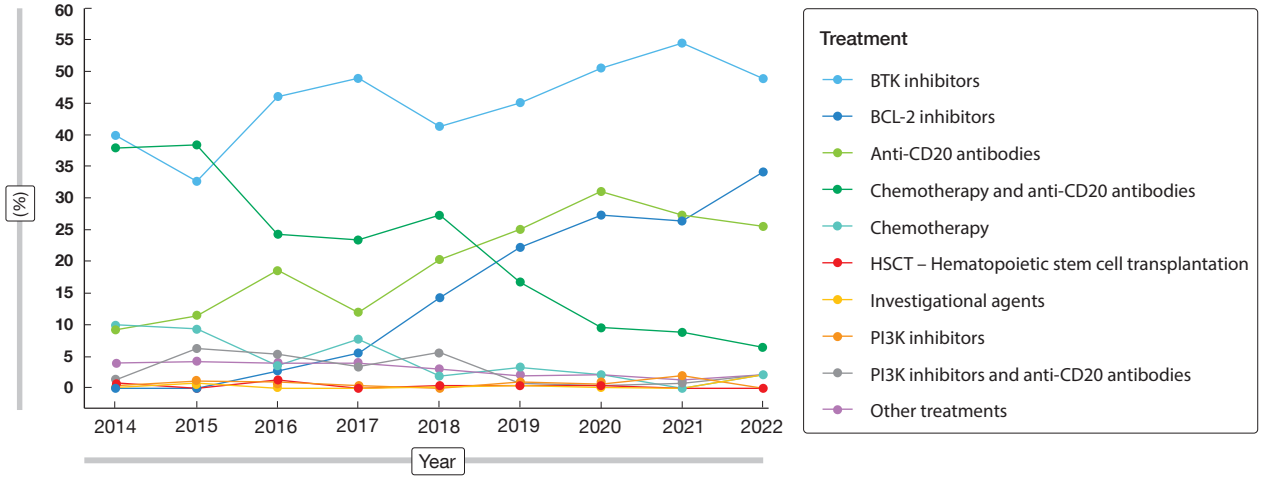


Figure 1: CLL treatment regimens administered in the USA between 2014 and 2022

cluding 673 patients with B-cell lymphoproliferative diseases was performed to assess real-world treatment patterns, discontinuation rates and clinical outcomes on BTK inhibitor therapy [2]. Median duration of treatment was 36.4 months in the entire cohort, and median post–BTK-inhibitor survival had not been reached yet. During follow-up, 43.8 % of patients permanently discontinued therapy, which was mostly due to progressive disease.

Early discontinuation during the first six months occurred in 26.3 %; here, patient outcomes were poor, with a median post-discontinuation survival of 6.9 months. According to multivariate analysis, discontinuation of BTK inhibitors due to toxicity as well as discontinuation within six months were independent predictors of survival. On the other hand, the decision between BTK inhibitor monotherapy and combination therapy did not significantly affect survival, which also applied to the choice of first-generation vs. second-generation agents. The authors concluded that BTK inhibitors are an effective and well-tolerated treatment for long-term use in Chinese patients. Considering the suboptimal outcomes after early discontinuation, these data emphasize the importance of treatment adherence.

German findings for BTK inhibition vs. venetoclax

An analysis by the German CLL Study Group Registry presented at iwCLL 2023 included patients with CLL who were treated with either BTK inhibitors (n = 915) or venetoclax (n = 274) between July 2014 and January 2023 [3]. BTK inhibitors and venetoclax constituted the first-line strategy in 38.5 % and 55.5 %, respectively. Pretreatment mostly consisted of chemoimmunotherapy.

The survival outcomes were comparable irrespective of the type of treatment. Median event-free survival and OS from the first BTK-inhibitor–containing regimen were 23.2 and 85.9 months, respectively; for venetoclax-containing regimens, this was 31.8 and 96.5 months, respectively. Similarly, time to next treatment (TTNT) did not differ, with median TTNT being 68.4 and 63.7 months for the BTK inhibitor and venetoclax groups, respectively.

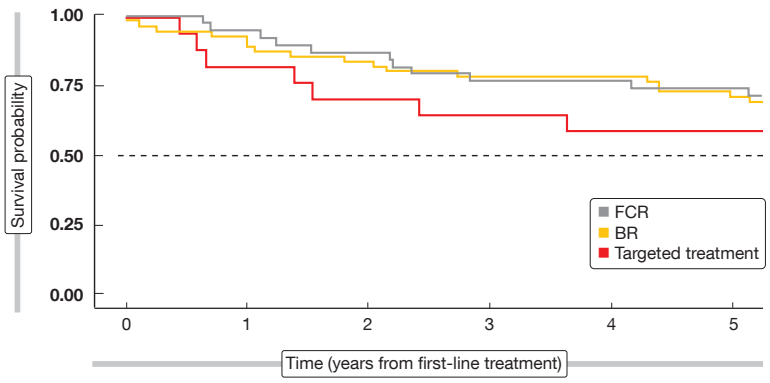


Figure 2: Overall survival from first-line chemoimmunotherapy (FCR, BR) and targeted agents in CLL patients with hypertension

Acalabrutinib & ibrutinib: differences in CV safety

Safety events and other outcomes were assessed for ibrutinib and acalabrutinib in an observational, retrospective study conducted in Spain [4]. The scientists identified a total of 91 patients at four centers. These had a median age of 73.2 years, and 58.2 % were males. Fifty-eight percent, 31.9 % and 9.9 % were treated in the first, second and subsequent lines, respectively. Acalabrutinib and ibrutinib were used in 27.5 % and 72.5 %, respectively.

No differences resulted across the two agents regarding PFS (p = 0.363) or OS (p = 0.216). However, the second-generation BTK inhibitor acalabrutinib displayed an improved cardiovascular toxicity profile compared to the first-generation agent. Hypertension was found in 14 ibrutinib-treated patients (21.2 %) but in none of those receiving acalabrutinib (p = 0.029). Overall, cardiotoxic events occurred in 24.2 % vs. 12.0 % (p = 0.32). No significant differences were reported in terms of other toxicities including infections, bleeding, hematological events or gastrointestinal events.

The impact of hypertension

Based on data from four Danish registries, Vainer et al. evaluated the impact of hypertension on the treatment and survival outcomes of 6,557 CLL patients [5]. Hypertension is highly prevalent in newly diagnosed CLL and a common adverse event of BTK inhibition. The population had a median age of 71 years, and 46 % had been diagnosed with hypertension.

According to this analysis, hypertension was associated with shorter OS, particularly following first-line treatment. The risk of CLL-unrelated and CLL-related death was increased, with patients dying more often from infectious and cardiovascular causes compared to CLL patients without hypertension. Also, time to treatment initiation was comparatively longer. The scientists compared the OS outcomes from the first-line treatment for fludarabine/cyclophosphamide/rituximab, BR, and targeted therapies. In the group with hypertension, patients fared better with chemoimmunotherapy than with targeted agents (**Figure 2**), whereas there was no difference in those without hypertension. This might be taken into consideration at the time of CLL treatment selection, in addition to the observation that CLL patients with hypertension appear to be more vulnerable to infections. ■

REFERENCES

1 Davids MS et al., Real-world treatment patterns, reasons for discontinuation, and survival outcomes among patients with chronic lymphocytic leukemia/small lymphocytic lymphoma receiving second or later lines of therapy in a contemporary population treated in the United States. iwCLL 2023, poster 1109
2 Yan Y et al., Real-world treatment patterns, discontinuation and clinical outcomes in patients with B-cell lymphoproliferative diseases treated with BTK inhibitors in China. iwCLL 2023, poster 1127
3 Kutsch N et al., Targeted agents in chronic lymphocytic leukemia: data on outcomes and subsequent therapies of patients observed within the German CLL Study Group registry. iwCLL 2023, poster 1212
4 Lopez-Garcia A et al., Safety profile in patients with chronic lymphocytic leukemia undergoing treatment with 1st and 2nd generation Bruton tyrosine kinase inhibitors: multicentric real-world experience. iwCLL 2023, poster 1116
5 Vainer N et al., Association between hypertension and overall survival in chronic lymphocytic leukemia. iwCLL 2023, poster 1101

Issues in the management of CLL patients from an international point of view

Insights into patient needs

The CLL Advocates Network (CLLAN) is a global network of patient advocacy organizations dedicated to improving the outcomes of patients with CLL through collaboration with national organizations. Principles guiding the work of CLLAN include the support of local communities, sharing of best practices and advocacy for better care and access. Implementation of CLL-specific support in all countries is an important goal. At the same time, no direct support of patients and their families is provided; this remains in the scope of the national or regional advocacy associations and advocates.

Global multiple stakeholder surveys have been conducted and co-conducted by CLLAN to understand real-life experience and needs of patients and carers. Also, current gaps and opportunities are mapped to address equity, service and unmet need. At iwCLL 2023, Brian Koffman, MDCM, CLL Society, presented results from the CLL Patient Advocacy and Support Survey, the Global Leukemia Patient Experience Survey, and the Global Leukemia Carer Experience Survey. These online surveys were conducted between 2021 and 2022 with CLL patients, their carers, and support organizations from across the globe. Areas of interest included the provision of support services for CLL by patient advocacy organizations, access to CLL healthcare prior to the COVID-19 pandemic, and the impact of COVID-19 on the delivery of CLL care.

The investigators received responses from 1,202 patients, 137 carers and 57 support organizations across 40 countries. To understand and identify geographical impacts, the countries were segmented into low-and-middle-income countries (LMIC) and high-income countries (HIC).

Numerous gaps between LMIC and HIC

As the analysis showed, educational services were provided markedly more often in HIC, although awareness campaigns were conducted more frequently in LMIC. Regarding services that patient support organizations did not offer at the time of the survey but would like to offer, 42 % of responders from both HIC and LMIC mentioned clinical trials directories. Dr. Koffman noted that the need for news and conference coverage was much higher in LMIC (53 % vs. 8 % in HIC). However, lack of human resources/staff/volunteers was found to be a universal phenomenon (74 % for both LMIC and HIC).

Being able to afford care was definitely an issue for 32 % and 18 % of responders in LMIC and HIC, respectively. The question of whether enough approved therapies are available was answered with "no" in 58 % vs. 37 %. A huge difference emerged in terms of delayed diagnosis (**Figure**). Likewise, the results with respect to access to CLL specialist care centers and mental health resources after the CLL diagnosis favored HIC over LMIC, although the 18 % proportion of responders in HIC indicating definite availability of mental health care must be considered inappropriately low, as Dr. Koffman pointed out. Adequate opportunities to enter clinical trials are basically only available in HIC; here, this question was answered with "yes" in 21 % and with "yes, to some extent" in 50 %, while for LMIC, this was only 5 % and 11 %, respectively. Patients reported treatment delays due to the COVID-19 pandemic in 58 % vs. 38 % in LMIC vs. HIC.

Taken together, these responses suggest significant geographical disparities in patient access to best standard diagnostics and care, as well as support services. Patient organizations in HIC are more likely to provide wider services, especially for education and policy, than those from LMIC, which results in further gaps. Moreover, the unmet need of patients around their CLL diagnosis, treatment and support was higher in LMIC than in HIC, and delayed diagnoses were frequent. Dr. Koffman concluded that while support services are strong among patient organizations in LMIC, there is a need to build greater patient and professional educational services, grow involvement in policy decisions, and improve access to earlier

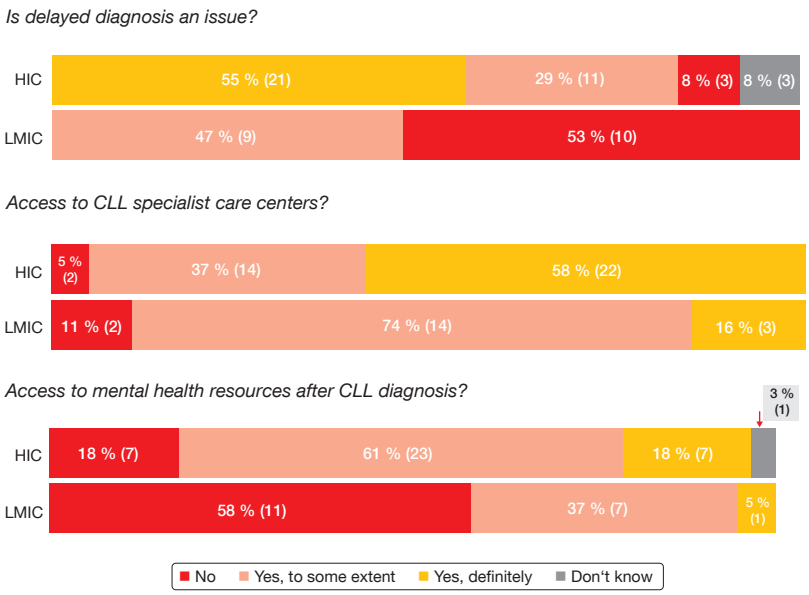


Figure: Responses to three survey questions in high-income countries (HIC) and low-and-middle-income countries (LMIC)

diagnosis, a greater number of therapies and clinical trials.

Capacity building program in Tanzania

William Frank Mawalla, MD, Muhimbili University of Health and Allied Sciencies, Daressalam, Tanzania, presented an update on the iwCLL Capacity Building Pilot Program that was initiated in Tanzania in March 2022 to improve treatment outcomes in patients with CLL. Four objectives have been defined that include promotion of practical training in flow cytometry and *TP53* mutation analysis, training of clinicians and nurses, provision of clinical supervision and mentorship in multidisciplinary team meetings, and clinical research capacity building.

As Dr. Mawalla reported, tremendous achievements on some of these objectives have already been obtained. Laboratory scientists and hematologists have been trained in flow panel setting and interpretation, as well as NGS *TP53* and IGHV mutation analysis. A clinical CLL guideline that reflects local needs and takes the diagnostic capacity into account is currently under review before being adopted into national guidelines. This went in hand in hand with the development of key laboratory SOPs on both immunophenotyping and molecular analysis.

Regarding clinical supervision and mentorship, weekly multidisciplinary meetings have been established with the aim of building a dedicated team that furthers the effort started by the program. The meetings involve laboratory scientists, clinicians, bioinformaticians, and students. In terms of clinical research capacity building, a REDCap database was developed that is hosted by the teaching hospital in Daressalam. To date, 32 patients have been enrolled. Dr. Mawalla expressed hope that this database will outlive the program and will continue to serve as a model for other malignancies beyond CLL. In addition, the experts actively engage in advocacy activities. Numerous dissemination events are being held both inside and outside of the university, and efforts are united to engage key stakeholders and supporting patient groups. ■

Source: Session "Global perspective on CLL management – real world data and patient experiences", iwCLL 2023, 9th October 2023, Boston, USA

Interview with John F. Seymour, MBBS, FRACP, PhD, Department of Haematology, Royal Melbourne Hospital, Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Victoria, Australia – conducted by Anna Fenzl, PhD.

Different perspectives on how to define success in CLL

Fortunately, the landscape of CLL treatment has dramatically transformed over the last ten years, shifting from chemotherapy to new targeted therapies. These advancements have not only extended patients' lifespans but also often enhanced their quality of life. Consequently, many patients now undergo continuous treatment throughout their lives and frequently pass away from causes unrelated to CLL. At this year's iwCLL, there was a debate and roundtable on how to define success in CLL. From a physician's perspective, how is success in CLL treatment defined?

The debate and roundtable aimed to facilitate a discussion, allowing participants to exchange a wide array of viewpoints on the diversity in CLL treatment approaches and perspectives since there is not a 'one-size-fits-all' solution in this context. With years of experience in treating people with CLL, I have adopted a long-term approach. Recognizing the chronic nature of CLL, it is clear that the vast majority of patients will have to use various tools, hopefully, over several decades. My definition of success in CLL treatment aligns with long-term survival, but it is equally important to consider minimizing the cumulative burden of the disease and its treatments over time. Therefore, the goal is not just long-term survival, but achieving it with minimal adverse impact from the disease and its treatment.

Having delved into the physician's perspective on the evolving landscape of CLL treatment and its implications for success, it becomes equally important to consider the other side of this equation. The patient's experience and viewpoint are crucial in shaping our understanding of treatment effectiveness and quality of life. With this in mind, how do patients typically perceive their journey through CLL treatment, and what factors do they consider when defining success in their treatment and overall wellbeing?

© Peter MacCallum Cancer Centre

John F. Seymour, MBBS, FRACP, PhD

One key observation in CLL treatment is the variability and evolution of patient perspectives. These viewpoints are uniquely personal and can shift significantly over time. For example, a patient might initially focus on a short-term goal, like being healthy for a significant

family event, such as a daughter's wedding. This goal serves as an immediate priority. However, once this short-term goal is achieved, their focus often shifts to longer-term objectives. This evolution in perspective is a natural and essential part of the patient's journey. It is a patient's right, as with all individuals, to reassess and modify their priorities over time. As clinicians, it is crucial to acknowledge these dynamics and support them. We should encourage open dialogue, inviting patients to continuously redefine what is most important to them at various stages of their treatment journey. Such a patient-centered approach ensures that we align treatment strategies with their evolving goals and preferences, thereby enhancing the overall effectiveness and relevance of the care we provide.

Reflecting on the individualized and dynamic nature of patient perspective in CLL treatment, we can see how crucial it is to align clinical objectives with patient-centered outcomes. This leads us to explore another vital dimension in the management of CLL. From a clinical scientist's perspective, which study endpoints might reflect treatment success in CLL most accurately?

The quest to pinpoint the most effective study endpoints in CLL is where we have to make the biggest progress as a group. We recognize overall survival (OS) as an endpoint which all of the panelists agreed is of very high priority, but its measurement poses challenges due to its long-term nature. In the context of clinical trials or assessment of a single drug's impact, OS becomes complex because it is influenced by the effectiveness of multiple treatments over time. Progression-free survival (PFS), which measures the duration of disease control, presents itself as a shorter key endpoint. However, its interpretation can be nuanced, particularly with intermittent treatments like venetoclax-obinutuzumab administered for 12 months. For instance, even if the disease reemerges post-treatment, it is often controllable with the same regimen, which leads to another phase of disease control. Therefore, the initial progression does not always signify the failure of a given therapy, nor does it account for the logistic or symptomatic burden on patients. Recently, there has been an excellent commission in Lancet Hematology that shed light on novel ways of accessing the global burden of treatment and symptoms of patients, both in terms of severity and persistence. For example, a single day of nausea differs significantly from enduring the same symptom persistently for months, yet both scenarios might be categorized as grade 1 nausea in clinical reports. Therefore, a refined approach to measuring overall symptom burden and incorporating ways of including the capacity to regain disease control are needed to develop more nuanced efficacy measures that go beyond OS and PFS. In conclusion, we have yet to establish an optimal measure for effectiveness in clinical trials for CLL, which underscores the need for ongoing research and development in this area. ■

www.memo inoncology.com

Expert interviews at iwCLL 2023

Lydia Scarfò describes prophylactic and therapeutic measures against SARS-CoV-2 in patients with CLL, potential risk factors for mortality, seroconversion in response to vaccination and areas of research and unmet need regarding prevention and treatment of COVID-19 infections in patients with CLL and hematologic malignancies in general. Finally, she gives insights into the clinical implications of XPO1 mutations in CLL patients.

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!

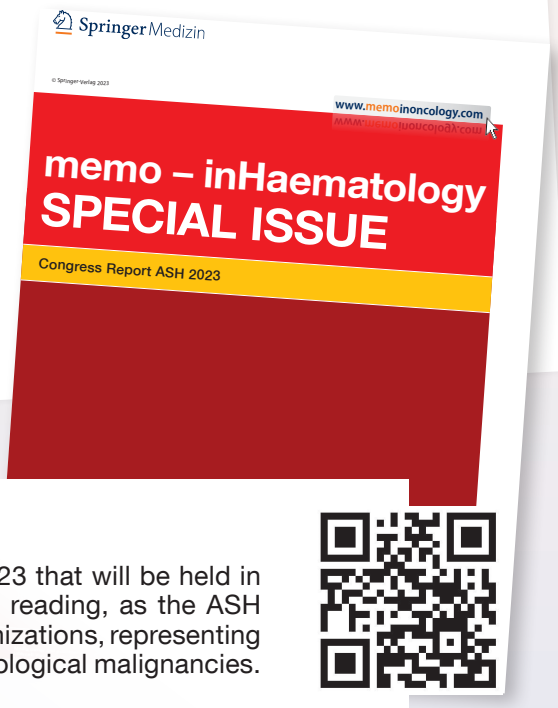
LinkedIn

For more expert interviews and educational materials around recent developments in oncology and haematology please visit our memo InOncology microsite (www.memoinoncology.com)
Here you will find the latest memo inOncology and inHaematology issues reporting on this and previous years' major oncology congresses!

Sign up for the memo inOncology Newsletter on memoinoncology.com to keep yourself updated on all exciting news and developments in haematology and oncology presented at the major conferences.

SUBSCRIBE

Scan to subscribe



Forthcoming Special Issue

This special issue will be offering a synopsis from the ASH 2023 that will be held in December 2023. The report promises to make for stimulating reading, as the ASH Congress itself draws on the input from a number of partner organizations, representing a multidiscplinary approach to the treatment and care of hematological malignancies. Stay tuned for the latest news in hematology.

ASH 2023
Annual Meeting
09. DECEMBER – 12. DECEMBER 2023