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Report from the American Society of Hematology (ASH) Annual Meeting, December 11–14, 2021

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Preface

Dear Colleagues,

The 63rd Annual Meeting of the American Society of Hematology (ASH) took place as a hybrid event that hosted participants both online and on-site in Atlanta, Georgia, USA. Among the multitude of updates and new insights presented from December 11 to 14, 2021, results obtained for targeted therapies in B-cell malignancies including chronic lymphocytic leukemia, mantle cell lymphoma, Waldenström's macroglobulinemia, and marginal zone lymphoma are summarized in this issue of memo inHaematology.

Clinical trials show that chemotherapy-free regimens based on the inhibition of targets such as BTK, BCL2, CD20 and PI3Kδ continue to induce superior outcomes compared to the previous chemo(immuno)therapy-based standards. BTK inhibitors have been a mainstay of treatment from the beginning of the targeted era. While later-generation representatives of this and other drug classes are being investigated as they offer improved efficacy and tolerability profiles over first-generation agents, other compounds such as bispecific antibodies and antibody-drug conjugates are gaining ground in various B-cell malignancies. Newer agents enable us to further increase patient responses even in later lines.

Potential advantages of modern targeted therapies include their ability to overcome unfavorable cytogenetics and the possibility of limited-duration treatment while providing long-term disease control. Approaches that are driven by the achievement of undetectable minimal residual disease might allow for tailored therapy in broad patient populations in the future, thus avoiding overtreatment and unnecessary health expenditures while addressing patient groups with the highest risk. From an economic point of view, adequate and timely treatment is important in these diseases that tend to relapse repeatedly over the course of years, with hospital treatment in particular incurring substantial costs. Local implementation of new insights in the best possible manner will enable us to reduce the significant burden of disease at both the patient and the societal level.

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Determining first-line CLL/SLL treatment strategies with optimized efficacy and safety

GAIA: FCR compared to targeted regimens

The international, randomized, phase III GAIA/CLL13 study was conducted to identify the optimal time-limited first-line treatment regimen for fit patients with chronic lymphocytic leukemia (CLL). Standard chemoimmunotherapy (CIT) consisting of fludarabine, cyclophosphamide and rituximab (FCR; patients ≤ 65 years) or bendamustin plus rituximab (BR; patients > 65 years) was compared to venetoclax-based, limited-duration strategies. Patients with CIRS ≤ 6 and normal creatinine clearance (> 70 mL/min), in whom *TP53* mutation and del(17) had been excluded, participated in the trial. The comparator regimens consisted of rituximab plus venetoclax (RVe), obinutuzumab plus venetoclax (GVe), and obinutuzumab plus ibrutinib and venetoclax (GIVe). Each arm contained approximately 230 patients. Co-primary endpoints of the study included the undetectable minimal residual disease (uMRD) < 10^{-4} rate at month 15 in peripheral blood by 4-color flow, and progression-free survival (PFS). At ASH 2021, Eichhorst et al. presented the results for the uMRD outcome [1]. The PFS interim analysis had been postponed to early 2022 due to the low number of events.

After a median follow-up of 27.9 months, the uMRD rate was significantly higher in the GVe and GIVe arms compared to CIT (86.5 % and 92.2 %, respectively, vs. 52.0 %; p < 0.0001 each; **Figure 1**). For the RVe regimen, this was 57 %, which meant that RVe was not superior to CIT. Overall response rates according to iwCLL were relatively high in all arms, although rates of complete responses with or without complete hematological recovery (CR/CRi) in the venetoclax-based arms exceeded those in the CIT arm (49.4 %, 56.8 % and 61.9 % for RVe, GVe and GIVe, respectively, vs. 31 % for CIT).

Neutropenia was the most frequent grade ≥ 3 adverse event (AE) across all arms. While febrile neutropenia occurred more frequently with CIT (11.1 %), severe infections were seen most commonly with GIVe (22.1 %) and CIT (19.9 %). The incidence of grade ≥ 3 tumor lysis syndrome ranged from 4.2 % (CIT) to 10.1 % (RVe). Grade ≥ 3 bleeding events and atrial fibrillation occurred in approximately 2 % in the GIVe arm and were very rare in the other arms. Twelve patients died due to AEs

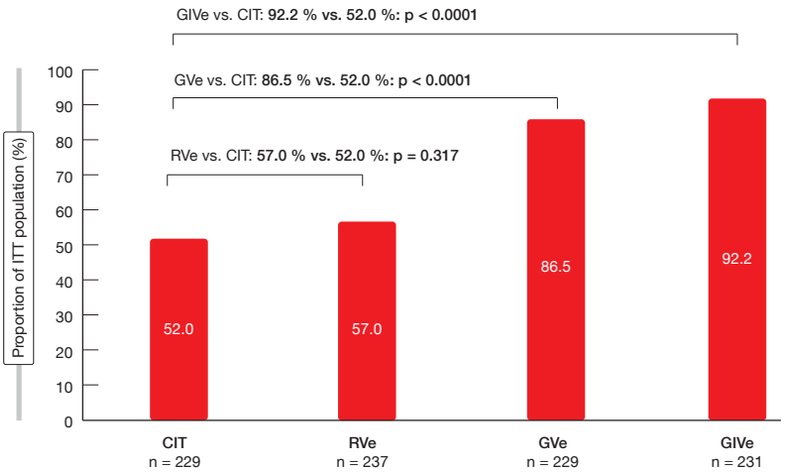

Figure 1: GAIA trial: uMRD < 10^{-4} rates in the peripheral blood at month 15 with chemoimmunotherapy (CIT) vs. venetoclax-based, limited-duration regimens

during treatment and until day 84 after the end of treatment; this was mostly due to infections. Fifteen deaths during the follow-up period were mostly due to secondary neoplasia. The rate of treatment discontinuation was low in all experimental arms.

FCR plus ibrutinib in fit patients

Ibrutinib-based treatment has been shown to prolong survival compared to FCR in CLL patients with unmutated IGHV [2]. It was hypothesized that combining ibrutinib with FCR (iFCR) as initial therapy would lead to high CR rates with uMRD in the bone marrow in a broad population of younger, fit CLL patients. The phase II study launched in 2014 enrolled a total of 85 patients at 7 US sites with a median age of 55 years. After a 1-week lead-in with ibrutinib alone, iFCR was administered for up to 6 cycles, followed by ibrutinib maintenance for 2 years. Patients who achieved uMRD at the end of this period discontinued therapy, while those who did not continued treatment until progression. Retreatment with ibrutinib was allowed in patients who relapsed. The primary endpoint of the trial was the CR rate with uMRD in the bone marrow 2 months after iFCR completion.

According to the first analysis published in 2019, the primary endpoint was met after a median follow-up of 16.5 months, with 33 % of patients achieving CR as defined above [3]. The best uMRD rate in the bone marrow by intent-to-treat (ITT) was 84 % at that time, which was higher than results obtained with any prior CIT or novel-agent–based regimen for initial CLL therapy.

Deepening of remissions

The updated efficacy analysis reported at ASH 2021 showed that the best CR rate with uMRD in the bone marrow by ITT had increased to 55 % with ibrutinib maintenance [4]. Complete remissions had deepened with ibrutinib maintenance from 34 % 2 months after FCR to 81 % as best rate; for patients with mutated IGHV, increases had occurred from 41 % to 88 %, and for those with unmutated IGHV, from 28 % to 76 %. The best rate of uMRD in the bone marrow by ITT remained at 84 %. In the 81 patients with *TP53* wildtype, the best MRD-negative rate by ITT in the bone marrow amounted to 91 %.

Two years after the end of treatment, 86.5 % of patients achieved MRD 10^{-4} in the peripheral blood by flow cytometry; by NGS, this was 91.0 %. Dynamic BH3 profiling suggested that increased CLL cell BCL-2 dependence after 1 week of ibrutinib treatment might predict deeper clinical responses. PFS and overall survival were promising, with rates of 97 % and 99 %, respectively, at a median follow-up of 40.3 months. All of the few patients who experienced recurrence responded to re-treatment with ibrutinib monotherapy.

Compared to the previous report, the updated safety analysis showed increases in the rates of grade 3/4 neutropenia (from 35 % to 40 %), febrile neutropenia (from 9 % to 12 %), and atrial fibrillation (from 3.5 % to 8 %). Grade 3/4 thrombocytopenia and anemia remained unchanged (32 % and 11 %, respectively). No Richter's syndrome has been observed to date. Overall, the safety profile was consistent with individual toxicities of ibrutinib and FCR. The authors concluded that iFCR warrants exploration in comparative studies in a broad population of younger, fit CLL patients with intact *TP53* who desire functional cure with time-limited treatment approaches.

FLAIR: FCR vs. ibrutinib/rituximab

The frontline comparison of FCR (n = 385) with ibrutinib/rituximab (IR; n = 386) in patients considered fit for FCR was at the heart of the randomized NRCI FLAIR trial. Rituximab was ad-

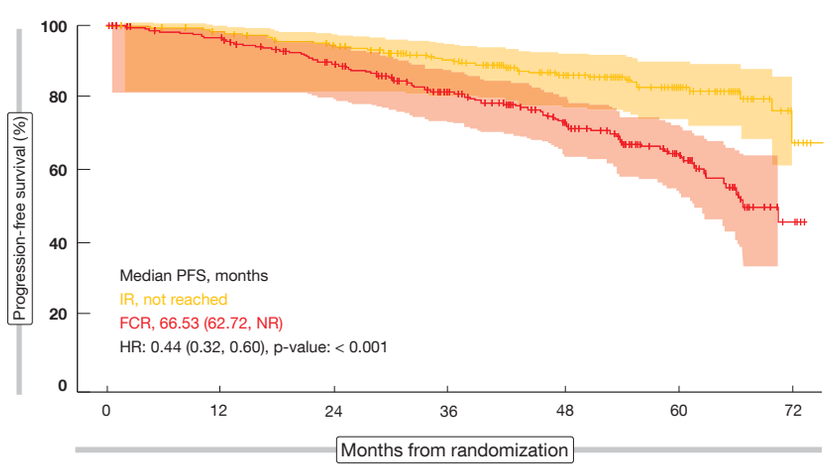

Figure 2: Primary endpoint of the FLAIR study: progression-free survival improvement with ibrutinib/rituximab vs. FCR

ministered for 6 cycles, while ibrutinib was taken orally for a maximum of 6 years or until sustained MRD negativity. The MRD status was assessed every 6 months based on blood.

After a median follow-up of 52.7 months, the primary endpoint of the FLAIR trial was met: IR was superior compared to FCR regarding PFS (not reached vs. 66.53 months; HR, 0.44; $p < 0.001$; **Figure 2**) [5]. PFS was significantly prolonged in the experimental arm in patients with unmutated IGHV (HR, 0.40; $p < 0.001$), whereas a non-significant improvement resulted in IGHV-mutated disease (HR, 0.68; $p = 0.197$). Moreover, significant PFS advantages emerged with IR in patients harboring 11q deletion and normal karyotype but not in those with trisomy 12 and 13q deletion. Three months after the end of treatment, greater proportions of FCR-treated patients showed CR (60.5 % vs. 21.0 %) and MRD negativity in the bone marrow (55.3 % vs. 3.9 %). Overall survival had not been reached yet in either arm, with superimposable curves (HR, 1.01); however, it must be noted that almost all patients relapsing after FCR received either ibrutinib or venetoclax plus rituximab.

Among the most frequent AEs reported within one year of randomization, anemia, nausea and decreased white blood cell counts were more common with FCR than with IR, as well as infusion-related reactions and grade ≥ 3 decreases of white blood cells, while diarrhea was substantially more common with IR. Twenty-nine and 30 patients died in the FCR and IR arms, respectively. Deaths in the FCR arm were predominantly due to secondary hematological malignancies, Richter's transformation, and infections. Those in the IR arm, on the other hand, were mostly related to cardiac causes and non-hematological malignancies. Sudden unexplained death or cardiac death occurred more commonly with IR than with FCR (8 vs. 2); most of these patients (7 of 8) had hypertension or a prior history of cardiac disorder requiring therapy at trial entry. The authors noted that FLAIR is not an outlier for sudden unexplained or cardiac deaths in ibrutinib-containing arms and is consistent with other phase III trials assessing ibrutinib-based regimens in CLL.

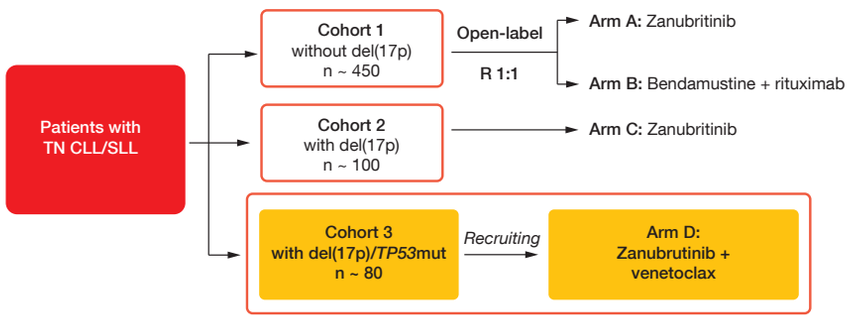

Figure 3: Design of the SEQUOIA trial assessing zanubrutinib as monotherapy and combination partner in patients with treatment-naïve CLL/SLL

Arms A and B of the SEQUOIA trial

Zanubrutinib is a highly selective second-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target effects [6, 7]. The phase III SEQUOIA trial assessed zanubrutinib as monotherapy and combination partner in treatment-naïve patients with CLL or small lymphocytic lymphoma (SLL) ≥ 65 years of age or unsuitable for FCR therapy (**Figure 3**). Results obtained for Arm C of the study already suggested efficacy and tolerability of single-agent zanubrutinib in patients with del(17p) [8, 9]. Arms A and B of the SEQUOIA study compared zanubrutinib to BR in patients who did not have del(17p). The analysis of this cohort presented by Tam et al. at ASH 2021 included 241 and 238 patients in the experimental and control arms, respectively [10].

Zanubrutinib was shown to induce a PFS benefit over BR according to independent review, with 24-month rates of 85.5 % vs. 69.5 % ($p < 0.0001$). This translated into a 58 % risk reduction (HR, 0.42) and was comparable to the PFS achieved with zanubrutinib monotherapy in Arm C of the SEQUOIA study that contained patients with del(17p). The novel BTK inhibitor performed better across all of the important prognostic subgroups, which also applied to high-risk groups with del(11q) and unmutated IGHV. Patients with unmutated IGHV achieved a 76 % reduction in the risk of progression or death on zanubrutinib treatment compared to BR (HR, 0.24; $p < 0.001$). For those with mutated IGHV status, this difference had not become significant yet (HR, 0.67; $p = 0.186$).

Consistent with other studies, zanubrutinib appeared to be well tolerated. Treatment with the novel BTK inhibitor, as compared to BR, was associated with lower grade ≥ 3 AEs (52.5 % vs. 79.7 %) and AEs leading to dose reduction (7.5 % vs. 37.4 %), dose interruption/delay (46.3 % vs. 67.8%), or treatment discontinuation (8.3 % vs. 13.7 %). Notably,

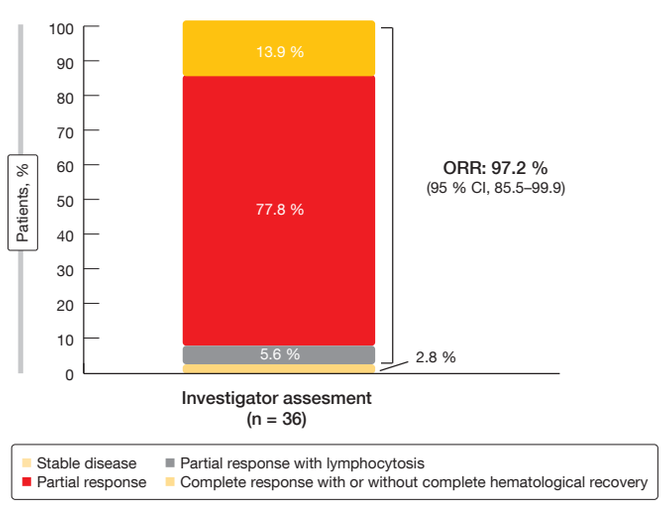

Figure 4: Responses obtained with zanubrutinib plus venetoclax in Arm D of the SEQUOIA study

cytopenias were observed less often, whereas bleeding occurred more commonly (45.0 % vs. 11.0 %). The rate of atrial fibrillation, which is a commonly observed AE of the first-in-class BTK inhibitor ibrutinib, was equally low in both arms (3.3 % vs. 2.6 %).

Zanubrutinib/venetoclax: Arm D

Moreover, early results for Arm D of the SEQUOIA study were reported at ASH 2021 [11]. In this arm, zanubrutinib for ≥ 27 cycles is being evaluated together with venetoclax for 12-24 cycles in patients with del(17) and/or *TP53* variants. Both drugs can be discontinued upon confirmed uMRD; for zanubrutinib, this is the case from cycle 28, and for venetoclax, from cycle 16. The analysis included 49 and 36 individuals in the safety and efficacy populations, respectively.

After a median follow-up of 12 months, zanubrutinib plus venetoclax gave rise to a high overall response rate of 97.2 % in this high-risk population **(Figure 4)**. Almost 14 % obtained CR/CRi; by 36 months, 4 patients had developed uMRD. The authors noted that responses appeared to deepen with longer treatment, as indicated by the achievement of CR/CRi and uMRD. After the 12-month follow-up, only one patient had developed progression, and one fatality occurred due to lung carcinoma prior to the initiation of venetoclax treatment. In the remaining group, treatment was ongoing. Fourteen patients had been treated with the combination for at least 12 months at the time of the analysis.

The combination was well tolerated, with no reported cases of clinical tumor lysis syndrome and relatively low incidences of neutropenia (all grades, 20.6 %), diarrhea (14.7), and nausea (14.7 %). Patients on combination treatment experienced grade ≥ 3 AEs in 38.2 %; in this group, AEs necessitated dose interruptions in 29.4 % but did not give rise to dose reductions or treatment discontinuation. No fatal AEs occurred. According to the investigators' conclusion, a more mature follow-up is needed to fully assess the depth of response and the safety of zanubrutinib plus venetoclax in this high-risk population.

Long-term results for ibrutinib-based strategies

Various ibrutinib-containing regimens are being compared with BR in patients aged ≥ 65 years in the randomized phase III A041202 trial. Arm 1 is receiving BR (n = 183), Arm 2 ibrutinib alone (n = 182), and Arm 3 IR (n = 182). According to the primary analysis published in 2018, median PFS was significantly longer in Arms 2 and 3 than in Arm 1 (HRs, 0.39 and 0.38, respectively; $p < 0.001$ each), while there was no significant difference between Arms 2 and 3 [12]. Updated findings were presented after the third planned interim analysis of Arms 2 and 3 vs. Arm 1, as well as the second planned interim analysis of Arm 3 vs. Arm 2 [13].

Pairwise comparisons after a median follow-up of 55 months revealed 64 % reductions in the risk of progression or death for both ibrutinib vs. BR and IR vs. BR ($p < 0.0001$ each). For IR vs. ibrutinib, the PFS difference was not significant (HR, 0.99; $p = 0.96$). Ibrutinib-based treatment performed better than BR in terms of PFS in all patient subgroups. Multivariable models were conducted to determine prognostic factors associated with PFS. When testing for interaction effects between treatment groups, it was shown that the treatment effect was significantly different for age, *TP53* abnormalities and Zap-70 methylation. Although the protective effect of ibrutinib was evident across subgroups, ibrutinib-based regimens appeared to be even more protective for younger patients and those harboring genomic abnormalities with the highest risk. Ibrutinib-treated patients experienced improved PFS compared to those receiving BR independent of the number of karyotype abnormalities. Patients with *TP53* aberrations derived a significant PFS advantage when treated with ibrutinib-based therapies (HR, 0.07); the same applied to Zap-70 methylation < 20 % (HR, 0.18).

With respect to toxicity, it was noted that atrial fibrillation and hypertension were more common in the groups receiving ibrutinib-based therapies than in the BR-treated cohort and increased over time on therapy. However, they did not appear to outweigh the superior efficacy of treatment in this particular setting.

MRD cohort of CAPTIVATE

The international phase II CAPTIVATE study is assessing first-line therapy with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib plus venetoclax in CLL/SLL patients aged ≤ 70 years. CAPTIVATE contains a fixed-duration cohort and an MRD cohort that was treated according to MRD-guided randomization after the completion of the 12 ibrutinib/venetoclax cycles **(Figure 5)**. Overall, 149 individuals were enrolled into this cohort. Patients who achieved confirmed uMRD (n = 86; 58 %) were randomized to either ibrutinib or placebo and those with unconfirmed uMRD (n = 63; 42 %) to either ibrutinib plus venetoclax or ibrutinib monotherapy. Randomizations were double-blind for those with confirmed uMRD and open-label for the unconfirmed uMRD group.

Confirmed uMRD was defined as uMRD $<10^{-4}$ by 8-color flow cytometry over at least 2 assessments at least 3 months apart and in both peripheral blood and bone marrow. Most patients showed high-risk features including del(17p)/*TP53* mutation, complex karyotype, and unmutated IGHV. Ghia et al.

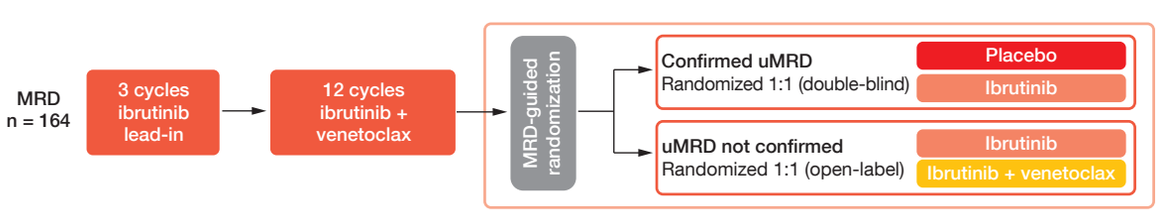

Figure 5: MRD cohort of the CAPTIVATE study: MRD-guided randomization

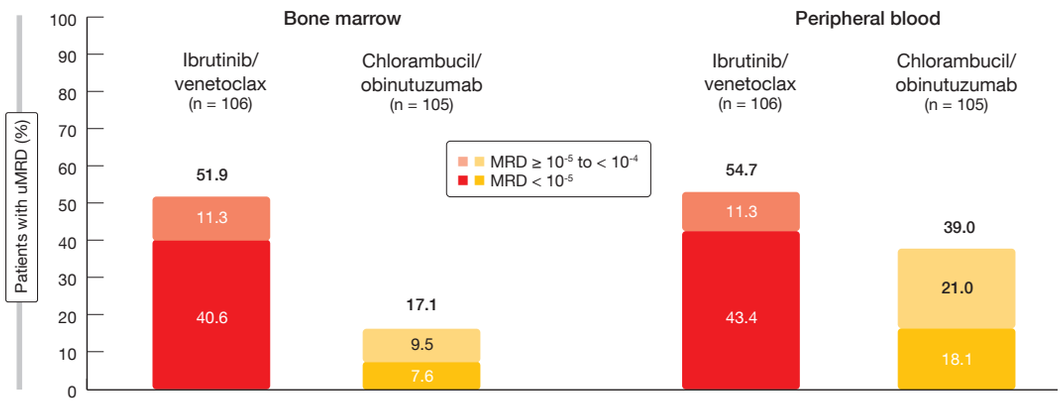

Figure 6: GLOW trial: superior uMRD < 10^{-5} rates with ibrutinib/venetoclax vs. chlorambucil/obinutuzumab in both bone marrow and peripheral blood

reported the updated findings obtained in the MRD cohort at ASH 2021 [14]. At the time of the analysis, the median post-randomization follow-up was 24.0 months.

The treatment was shown to provide deep and durable responses. In the group that had already achieved uMRD after ibrutinib/venetoclax, none of the patients receiving either ibrutinib or placebo experienced new MRD relapses, disease progression or deaths in the additional year of follow-up after the primary analysis presented at ASH 2020 [15]. Both patients with and without uMRD obtained high PFS rates irrespective of their treatment; all four arms showed 3-year PFS rates of ≥ 95 %. At 36 months, 99 % of all patients were alive.

Potential for treatment-free remission

The greatest CR rate improvements noted in the MRD cohort of the CAPTIVATE trial occurred during the first year of randomized treatment. In patients with unconfirmed uMRD, increases in CR rates were similar with ibrutinib/venetoclax and ibrutinib alone. Likewise, the greatest uMRD rate improvements emerged during the first year of randomized therapy in this group, with ibrutinib/venetoclax inducing more pronounced benefits than single-agent ibrutinib. uMRD rates improved in a similar manner in patients achieving CR and partial response (PR).

Adverse events remained consistent with the known profiles for single-agent ibrutinib and venetoclax after the extended follow-up. Grade ≥ 3 AEs were infrequent across the randomized arms with the exception of neutropenia. The overall pre-randomization prevalence decreased across the four arms over time. Any-grade atrial fibrillation and major hemorrhage occurred in 10 % and 2 %, respectively. Dose reductions or discontinuations after randomization were uncommon.

According to the authors' conclusion, the results obtained in patients with confirmed uMRD support the potential for treatment-free remission with first-line, fixed-duration ibrutinib/venetoclax treatment. Moreover, early data suggest that patients who progress after fixed-duration ibrutinib/venetoclax can be successfully retreated with single-agent ibrutinib. These findings were obtained in the MRD placebo arm and the fixed-duration cohort; here, all 9 patients with available responses achieved PR.

GLOW study: ibrutinib/venetoclax

Munir et al. presented the MRD outcomes and correlation with PFS observed in the phase III GLOW study that tested ibrutinib/venetoclax for 12 cycles after a 3-cycle ibrutinib lead-in compared to 6 cycles of chlorambucil plus obinutuzumab in elderly or unfit patients [16]. CLL patients without del(17p) or known *TP53* mutation participated in this study; they were either ≥ 65 years old or < 65 years with CIRS scores > 6 or creatinine clearance < 70 mL/min. The primary analysis after a median follow-up of 27.7 months had yielded a 78 % reduction in the risk of progression or death (median PFS, not reached vs. 21 months; HR, 0.216; p < 0.0001) [17]. For the current analysis, MRD was evaluated with next generation sequencing and reported with cut-offs of < 10^{-4} and < 10^{-5}.

After 34.1 months of follow-up, superior PFS was maintained with ibrutinib/venetoclax vs. chlorambucil/obinutuzumab (HR, 0.212; p < 0.0001). At 30 months, the PFS rates amounted to 80.5 % vs. 35.8 %. Three months after the end of treatment, the uMRD < 10^{-4} rates were significantly higher with ibrutinib/venetoclax than with chlorambucil/obinutuzumab in both bone marrow (51.9 % vs. 17.1 %; p < 0.0001) and peripheral blood (54.7 % vs. 39.0 %; p = 0.0259). In the experimental arm, but not in the control arm, most patients with MRD < 10^{-4} had deep responses of < 10^{-5} **(Figure 6)**. Depth of MRD response was similarly pronounced in peripheral blood and bone marrow for patients with unmutated IGHV; also, among patients with mutated *TP53*, 5 of 7 achieved uMRD < 10^{-5} in both blood and marrow with ibrutinib/venetoclax. Assessment of the MRD dynamics after the end of treatment showed that molecular and clinical relapses were less frequent during the first year in the experimental arm as uMRD was sustained more efficiently than in the control arm. Sustained uMRD 10^{-4} was observed in 84.5 % vs. 29.3 %, and sustained uMRD 10^{-5} occurred in 80.4 % vs. 26.3 %. Detectable MRD ≥ 10^{-4} was less likely to worsen or lead to progression with ibrutinib plus venetoclax.

PFS according to response

In terms of correlation with PFS, the analysis demonstrated a less pro-

nounced impact of CR/CRi vs. PR on PFS in the experimental arm. While the 30-month PFS rates remained > 85 % for patients with CR/CRi or PR here, most patients in the control arm who had obtained PR progressed on treatment. In patients with uMRD < 10^{-4} in the marrow 3 months after the end of treatment, the PFS rate was sustained more effectively after ibrutinib/venetoclax than after chlorambucil/obinutuzumab. Similarly, those with detectable MRD ≥ 10^{-4} fared better with the ibrutinib-based regimen, as PFS rates > 90 % were sustained during the first post-treatment year independent of the MRD status, while early relapses frequently occurred with chlorambucil/obinutuzumab. Moreover, lymph node responses were better maintained in the experimental arm over time in patients with detectable minimal residual disease.

In their summary of the results obtained in the GLOW study, the authors noted that the unique relationship between MRD status and PFS might be explained by broader clearance of multiple disease compartments resulting from complementary mechanisms of ibrutinib and venetoclax. Additional follow-up is warranted to confirm the longer-term impact of the MRD status on PFS. ■

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Management of patients with relapsed/refractory CLL: what is new?

VISION: stop-start approach with ibrutinib/venetoclax

The optimal novel-agent approach for patients with chronic lymphocytic leukemia (CLL) is subject to research. Targeted therapies have become the undisputed standard of care in both relapsing/refractory and treatment-naïve settings. The choice of regimen remains, however, disputable. Continuous BTK inhibition confers the risk of cumulative toxicity and acquired resistance, while time-limited combination therapies may result in relatively high adverse event (AE) rates and lead to overtreatment of patients with favorable risk. Discontinuation of treatment based on the depth of response constitutes a possible strategy. Furthermore, most of the randomized comparisons are conducted with the first-generation BTK inhibitor ibrutinib that is potentially cardiotoxic. Therefore, this is not an optimal drug for the elderly, comorbid population.

In the setting of relapsed/refractory CLL, the phase II VISION HO141 trial assessed the feasibility of observation alone in patients who had achieved undetectable minimal residual disease (uMRD) after 15 cycles of ibrutinib plus venetoclax [1]. This strategy was compared to ibrutinib maintenance following the combination period. Once patients in the observation arm showed CLL progression, the combined treatment was reinitiated. Progression was determined according to the iwCLL criteria or MRD > 10^{-3} plus MRD > 10^{-2} at least 1 month later. Venetoclax treatment after progression was limited to 12 months, while ibrutinib was administered until progression. The primary endpoint was the progression-free sur-

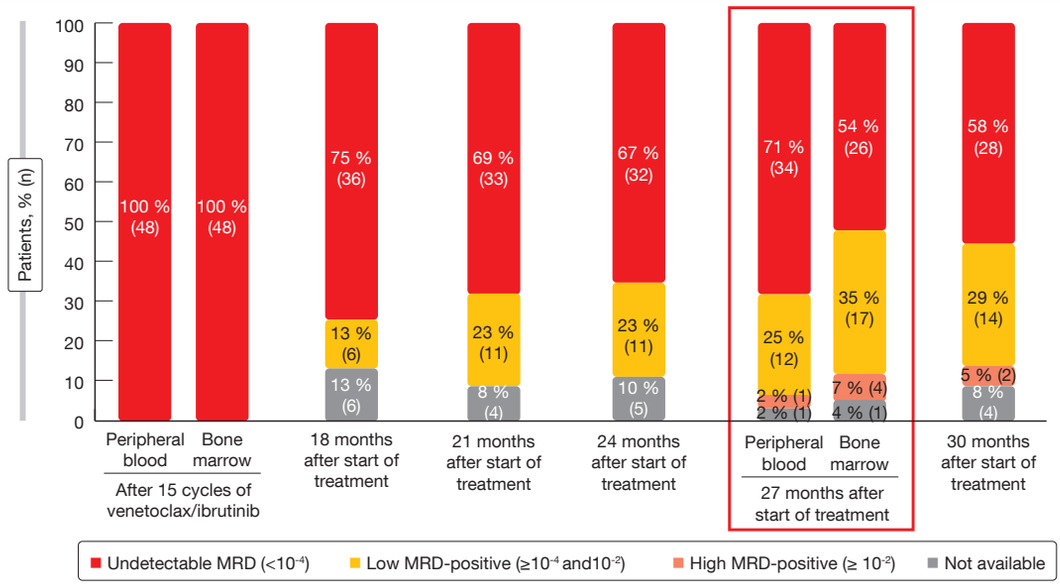

Figure 1: Minimal residual disease development after the end of fixed-duration treatment with 15 cycles of ibrutinib/venetoclax

vival (PFS) rate 12 months after treatment discontinuation in the observation arm.

Freedom from progression in 98 %

Among 197 patients who received the initial combination regimen and underwent MRD assessment by flowcytometry, 72 developed uMRD, while MRD remained detectable in 125 individuals. The latter were treated with ibrutinib maintenance in a non-randomized manner. In the uMRD group, 24 and 48 patients were randomized to ibrutinib maintenance and observation, respectively.

The primary endpoint of the trial was met. One year after treatment discontinuation, 98 % of patients in the observation arm were progression-free. At that time, 71 % had uMRD ($< 10^{-4}$) in the peripheral blood **(Figure 1)**. In patients without uMRD who had been assigned to non-randomized ibrutinib maintenance, MRD levels have remained stable for one year. Overall survival (OS) rates at 27 months were 100 %, 98 % and 92 % for patients on ibrutinib maintenance, observation, and non-randomized ibrutinib maintenance.

Seven patients in the observation arm reinitiated combined treatment with ibrutinib and venetoclax upon MRD positivity; six of these achieved de-novo complete remission within 3 cycles, and the 7th patient was awaiting evaluation at the time of the analysis. AE rates naturally decreased in the observation arm compared to the other patient groups after cycle 15. The authors concluded that an MRD-guided stop-start strategy of ibrutinib/venetoclax is feasible in patients with relapsed/refractory CLL and can be recommended.

MRD-driven triple therapy

Roeker et al. conducted a phase II study with the aim of identifying a subset of patients responding to ibrutinib monotherapy who have persistent MRD and might benefit from a combined strategy [2]. After ≥ 6 months of ibrutinib treatment in any line, the PI3Kδ inhibitor umbralisib and the anti-CD20 antibody ublituximab (U2) were added to ibrutinib in patients with detectable MRD. Treatment continued until they achieved uMRD in the peripheral blood on two sequential occasions. Overall, the triplet therapy was administered for a maximum of 24 cycles until the initiation of treatment-free observation regardless of MRD status. Durability of remission following treatment discontinuation was monitored using sequential MRD assessments. The study design permitted retreatment with ibrutinib and U2 upon clinical progression after ≥ 6 months of treatment-free observation. Twenty-eight and 27 patients were evaluable for safety and efficacy, respectively. Two thirds and one third had received ibrutinib in the first line and for relapsed/refractory disease, respectively. The uMRD rate was defined as the primary endpoint.

This was the first non–venetoclax-containing MRD-driven, time-limited approach utilizing the combination of BTK and PI3Kδ inhibitors with an anti-CD20 antibody. It gave rise to deep remissions, with a uMRD rate of 77 % and median time to first uMRD of 7.4 months. Only 4 % of patients completed 24 cycles of ibrutinib plus U2 without achieving MRD negativity, and 19 % remained on therapy with detectable MRD at the time of the analysis. PFS from study entry and from entering treatment-free observation was excellent, with only one progression event.

The AE profile of ibrutinib remained unchanged after the addition of U2. Most AEs observed in the study were rated as low-grade. Two patients discontinued all therapy due to AEs including rash and arthralgia; both had uMRD at that time and were able to enter treatment-free observation. Overall, this add-on approach for patients on continuous ibrutinib allowed for tailored, time-limited therapy and sustained treatment-free observation. The study continues to enroll, with other cohorts exploring the addition of U2 to acalabrutinib or venetoclax.

Three-year follow-up of ASCEND

Compared to ibrutinib, the next-generation BTK inhibitor acalabrutinib is

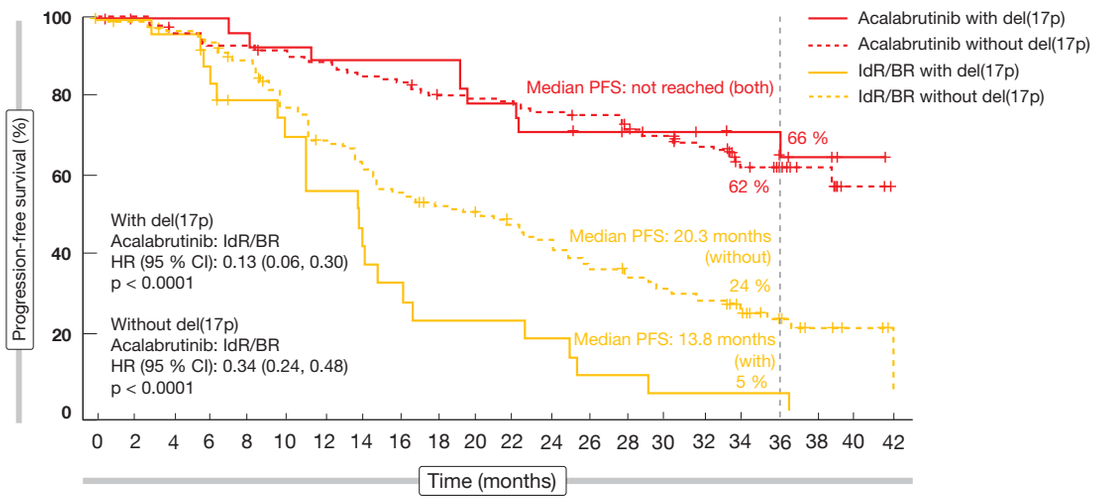

Figure 2: ASCEND: acalabrutinib vs. idelalisib/rituximab and bendamustine/rituximab according to del(17p) status

more selective and has decreased alternative-target activity *in vitro* [3, 4]. According to the primary analysis of the phase III ASCEND trial after a median follow-up of 16.1 months, acalabrutinib monotherapy exhibited superior PFS and a favorable safety profile compared with physicians' choice, i.e., idelalisib/rituximab (IdR) or bendamustine/rituximab (BR) in patients with relapsed/refractory CLL after ≥ 1 systemic therapy [5]. Both the acalabrutinib arm and the IdR/BR arm contained 155 patients. As most of the doctors chose IdR (118 of 153 patients in the comparator arm), the study was in fact the first randomized comparison of BTK and PI3K inhibitors in relapsed/refractory CLL.

The updated results at 3 years of follow-up presented at ASH 2021 by Jurczak et al. showed maintained efficacy and safety of acalabrutinib that was favorable compared to the standard-of-care regimens [6]. Median PFS for the experimental arm had not been reached yet, while this was 16.8 months in the control arm (HR, 0.29; p < 0.0001). At 36 months, the PFS rates amounted to 63 % vs. 21 %. Within the control population, patients treated with IdR fared better than those receiving BR; the 36-month PFS rates were 25 % vs. 9 % for IdR and BR, respectively. Acalabrutinib reduced the risk of progression or death by 69 % and 75 %, respectively (p < 0.0001 each). The advantage conferred by the novel BTK inhibitor held true irrespective of the presence of high-risk genetic features. In patients without and with del(17p), median PFS had not been reached on acalabrutinib treatment, while this was 20.3 and 13.8 months, respectively, in the control arm **(Figure 2)**. A similar picture emerged with respect to IGHV mutation status. The PFS results favored acalabrutinib in all subgroups (e.g., number of prior therapies, presence of bulky disease, Rai stage at screening). Median OS had not been reached in either arm. At 36 months, 80 % vs. 73 % of patients were alive despite the crossover offered to 76 patients progressing in the control arm. Also, the overall response rates did not differ between acalabrutinib and IdR/BR (83 % vs. 85 %; p = 0.62).

The longer-term follow-up did not reveal any new safety findings in the experimental arm. Acalabrutinib maintained an acceptable tolerability profile, and fewer patients discontinued treatment due to AEs despite longer exposure. As the authors noted, these data support the use of acalabrutinib in patients with relapsed/refractory CLL including those with high-risk features.

Acalabrutinib: AE and Q-TWiST analyses

The randomized, phase III ELEVATE-RR study compared acalabrutinib with ibrutinib, demonstrating non-inferior PFS and improved tolerability in pretreated patients with del(17p) and/or del(11q) [7]. Seymour et al. conducted a post-hoc analysis of the study to further characterize the BTK-inhibitor–associated AEs and the safety profile of acalabrutinib [8]. Event-based analyses demonstrated a higher BTK-inhibitor–related toxicity burden with ibrutinib. Acalabrutinib showed comparatively lower incidence, exposure-adjusted incidence, and exposure-adjusted time spent with cardiovascular-related toxicities including atrial fibrillation/flutter, hypertension, and bleeding. Moreover, cumulative incidences of hypertension and atrial fibrillation/flutter were lower with acalabrutinib in patients without a history of these events.

Based on the ASCEND and ELEVATE-RR trials, a quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis assessed the quality-adjusted survival benefits of acalabrutinib *versus* the comparator agents [9]. The results reported at ASH 2021 indicated significant quality-adjusted survival benefit of acalabrutinib compared with idelalisib or bendamustine plus rituximab. Compared with ibrutinib, survival gains varied by toxicity definition, but were numerically higher in all analyses.

Pirtobrutinib after BTK pretreatment

The benefits achieved with covalent BTK inhibitors are often diminished due to resistance [10]. Available subsequent treatment options include BCL2 inhibitors, combination regimens and, last but not least, third-generation BTK inhibitors. The potent non-covalent BTK inhibitor pirtobrutinib shows > 300-fold selectivity for BTK vs. 370 other kinases and favorable pharmacologic properties [11].

Mato et al. reported the findings achieved with pirtobrutinib in BTK-pretreated CLL/SLL patients enrolled in the

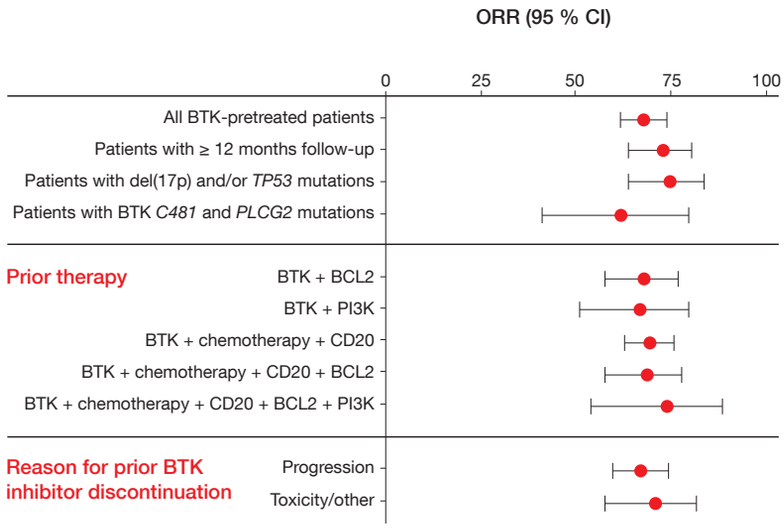

Figure 3: Responses obtained with pirtobrutinib irrespective of patient and pretreatment characteristics

phase I/II BRUIN study [12]. In 252 efficacy-evaluable individuals, the overall response rate amounted to 68 % and remained stable over time. Pirtobrutinib was effective irrespective of the presence of high-risk genetic aberrations, the type of pretreatment, and the reason for prior BTK inhibitor discontinuation **(Figure 3)**. Median PFS in patients who were at least BTK-inhibitor–pretreated (median number of prior lines, 3) had not been reached yet; in those who had at least received BTK and BCL2 inhibitors (median number of prior lines, 5), median PFS was 18 months. Moreover, the treatment proved efficacious in patients failing previous chemotherapy, monoclonal antibodies, covalent BTK inhibitors, BCL2 inhibitors, and PI3K inhibitors (i.e., the so-called "penta failures").

The favorable safety and tolerability profile observed in the study was consistent with the design of pirtobrutinib as a highly selective and non-covalent reversible BTK inhibitor. No dose-limiting toxicities were reported, and the maximum tolerated dose had not been reached. AEs of special interest included bruising, rash, and arthralgia. In their conclusion, the authors summarized that pirtobrutinib demonstrates promising efficacy in CLL/SLL patients previously treated with BTK inhibitors. Randomized global, phase III trials including BRUIN CLL-321, BRUIN CLL-322 and BRUIN CLL-313 are currently evaluating this agent in the setting of CLL/SLL.

MK-1026

Resistance against BTK inhibitors develops primarily through mutations at the cysteine binding site (C481) or PLCγ2 [13, 14]. MK-1026 has been developed as a non-covalent, potent inhibitor of both wild-type and *C481S*-mutated BTK [15]. The preliminary recommended phase II dose was determined at 65 mg/d in a phase I/II dose escalation and expansion study performed in patients with hematologic malignancies. At ASH 2021, Woyach et al. presented the efficacy and safety of MK-1026 65 mg/d in study participants with CLL/SLL treated during the dose expansion phase [16].

MK-1026 was shown to have promising anti-tumor activity, with a manageable safety profile. Among 38 efficacy-evaluable patients, 57.9 % responded to treatment. Median duration of response had not been reached yet at the time of the analysis. Almost 94 % achieved decreases in tumor volume, and decreases ≥ 50 % were seen in 69.7 %. Responses occurred in heavily pretreated patients and in those progressing on prior covalent BTK inhibition.

The most common AEs comprised fatigue (33.1 %), constipation (31.4 %), and dysgeusia (28.0 %). Grade ≥ 3 AEs predominantly included hypertension (9.3 %) and fatigue (3.4 %). Further evaluation of MK-1026 in B-cell malignancies at doses of ≥ 65 mg is ongoing. ■

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Mantle cell lymphoma: refining clinical outcomes beyond the current boundaries

Parsaclisib: primary analysis of CITADEL-205

Targeted therapies including BTK inhibitors are used in the second- and later-line treatment of patients with mantle cell lymphoma (MCL), although intolerance and treatment failure are common, with poor survival outcomes in the relapsed and refractory setting [1, 2]. This highlights the need for novel agents such as the potent and highly selective next-generation PI3Kδ inhibitor parsaclisib. The phase II CITADEL-205 study assessed parsaclisib in patients with relapsed/refractory MCL previously treated with or without the BTK inhibitor ibrutinib. At ASH 2021, Mehta et al. presented the primary efficacy and safety analysis for the cohort of BTK-inhibitor–naïve patients [3].

These patients were originally divided into a weekly dosing group and a daily dosing group. After an interim analysis, enrollment was closed in the weekly dosing group. The recommended dose is parsaclisib 20 mg/d for 8 weeks followed by 2.5 mg/d. Data were reported for the daily dosing group (n = 77) and for all treated patients (n = 108) who included those that switched from 20 mg once weekly to 2.5 mg/d. The objective response rate (ORR) constituted the primary endpoint.

Tumor reductions in almost all patients

Parsaclisib showed excellent activity, with ORRs of approximately 70 % in both evaluated groups **(Figure 1)**. In 89 % of all responders, responses were observed already at the time of the first disease assessment at 8 weeks. Regression of target lesions occurred in 96 % of evaluable patients, with 84 % showing > 50 % reductions in best percentage change from baseline. Progression-free survival was 13.6 and 12.0 months for the daily dosing group and all treated patients, respectively. Regarding duration of response, this was 12.1 and 13.7 months, respectively. Median overall survival had not been reached yet in either group. Eighty percent of patients were alive at 1 year.

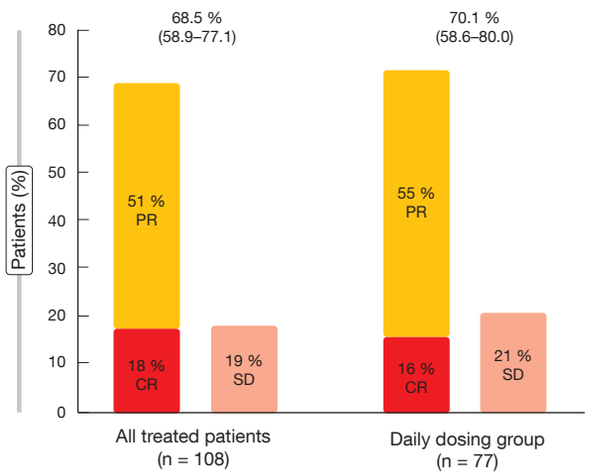

Figure 1: Objective responses observed with parsaclisib in all treated patients and in the daily dosing group. PR, partial response; CR, complete response; SD, stable disease

In general, the patients tolerated the treatment well. Diarrhea was the most frequently observed adverse event (AE; 40 % and 34 % in the daily dosing group and all treated patients, respectively), followed by pyrexia (17 % and 18 %, respectively). The most common treatment-emergent AEs leading to dose interruption in the daily dosing group were diarrhea (14 %) and neutropenia (9 %). Dose discontinuation was mainly due to diarrhea (16 %) and colitis (6.5 %). Grade ≥ 3 diarrhea occurred in 18 % and 14 %, respectively, after a median of 5.1 and 4.3 months, respectively. For colitis, grade ≥ 3 events were seen in 5 % and 4 %, respectively, after a median of 3.1 months. Improvement to grade ≤ 2 was noted after approximately 11 days for diarrhea and 20 days for colitis. According to the authors, parsaclisib represents a potentially new treatment option for BTK-inhibitor–naïve patients with relapsed/refractory MCL and is a first-in-class PI3Kδ inhibitor in the setting of MCL.

TP53-mutant disease: BOVen

Patients with *TP53*-mutant MCL constitute a high-risk subset that shows poor survival when treated with intensive chemoimmunotherapy [4]. Given the lack of a standard frontline regimen, the combination of zanubrutinib, obinutuzumab, and venetoclax (BOVen) was hypothesized to be well tolerated and efficacious in this setting. It has already been demonstrated that the combination of a BTK inhibitor with a BCL2 inhibitor is synergistic and active in relapsed/refractory MCL, including patients with *TP53* mutation [5]. Ibrutinib, obinutuzumab, and venetoclax has given rise to high response rates in relapsed and untreated MCL [6].

The preliminary analysis of a multicenter, investigator-initiated phase II study presented at ASH 2021 by Kumar et al. showed promising efficacy and good tolerability of BOVen in 17 patients with previously untreated MCL and *TP53* mutation [7]. Fourteen patients were evaluable for efficacy. After a median follow-up of 4 months, the ORR was 86 %, with a CR rate of 64 %. At cycle 3, peripheral blood flow cytometry became negative in all patients. Grade ≥ 3 AEs occurred in 11 %. Serious AEs included grade 3 lung infection, grade 4 tumor lysis syndrome, and grade 1 non-neutropenic fever. No events resulted in drug discontinuation. Longer follow-up is required to further assess the outcomes over time.

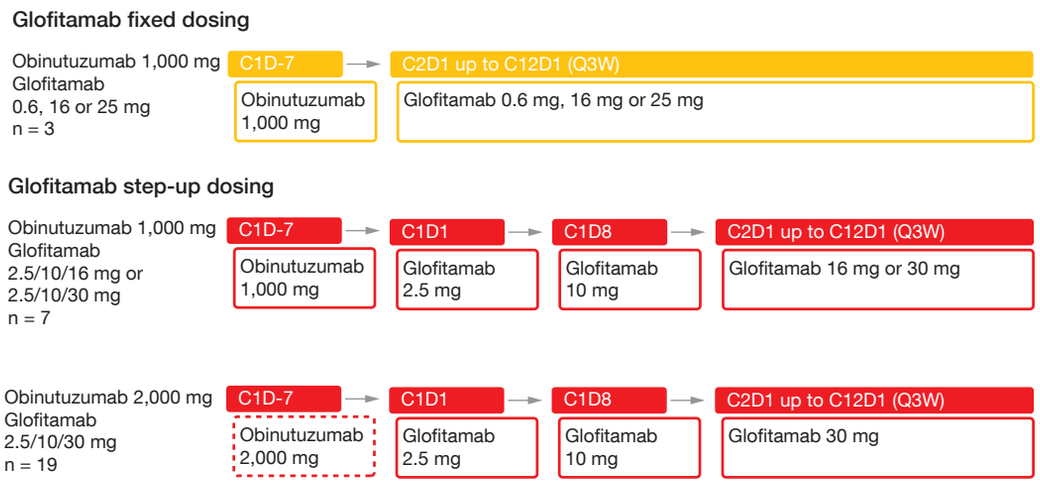

Figure 2: Design of the phase I dose escalation study assessing step-up dosing of glofitamab after obinutuzumab

Step-up dosing of glofitamab

The bispecific antibody glofitamab redirects T cells to eliminate malignant B cells by targeting both CD20 and CD3 [8]. Glofitamab has shown promising efficacy and manageable safety as monotherapy and in combination with obinutuzumab in patients with heavily pretreated relapsed/refractory B-NHL [9, 10]. Obinutuzumab pretreatment and/or cycle 1 step-up dosing enabled effective mitigation of cytokine release syndrome (CRS). At ASH 2021, Phillips et al. reported data on obinutuzumab followed by glofitamab monotherapy in patients with relapsed/refractory MCL who were treated in the phase I dose escalation setting [11]. The study contained 3 arms. Glofitamab was assessed with fixed dosing after obinutuzumab 1,000 (n = 3), and with step-up dosing over 12 cycles (2.5 mg up to 30 mg) after obinutuzumab administered at doses of either 1,000 mg (n = 7) or 2,000 mg (n = 19) **(Figure 2)**.

This approach gave rise to high response rates, with activity observed across the dosing regimens. For fixed dosing of glofitamab after obinutuzumab 1,000 mg, responses occurred in 67 %, and for step-up dosing after obinutuzumab 1,000 mg and 2,000 mg, this was 71 % and 91 %, respectively. Prior BTK inhibitor therapy did not affect the results; response rates in patients with and without prior BTK inhibition amounted to 83 % and 75 %, respectively. Overall, 81 % of patients in the entire group responded, and complete metabolic responses arose in 67 %. At the time of the data cutoff, most patients had ongoing responses, and 85.7 % of those with a CR remained in remission. The treatment demonstrated favorable safety. Glofitamab-related grade 3/4 AEs occurred in 24.1 % of all patients. No fatal AEs or AEs leading to treatment discontinuation were reported. CRS represented the most common all-grade AE (58.6 %). Most CRS events were observed during cycle 1, were grade 1 or 2, and resolved. Immune effector cell-associated neurotoxicity syndrome (ICANS) grade 1 emerged in one patient (3.4 %) in the 1.000 mg obinutuzumab plus glofitamab step-up dosing cohort. No grade ≥ 2 ICANS or grade ≥ 3 tumor flare events were noted.

The authors pointed out that these results support a future confirmatory trial. Glofitamab, which is a fixed-duration regimen with off-the-shelf availability, continues to be evaluated in patients with relapsed/refractory MCL after BTK inhibitor treatment.

Treatment patterns and health economics aspects

The retrospective US-based study conducted by Shah et al. examined charac-

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teristics of patients with MCL receiving BTK inhibitors, as well as treatment patterns and costs in the real-world setting [12]. Adult MCL patients with ≥ 1 BTK inhibitor prescription claim for 12 months were identified in the Symphony Health's IDV, an open-source claims database. The final population consisted of 1,653 active patients on BTK inhibitor treatment. This analysis provides the first real-world evidence on patients with MCL treated with all currently available BTK inhibitors (i.e., ibrutinib, zanubrutinib, acalabrutinib).

The most common comorbidity at BTK inhibitor initiation was hypertension, followed by dyslipidemia and diabetes. NSAIDs and proton pump inhibitors were the two most common concomitant medications across the three drugs. More than half of the ibrutinib use took place in the frontline setting (68.4 %), while acalabrutinib and zanubrutinib were mainly used in relapsed/refractory disease (68.9 % and 80.6 %, respectively). Among zanubrutinib users, 22 % were switched from ibrutinib and 7 % from acalabrutinib; among acalabrutinib users, 21 % were switched from ibrutinib. The compliance rate was higher for zanubrutinib (65 %) than for acalabrutinib (62 %) and ibrutinib (59 %).

Among patients with ≥ 1 hospitalization, the average length of stay was found to be 5.9 days. Patients in the zanubrutinib group had shorter length of stay (4.0 days) than those treated with acalabrutinib (5.8 days) and ibrutinib (5.9 days). On average, the total submitted inpatient charge per stay was lower for patients in the zanubrutinib group (51,051 $) than for those in the acalabrutinib (74,546 $) and ibrutinib (79,482 $) groups. Future studies are needed to further understand factors associated with treatment selection and outcomes. ■

Marginal zone lymphoma: PI3Kδ inhibition and beyond

CITADEL-204: parsaclisib in BTK-inhibitor–naïve patients

First-line treatment for patients with marginal zone lymphoma (MZL) typically includes anti-CD20-based regimens that generally evoke high response rates [1, 2]. However, in most cases, serial relapses eventually require several lines of therapy. The phase II CITADEL-204 trial evaluated the highly selective, next-generation PI3Kδ inhibitor parsaclisib in patients with relapsed/refractory MZL with or without prior exposure to ibrutinib. All patients had received ≥ 1 prior systemic therapy, including ≥ 1 anti-CD20 antibody.

Enrollment in the ibrutinib-experienced cohort was closed for feasibility reasons. Within the BTK-inhibitor–naïve cohort, patients were allocated into a weekly dosing group (i.e., parsaclisib 20 mg/d for 8 weeks followed by 20 mg once weekly) and a daily dosing group (i.e., parsaclisib 20 mg/d for 8 weeks followed by 2.5 mg/d continuously). Following an interim analysis, enrollment continued in the daily dosing group and was closed in the weekly dosing group. Daily dosing has been established as the recommended regimen. At ASH 2021, Phillips et al. reported the primary efficacy and safety analysis for all treated patients (n = 100) and the daily dosing group (n = 72) [3]. The entire treated cohort included patients who had switched from 20 mg once weekly to 2.5 mg/d.

Rapid and durable responses

Objective responses by independent review committee, which were defined as the primary endpoint, occurred in 58.0 % and 58.3 % of patients in the all-treated and daily dosing groups, respectively. Complete remissions were noted in 6 % and 4 %, respectively. Two thirds of all responders showed their first response already at the first disease assessment after 8 weeks. Comparable responses rates were observed in patients with nodal, extranodal, and splenic MZL. Median duration of response and median progression-free survival were 12.2 months and 16.5 months, respectively, for both the entire treated cohort and the daily dosing group. All evaluable patients had regression at target lesions or spleen, with 83 % experiencing > 50 % reduction in best percentage change from baseline.

Parsaclisib showed a manageable safety profile. Treatment-emergent adverse events (TEAEs) primarily included diarrhea (47 % and 53 % in all treated patients and the daily dosing group, respectively), cough (23 % and 26 %, respectively), and rash (18 % for both groups). Two deaths due to AEs (i.e., febrile neutropenia with sepsis/respiratory distress in one patient and sepsis in another) were deemed related to parsaclisib. The TEAEs most commonly leading to dose interruption were diarrhea (15 %) and neutropenia (6 %). Treatment discontinuation was mainly due to diarrhea (12.5 %) and colitis (7 %). Grade ≥ 3 diarrhea emerged in 12 % and 15 % in all treated patients and the daily dosing group, respectively, after a median of 5.6 and 5.1 months, respectively. Grade ≥ 3 colitis was reported in 7 % and 10 %, respectively, after a median of 5.6 months. Improvement to grade ≤ 2 occurred after 11-12 days for diarrhea and 21 days for colitis.

Favorable findings for U2

In relapsed/refractory MZL patients, the PI3Kδ inhibitor umbralisib as monotherapy has been shown to give rise to a 49.3 % objective response rate (ORR) with complete remissions in 16 % [4]. Umbralisib combined with the anti-CD20 antibody ublituximab (U2) has demonstrated clinical benefits in patients with relapsed/refractory non-Hodgkin lymphoma, with a manageable safety profile [5]. Chavez et al. presented

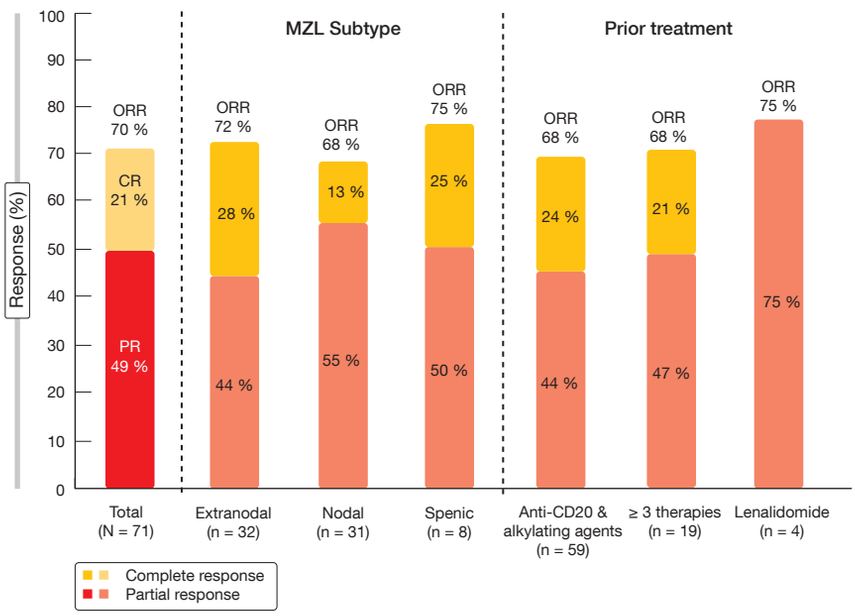

Figure: Responses to umbralisib plus ublituximab: overall, according to MZL subtype and according to prior treatment

results for the MZL cohort included in the global phase II UNITY-NHL study at ASH 2021 [6]. Patients with relapsed/refractory MZL who had been pretreated with ≥ 1 anti-CD20 agent received continuous umbralisib in combination with fixed-duration ublituximab for a maximum of 24 cycles. ORR by independent review committee constituted the primary endpoint. The efficacy-evaluable group contained 71 individuals.

Overall, 70 % of these patients responded to treatment, with 21 % achieving complete remission **(Figure)**. Disease control was obtained in 93 %. Responses were similar regardless of MZL subtype and prior treatment, as depicted in the Figure. At the time of the analysis, median duration of response had not been reached yet. Eighty-eight percent of patients experienced reductions in tumor burden from baseline. Median progression-free survival was 17.61 months; after censoring of COVID19-related deaths, this endpoint had not been reached yet.

The U2 regimen demonstrated an acceptable safety profile. Diarrhea occurred most commonly (49 %), followed by nausea (42 %) and fatigue (38 %). Dose reductions were resorted to as a measure for controlling AEs in 22 patients (31 %). Among PI3K-specific events, transaminase elevations and diarrhea were the main reasons for dose reductions (11 % and 4 %, respectively). Only 1 patient out of 9 who developed grade 3/4 diarrhea required steroids. Two cases of grade 3/4 non-infectious colitis occurred (2.8 %). As the authors pointed out, use of the U2 regimen resulted in increased response rates compared to the cohort previously treated with umbralisib alone. In all, the combination showed favorable clinical activity and might constitute a novel non-chemotherapy approach for patients with relapsed/refractory MZL. ■

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Phase II data on novel BTK inhibitors for patients with Waldenström's macroglobulinemia

Orelabrutinib: rapid and lasting responses

Second-generation BTK inhibitors such as orelabrutinib and tirabrutinib are currently being evaluated in the treatment of Waldenström's macroglobulinemia (WM). Orelabrutinib is a BTK inhibitor with excellent target selectivity and almost 100 % BTK occupancy [1]. At ASH 2021, Zhou et al. reported the results for 47 patients with relapsed/refractory WM who received orelabrutinib 150 mg/d in the single-arm, multicenter, open-label, phase II ICP-CL-00105 study [2]. The major response rate (MRR; complete, partial, and very good partial responses) was defined as the primary endpoint.

Major responses were achieved quickly, after a median of 1.99 months.

TABLE
Best overall response with orelabrutinib in 47 patients with relapsed/refractory Waldenström's macroglobulinemia

Complete response, n (%)	0
Very good partial response, n (%)	7 (14.9)
Partial response, n (%)	30 (63.8)
Minor response, n (%)	4 (8.5)
Stable disease, n (%)	5 (10.6)
Disease progression, n (%)	0
Unknown, n (%)	1 (2.1)
Major response rate, %	78.7
Overall response rate, %	87.2
Disease control rate, %	97.9

The MRR was 78.7 %, and the overall response rate amounted to 87.2 % **(Table)**. Disease control resulted in 97.9 %. Remissions proved durable, which was mirrored by the 12-month rates: for major responses, this was 91.3 %, and for responses in general, 92.6 %. Subgroup analyses showed a consistent treatment effect across the prespecified groups. At 12 months, 93.6 % of participants were alive, and 89.3 % were progression-free. Durable improvement in hemoglobin level was found in 78.7 %, with a median maximal increase of 33 g/L. For serum IgM levels, the median reduction from baseline amounted to 79.7 %.

Orelabrutinib demonstrated a favorable safety profile, with relatively low rates of off-target toxicities. The most common adverse events (AEs) included thrombocytopenia (all grades, 27.7 %), hemorrhage (27.7 %), infections (21.3 %), and neutropenia (19.1 %), which were mostly mild to moderate. No treatment-emergent grade ≥ 3 events were reported for diarrhea, atrial fibrillation/flutter, hypertension, and hemorrhage. Treatment-related AEs prompted dose reduction and study drug discontinuation in 6.4 % and 2.1 %, respectively. Summarizing these findings, the authors noted that orelabrutinib has the potential to be the agent of choice for patients with relapsed/refractory WM.

Two-year update for tirabrutinib

Tirabrutinib, a BTK inhibitor with kinase selectivity comparable to or greater than other BTK inhibitors, has already been approved in Japan for use in treatment-naïve or relapsed/refractory WM based on the results of a phase II study [3, 4]. Cohort A of this trial included 18 treatment-naïve patients, while Cohort B consisted of 9 patients with relapsed/refractory WM. Tirabrutinib was administered orally under fasting conditions at a daily dose of 480 mg. The MRR constituted the primary endpoint. According to the primary analysis, the trial met the primary endpoint despite the relatively short follow-up [4]. In Cohort A, MRR and overall response rate were 88.9 % and 94.4 %, respectively. In Cohort B, these amounted to 88.9 % and 100 %, respectively.

The updated results after a 2-year follow-up presented at ASH 2021 showed that responses deepened over time [5]. At data cutoff, 83 % and 78 % of patients in Cohorts A and B, respectively, were still on treatment. All patients were alive at 24 months, and freedom from progression was present in 94.4 % and 88.9 %, respectively. The MRR was 94.4 % and 88.9 %, respectively. Overall, 94.4 % and 100 % of patients responded. Median duration of response had not been reached yet in either cohort. Patients who remained on treatment demonstrated continued reductions in tumor size and serum IgM levels.

The most common AEs of special interest were skin-related disorders. Rash occurred in 44.4 % in the total population (61.1 % and 11.1 % in Cohorts A and B, respectively) but was restricted to grade 1 and 2. In 57 % of cases, the patients developed skin-related AEs within the first month of treatment; no onset was observed after 7 months. Neutropenia ranged second among the AEs, with 16.7 % and 66.7 % in treatment-naïve and pretreated patients, respectively. During the extended follow-up period, no new grade ≥ 3 treatment-related AEs were noted except for hypertriglyceridemia (3.7 %). The authors concluded that tirabrutinib is a useful treatment option for patients with Waldenström's macrogobulinemia. ■

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Promising novel approaches in various B-cell malignancies

POLARIX: polatuzumab vedotin in DLBCL

For more than 20 years, the R-CHOP regimen consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone has been the standard of care in the first-line treatment of diffuse large B-cell lymphoma (DLBCL). However, as only 60-70 % of patients achieve cure [1, 2], there is a need to improve on these results. The antibody-drug conjugate polatuzumab vedotin that targets CD79b has already shown activity in combination with rituximab or obinutuzumab plus cyclophosphamide, doxorubicin, and prednisone (CHP) in a phase II study conducted in the first-line setting of DLBCL [3]. Based on these insights, the international, randomized, double-blind, phase III POLARIX trial tested polatuzumab vedotin in combination with rituximab and CHP (Pola-R-CHP) against R-CHOP for 6 cycles. This was followed by 2 additional doses of rituximab.

Patients with previously untreated DLBCL and International Prognostic Index (IPI) scores of 2-5 participated in the trial. Progression-free survival (PFS) was defined as the primary endpoint. The primary analysis presented by Tilly et al. at ASH 2021 after a median follow-up of 28.2 months included approximately 440 individuals in each arm [4]. Seventy percent of them were older than 60 years, more than 85 % had Ann Arbor stages III or IV, and 62 % in each arm had high-intermediate or high risk according to IPI.

Lasting complete remissions with Pola-R-CHP

The primary endpoint of the POLARIX study was met. Pola-R-CHP significantly prolonged PFS compared to R-CHOP, demonstrating a 27 % reduction in the risk of disease progression or death (HR, 0.73; p < 0.02). At 24 months, 76.7 % vs. 70.2 % of patients in the experimental and control arms, respectively, were progression-free. Consistent with the PFS finding, the event-free survival analysis yielded a 25 % risk reduction (HR, 0.75; p = 0.02). In both arms, approximately 95 % of patients responded to treatment. Complete response (CR) rates were similar at 86.6 % and 82.7 %, respectively. However, disease-free survival findings indicated that patients who achieved CR with Pola-R-CHP were more likely to maintain remission than those obtaining CR on R-CHOP treatment (HR, 0.70). Overall survival did not differ yet at the time of the analysis.

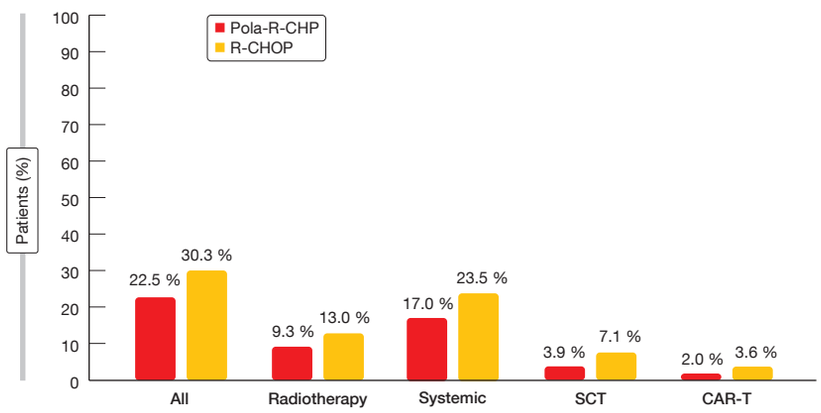

Figure 1: Percentages of patients treated with Pola-R-CHP and R-CHOP in the POLARIX trial who received subsequent anti-lymphoma therapies

The percentages of patients receiving subsequent treatments were lower in the experimental arm for all types of therapies **(Figure 1)**. Regarding safety, the regimes showed comparable profiles; peripheral neuropathy, nausea, neutropenia, and anemia were among the most commonly observed adverse events (AEs) for both strategies. However, the incidence of diarrhea was increased in the Pola-R-CHP arm compared to the R-CHOP arm, as well as the rates of febrile neutropenia episodes without more profound neutropenia or specific infections. In both arms, grade 3/4 events occurred in approximately 58 %, and AEs leading to discontinuation of any study drug emerged in 6.2 % vs. 6.6 %. Fewer dose reductions of any study drug due to AEs were observed in the Pola-R-CHP arm (9.2 % vs. 13.0 %).

As the authors emphasized, these results support the use of Pola-R-CHP in the initial management of patients with DLBCL and intermediate or high risk. Exploratory analyses of the POLARIX trial are ongoing regarding various subgroups and other prognostic classification systems.

Bispecific antibody mosunetuzumab: phase II expansion

Mosunetuzumab is a bispecific antibody that redirects T cells to eliminate malignant B cells by binding to CD3 on T cells and CD20 on B cells [5]. In patients with relapsed/refractory follicular lymphoma (FL) and ≥ 2 prior therapies, mosunetuzumab has shown encouraging efficacy and manageable safety in the phase I setting [6]. Findings obtained in the international, single-arm, pivotal phase II expansion study were presented by Budde et al. at ASH 2021 [7].

This analysis included 90 patients with FL grade 1-3a after ≥ 2 prior regimens including ≥ 1 anti-CD20 antibody and ≥ 1 alkylating agent. They received fixed-duration treatment with 3-weekly mosunetuzumab; those who achieved CR after 8 cycles discontinued their treatment at that time, while those who showed partial response or disease stabilization after 8 cycles went on to receive a total of 17 cycles. Step-up dosing was performed in cycle 1 to mitigate cytokine release syndrome (CRS) and to allow for a higher targeted dose. Hospitalization was not mandatory. CR as best response by independent review facility constituted the primary end-

TABLE 1
Naratuximab emtansine plus rituximab in the phase II setting: treatment summary

	R/R DLBCL Q3W (n = 50)	R/R DLBCL QW (n = 30)	Other R/R NHL Q3W (n = 20)
Completed ≥ 6 cycles, n (%)	18 (36)	15 (50)	12 (60)
Median cycles, n (range)	3 (1-38)	5.5 (1-30)	7 (1-52)
Discontinued study treatment (both drugs):			
Due do disease progression, n (%)	29 (58)	16 (53)	6 (30)
Due to AEs not leading to death, n (%)	3 (6)	0	3 (15)
Due to AEs leading to death, n (%)	1 (2)	1 (3)	0

point and was assessed against the 14 % historical control CR rate [8]. After a median number of 3 prior treatment lines, approximately 50 % of patients were double refractory to any prior anti-CD20/alkylator therapy. Likewise, more than 50 % had experienced disease progression within 24 months (POD24). These are indicators for advanced disease and elevated risk commonly associated with poor prognosis.

Deep responses in heavily pretreated FL patients

After a median follow-up of 18.3 months, 60 % of patients had completed treatment. Eight and 17 cycles had been administered in 58.9 % and 12.2 %, respectively. The study met its primary endpoint, with the 60 % CR rate being significantly greater than the historical control rate ($p < 0.0001$). Overall, 80 % of patients responded to treatment. Subgroup analyses demonstrated that high-risk groups including those with double-refractory disease and POD24, as compared to other groups, obtained similar response rates. Median duration of response was 22.8 months both in all responders and complete responders. At 18 months, 70 % of complete responders were event-free. Median PFS amounted to 17.9 months.

Mosunetuzumab showed a favorable tolerability profile. Treatment-related grade 3/4 AEs and AEs necessitating discontinuation occurred in 51.1 % and 2.2 %, respectively. No patient died due to mosunetuzumab-related AEs. CRS was the predominant AE, with an any-grade incidence rate of 44.4 %. Most events were low-grade and were confined to cycle 1. CRS management required the administration of corticosteroids and tocilizumab in 11.1 % and 7.8 %, respectively. All events eventually resolved. Immune effector cell-associated neurotoxicity syndrome events were infrequent (4.4 %) and confined to grade 1 and 2. No cases of aphasia, seizures, encephalopathy, or cerebral edema occurred. As the authors noted in their conclusion, mosunetuzumab is the first T-cell–engaging bispecific antibody to demonstrate clinically meaningful outcomes for patients with relapsed/refractory FL in the pivotal phase II setting.

Naratuximab emtansine plus rituximab

A medical need for new treatment options is evident in patients with relapsed/refractory non-Hodgkin lymphoma (NHL), particularly relapsed/refractory DLBCL, who are no candidates for stem cell transplant or CAR-T cell therapy. The CD37-targeting antibody-drug conjugate naratuximab emtansine was tested in combination with rituximab in an open-label, multicenter, adaptive phase II study conducted in patients with DLBCL and other NHL B-cell lymphomas after 1-6 treatment lines [9]. The study consisted of two parts. Patients included in Part 1 had a confirmed diagnosis of relapsed/refractory NHL including DLBCL, FL, mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL). These were treated 3-weekly (Q3W). Part 2 was limited to patients with relapsed/refractory DLBCL ineligible for stem cell transplantation; here, two dosing strategies were evaluated. Cohort A was dosed Q3W, while Cohort B received weekly treatment (QW). Overall, 50 and 30 DLBCL patients received Q3W and QW treatment with naratuximab emtansine, respectively. Another 20 had other types of NHL and were treated Q3W **(Table 1)**.

This study enrolled patients who are often excluded from DLBCL trials due to double- or triple-hit morphologies, bulky disease, transformed lymphoma, and primary refractory disease or disease refractory to the last treatment. Thus, the population mirrored the difficult-to-treat patients seen in everyday practice. The overall response rate was defined as the primary endpoint.

Efficacy across lines and treatment schemas

Substantial proportions of patients in the three groups managed to complete ≥ 6 cycles **(Table 1)**. In the efficacy-evaluable DLBCL population (n = 76), 44.7 % of patients responded, and 31.6 % achieved complete responses. CR rates were 43.3 % and 33.3 % for Cohorts A (Q3W) and Cohort B (QW). The objective response rate (ORR) was 50 % for both cohorts. Similar rates resulted in patients treated in the third and later lines who were non-primary refractory (ORR, 46.4 %; CR, 32.1 %). Patients with relapsed/refractory FL obtained an ORR of 57.1 %. Median duration of response had not been reached for either DLBCL or FL. Sixty-six percent of patients with DLBCL showed a duration of response > 12 months.

The most frequently observed grade 3/4 treatment-emergent AEs (TEAEs) were hematological in nature and manageable. G-CSF prophylaxis was offered to 22 % of patients. Three liver TEAEs grade ≥ 3 occurred, as well as 2 cases of non-serious neuropathy grade ≥ 3. Most of the patients discontinued treatment because of disease progression rather than AEs **(Table 1)**. Ten patients died due to TEAEs; 2 of these were considered related to the treatment. According to the assessment of health-related quality of life, the administration of naratuximab emtansine was associated with a significant increase in well-being in 38 % of responders. The vast majority of patients reported that they were not or hardly bothered by the side effects of treatment. In their summary, the authors noted that naratuximab emtansine plus rituximab might represent a new option for patients with relapsed/refractory NHL, especially DLBCL, including heavily pretreated patients.

TABLE 2
Response to cerdulatinib as single agent or in combination with rituximab in patients with follicular lymphoma

	Cerdulatinib monotherapy			Cerdulatinib + rituximab		
	Total FL population (n = 34)	≤ 3 prior regimens (n = 24)	≥ 4 prior regimens (n = 10)	Total FL population (n = 26)	≤ 3 prior regimens (n = 16)	≥ 4 prior regimens (n = 10)
ORR, n (%)	18 (52.9)	12 (50.0)	6 (60.0)	20 (76.9)	15 (93.8)	5 (50.0)
CR, n (%)	8 (23.5)	7 (29.2)	1 (10.0)	6 (23.1)	5 (31.3)	1 (10.0)
PR, n (%)	10 (29.4)	5 (20.8)	5 (50.0)	14 (53.8)	10 (62.5)	4 (40.0)
SD, n (%)	9 (26.5)	7 (29.2)	2 (20.0)	6 (23.1)	1 (6.3)	5 (50.0)
PD, n (%)	6 (17.6)	5 (20.8)	1 (10.0)	0	0	0
TTR, months	2.8	3.8	1.8	1.8	1.8	1.8
DOR, months	Not reached	Not reached	Not reached	16.6	11.2	Not reached

ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TTR, time to response; DOR, duration of response

Cerdulatinib alone and combined with rituxmab

The dual SYK/JAK kinase inhibitor cerdulatinib is being evaluated as monotherapy and in combination with rituximab in an open-label, phase IIa study conducted in adult patients with relapsed/refractory B-cell and T-cell malignancies. Hamlin et al. presented the results for patients with FL at ASH 2021 [10]. Forty-two and 26 of these had been treated with cerdulatinib monotherapy and cerdulatinib plus rituximab, respectively. The median number of prior regimens was 2 and 3, respectively. In FL, the proposed mechanisms of action of cerdulatinib include disruption of survival signals imparted by BCR and JAK/STAT signaling pathways, as well as disruption of the supportive tumor microenvironment and forced mobilization of tumor-infiltrating leukocytes [11-15].
Cerdulatinib monotherapy gave rise to an ORR of 52.9 %. Both patients after ≤ 3 and ≥ 4 prior regimens responded to treatment **(Table 2)**. In the combination group, the ORR was 76.9 %; here, patients treated in early lines showed higher responses. Median PFS was 12.7 and 18.3 months for single-agent cerdulatinib and the combination, respectively. Cerdulatinib was generally well tolerated. No differences emerged between the safety profiles of cerdulatinib monotherapy and cerdulatinib plus rituximab. The most frequent grade ≥ 3 AEs included increases of lipase levels, neutropenia, and pneumonia.

Overall, these data demonstrated that targeting the JAK/STAT pathway with oral cerdulatinib can provide clinical benefit in relapsed/refractory FL, thus supporting registrational studies. The novel mechanism of action of cerdulatinib did not appear to be subject to cross-resistance with other agents, which makes combination therapy attractive.

Zanubrutinib in BTK inhibitor-intolerant patients

Although BTK inhibitors are an effective option in the setting of several B-cell malignancies, duration of treatment is limited due to AEs leading to discontinuation [16-18]. The multicenter, US-based, single-arm, open-label, phase II BGB-3111-215 study assessed the safety and efficacy of zanubrutinib in patients intolerant to ibrutinib and/or acalabrutinib with previously treated B-cell malignancies including CLL/SLL, Waldenström's macroglobulinemia (WM), MCL, and MZL. Cohort 1 was intolerant to ibrutinib, and Cohort 2 was intolerant to acalabrutinib ± ibrutinib. Results for the safety of zanubrutinib were compared with the patients' ibrutinib and/or acalabrutinib intolerance as assessed by the recurrence and the change in severity of AEs. The analysis reported at ASH 2021 related to 57 and 10 patients in Cohorts 1 and 2, respectively [19].

Within a median follow-up of 12.0 months, most ibrutinib and acalabrutinib intolerance events (i.e., 70.4 % and 83.3 %, respectively) did not recur on zanubrutinib. If they recurred, their severity was equal or reduced. Of the 34 recurrent ibrutinib intolerance events, 76.5 % recurred at lower severity, and 23.5 % recurred at the same severity. Among the 3 recurrent acalabrutinib intolerance events, 1 and 2 recurred at lower and the same severity, respectively. Almost 60 % and 70 % of patients who took ibrutinib and acalabrutinib, respectively, did not have recurrence of any intolerance event. In the category of grade 3 intolerance events, 65.8 % and 75 %, respectively, did not recur while on zanubrutinib. No grade 4 events recurred. The most common grade ≥ 3 AEs on zanubrutinib treatment were neutropenia/neutrophil count decrease (12.0 %). At the time of data cutoff, 83.6 % of patients remained on zanubrutinib, and 7.5 % had discontinued due to AEs.

Regarding efficacy, zanubrutinib was shown to at least maintain response. In 93.8 %, disease control was achieved, and the ORR amounted to 64.1 %. An exploratory biomarker analysis indicated that relapse on zanubrutinib was associated with BTK inhibitor resistance mutations. In their entirety, these data suggested that zanubrutinib might provide a therapeutic option in patients intolerant to other BTK inhibitors across hematologic malignancies.

Early results for novel BCL2 inhibitor BGB-11417

BCL2 inhibitors have been shown to be safe and effective, although treatment with the currently approved BCL2 inhibitor venetoclax can be limited by gastrointestinal toxicities, neutropenia, and the emergence of specific *BCL2* mutations around the BH3-binding groove causing resistance [20, 21]. BGB-11417 has been developed as a potent

and highly selective BCL2 inhibitor with a favorable pharmacokinetic profile providing excellent bioavailability and selectivity for BCL2 at concentrations < 1 nM [22]. At ASH 2021, Tam et al. reported preliminary results of the open-label, multicenter, phase I, dose-escalation and dose-expansion BGB-11417-101 trial that is assessing BGB-11417 alone (Parts 1 and 2) and in combination with zanubrutinib (Parts 3 and 4) in patients with relapsed/refractory B-cell malignancies [23]. At the time of the analysis, 36 patients had been treated, with 25 and 11 having received the monotherapy and the combination, respectively. In the monotherapy group, 19 and 6 had NHL and CLL/SLL, respectively. The combination group contained 10 and 1 patients with CLL/SLL and mantle cell lymphoma, respectively.

These early findings suggested that BGB-11417 is tolerable in patients at the dose levels tested. One dose-limiting toxicity of grade 3 febrile neutropenia was observed across 4 dose levels assessed in NHL, and 1 DLT of grade 4 neutropenia was seen in a CLL cohort. Among TEAEs regardless of causality, nausea emerged most commonly in both monotherapy and combination groups. With respect to BCL2 inhibitor events of interest, it was noted that one patient receiving monotherapy with high baseline tumor lysis syndrome (TLS) risk had a marked tumor flare on BTK inhibitor withdrawal and developed laboratory TLS in late ramp-up. This patient experienced no sequelae, and BGB-11417 did not need to be held. Neutropenia was the most frequent grade ≥ 3 AE as it occurred in 5 of 6 patients receiving monotherapy.

Efficacy data were limited as dose escalation was not complete for any cohort and not all patients had reached their first response assessment. Nevertheless, responses were observed, with decreases in sum of the products of perpendicular diameters at all dose levels. Substantial decreases in absolute lymphocyte counts occurred during ramp-up for CLL patients **(Figure 2)**. Evaluation of patients with MCL, treatment-naïve CLL and WM is planned for future cohorts.

Real-world burden of NHL

Survival spanning several years with multiple interspersed treatment periods due to frequent relapses is typical of the NHL subtypes CLL, MCL, MZL, and WM. Chanan-Khan et al. retrospectively assessed real-world treatment patterns, costs, and resource utilization of hospital-based care among patients with these lymphomas [24]. The data source was the PINC AITM Healthcare Database, a hospital administrative database currently containing data from more than 1 billion inpatient and outpatient encounters in the USA. Overall, 31,805 patients received treatment from January 2014 to October 2019. Those with CLL constituted the largest group (n = 23,952). In all lymphoma types, the majority were older than 65 years. Medicare was the most frequent insurance in all cohorts, followed by commercial insurance.

CLL and MCL patients received chemo-immunotherapy as the most frequently used treatment aside from steroids alone. In MZL and WM patients, rituximab was the most frequent therapy other than steroids alone. High proportions were treated with steroids alone to control their symptoms; for CLL, this was 74.7 %, for MCL, 40.3 %, for MZL, 51.3 %, and for WM, 59.7 %.

Once patients were hospitalized, they incurred considerable costs, with significantly higher impact to minority populations. Patients aged ≤ 65 years, males and those who were non-white had higher hospital costs in all 4 lymphoma types. Hispanic patients incurred higher costs compared to non-Hispanics in CLL, MCL, and MZL, but not in the WM group. Disparities across primary payor were seen in WM patients, with Medicaid patients associated with increased total hospital cost compared to Medicare patients. Total hospital costs increased significantly during the follow-up period when patients received supportive care (i.e., blood transfusion, G-CSF) and regimens including any chemotherapy, immunotherapy, and targeted therapy.

The authors noted in their conclusion that given the increased availability of effective oral therapeutics, optimal and timely disease control in the outpatient setting can potentially prevent or decrease hospitalizations and reduce economic burden on healthcare sys-

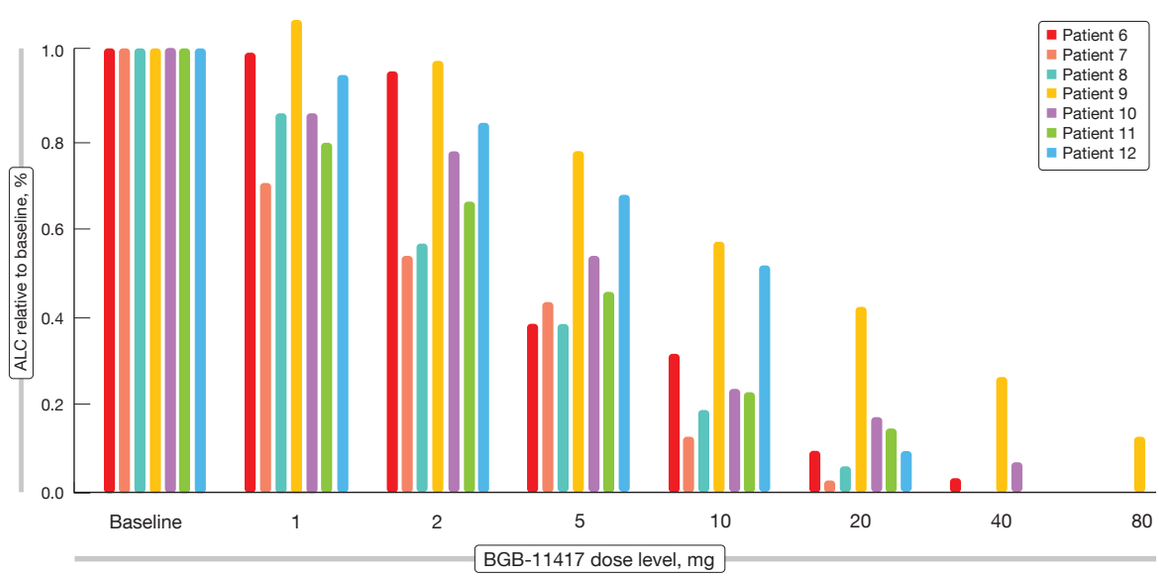

Figure 2: Reduction in absolute leukocyte counts on BGB-11417 plus zanubrutinib during ramp-up in CLL patients

tems and payors. Future studies should explore the reasons for admission, clinical outcomes, and potential preventive interventions. As the analyzed period ended in 2019, the overall cost structure is likely to have changed in recent years due to the increased use of novel drugs.

Productivity loss among patients and caregivers

NHL patients are often heavily reliant upon caregiver support. At the same time, many of both patients and caregivers are of working age. A retrospective cohort study evaluated the productivity loss and indirect costs for patients with CLL, MCL, MZL and WM, and their caregivers [25]. De-identified US claims data from the IBM MarketScan® Commercial and Health Productivity and Management Databases were obtained from January 2009 to December 2019. Mean age of the NHL patients ranged from 52.1 to 54.0 years, and mean age of the caregivers ranged from 51.2 to 52.9 years.

For all NHL types, average illness-related absentee hours were higher in patients than in caregivers; a similar pattern was observed for short-term disability days. Average per-patient-per-month indirect costs were higher for patients with long-term disability than with short-term disability or absentee claims, except for patients with MCL. Costs of absenteeism, short-term disability and long-term disability were substantial for all NHL types and ranged from 365 $ to 2,056 $ per patient per month **(Figure 3)**.

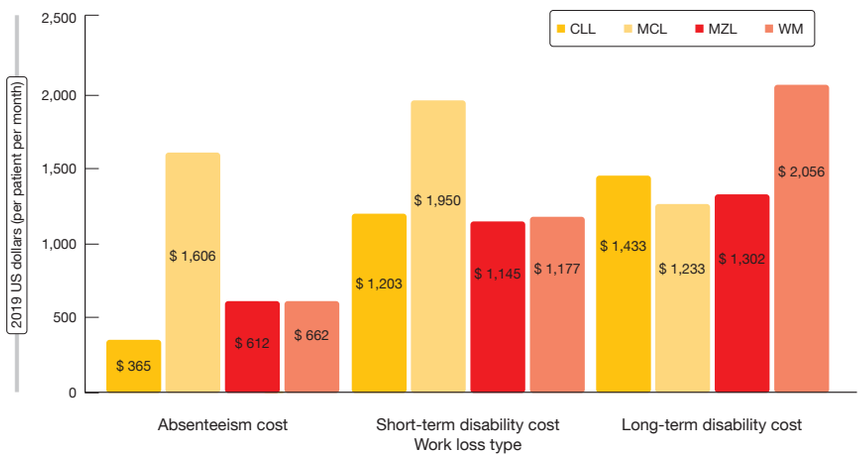

Figure 3: Costs of absenteeism, short-term disability, and long-term disability among patients with CLL, MCL, MZL, and WM in the USA

Similar trends emerged among caregivers, although indirect costs due to absenteeism and short-term disability were comparatively higher in patients. The authors concluded that effective treatments offering cure or better remission rates, longer duration and/or less toxicities might not only enhance patients' and caregivers' quality of life, but also reduce work loss. Future studies are required to understand the impact of therapies that result in higher remission and more manageable toxicities, such as oral targeted agents, on work loss and indirect costs of NHL. ■

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Real-world risk assessment, outcomes and adoption of novel drugs in CLL patients: insights from US databases

Testing patterns after diagnosis

Prognostic testing including IGHV mutation status, cytogenetic abnormalities by FISH, and immunophenotyping has been recommended after diagnosis of CLL/SLL prior to treatment initiation. This also applies to previously treated patients in some settings. As disease with high-risk genetic features is better managed with novel agents than with chemoimmunotherapy, the need for testing has recently become more relevant as all patients are advised to complete risk-factor testing for both prognostication and selection of optimal, evidence-based therapy. Chanan-Khan et al. performed a retrospective evaluation of real-world patterns of testing which showed that despite these recommendations, a significant number of patients do not undergo FISH and/or IGHV mutation status testing prior to therapy [1]. Based on the Flatiron Health EHR-derived database, a total of 3,037 newly diagnosed patients with CLL/SLL were identified between July 2014 and February 2021. Their median age was 73 years, and 62.3 % were male. The majority (92 %) received treatment in community practices, with 54.1 % being commercially insured.

Over half of these patients did not receive risk factor testing **(Figure 1)**. Almost all of those who underwent testing had it done once prior to the initiation of first-line therapy. Older individuals, females, and those living in the west of the US were significantly less likely to receive IGHV and FISH testing. A multivariable analysis revealed that patients who lived in the northeast or west had decreased likelihood to receive immunophenotyping tests.

Differences according to age and gender

Among those who underwent testing, the presence of high-risk biomarkers was as follows: unmutated IGHV, 56.1 %; del(17p), 14.4 %; del(11q), 16.9 %; CD38, 30.8 %. Compared to patients < 65 years of age, testing in patients ≥ 65 years demonstrated a lower presence of unmutated IGHV and del(11q), while del(17p) and trisomy 12 were identified more frequently. No significant disparity was observed for white vs. non-white patients, except for a lower incidence of mutated IGHV and del(13q). Compared to tested men, tested women had lower rates of unmutated IGHV, del(11q), and CD38, while del(17p) was found more commonly.

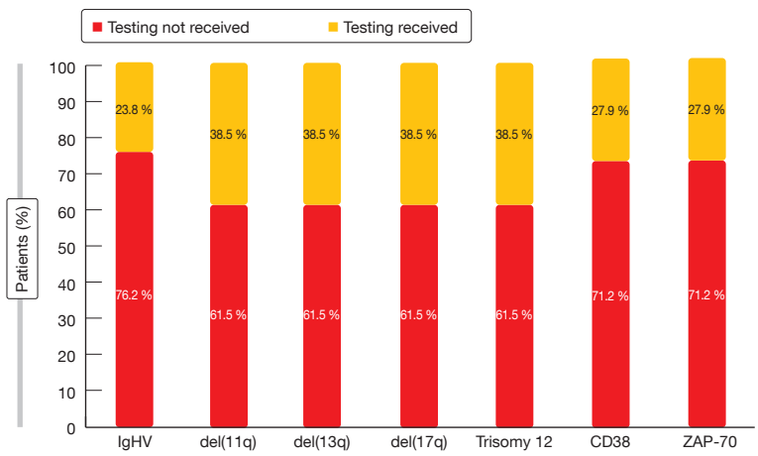

Figure 1: Real-world frequency of risk factor testing in patients with newly diagnosed CLL/SLL

The authors went on to investigate the impact of risk testing on therapy selection. According to this, patients with del(17p) had a higher likelihood of receiving novel agents including ibrutinib, acalabrutinib, and venetoclax than those who tested negative. In contrast, 26.4 % of those in whom del(17p) was identified and 39.8 % of those who did not get tested received chemotherapy. Overall, these data did not only identify a significant gap in testing but showed that suboptimal assessment is more common in vulnerable populations. The authors pointed out that there is an unmet need for further education and refinement of clinical practice, which is necessary to achieve the best clinical outcome through robust risk-assessment testing and optimal therapeutic triaging.

Impact of atrial fibrillation

Atrial fibrillation (AF) is a common type of arrhythmia and increases the risk of other cardiovascular complications such as stroke, bleeding events and heart failure. The clinical and economic impact of AF was assessed by Mohan et al. in CLL patients who are typically older and therefore likely to develop this type of arrhythmia [2]. Newly diagnosed CLL patients were identified in the IBM MarketScan Treatment Pathway from January 2009 to July 2020. Among 23,756 patients, 11.07 % had AF within 1 year of CLL diagnosis. Compared to CLL patients without AF, they were older on average (median age, 82 vs. 67 years), and more patients were male (65.1 % vs. 56.9 %).

Patients with AF demonstrated significantly increased prevalence of stroke (12.67 % vs. 4.97 %), bleeding events (17.45 % vs. 8.53 %), and heart failure (31.14 % vs. 4.7 %). They showed significantly higher median rates of emergency room visits (46 % vs. 24 %) and inpatient admissions (45 % vs. 19 %); overall, they were twice as likely to be hospitalized. Moreover, significant ef-

fects became apparent with respect to median outpatient, pharmacy, and total costs. The cost ratio for AF vs. no AF was 1.44 ($p < 0.0001$). According to the authors, better disease management, monitoring for AF, and improved CLL therapeutics with a lower AF risk or cardiovascular toxicity are required to minimize the incidence of AF in CLL.

Treatment in older patients

Given limited information on prescribing habits or characteristics of individuals receiving CLL treatment, Onukwugha et al. conducted an analysis using Medicare Claims data to characterize CLL treatment patterns and timing of treatment and to identify factors associated with the receipt of CLL treatment in patients aged ≥ 65 years [3]. The final sample included 3,440 individuals of whom 16 % (n = 556) were treated for CLL during follow-up (median, 540 days). Median time to receipt of treatment was 61 days.

Gender and age displayed a statistically significant association with treatment receipt. Males were more likely to be treated than females (55 % vs. 45 %; $p < 0.01$). Those aged 65-74 and 75-84 years received treatment more frequently than those ≥ 85 years (43 % and 42 % vs. 15 %, respectively), with a significant difference between the oldest and youngest groups ($p < 0.01$). The most common agents administered comprised ibrutinib (35 %) and rituximab (34 %) monotherapies. Less than half of the patients treated with bendamustine/rituximab completed six doses.

CLL/SLL-associated burden among veterans

Using the Veteran Health Administration dataset, a retrospective analysis assessed the real-world CLL/SLL-related burden in US veterans, who are at increased risk of these diseases especially after exposure to Agent Orange or other herbicides during military service [4]. Also, the clinical and economic outcomes associated with current treatments were evaluated. Between October 2014 and September 2019, 13,664 veterans newly diagnosed with CLL/SLL were identified. The final study population consisted of 2,861 patients with a median age of 70 years who received ≥ 1 line of CLL/SLL therapy. Average time to first-line treatment initiation from diagnosis was 315 days. In 26.9 %, the patients went on to receive second-line therapy, and third-line treatment was administered in 7.0 %. Ibrutinib was the most common treatment regimen across all lines **(Figure 2)**.

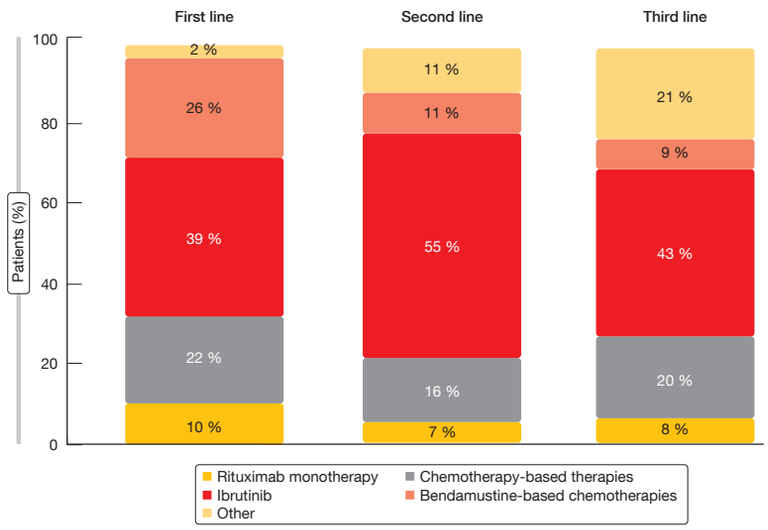

Figure 2: Treatment patterns among patients with CLL/SLL by line of therapy

Overall, treatment discontinuation rates were high across current regimens in each treatment line (73 %, 66 % and 59 %, respectively). They were generally highest for bendamustine-based chemotherapies, with 85 %, 84 % and 89 % of patients discontinuing in the first, second and third lines, respectively. The overall treatment switching rate was highest in third line (26 %), followed by 23 % in second line and 10 % in first line. Hospitalizations due to CLL/SLL occurred in 39 %, with an average length of stay of 7 days. Total all-cause and CLL/SLL-related per-patient-per-month healthcare costs increased by treatment line. After adjustment for patient clinical and demographic covariates, the analysis showed that treatment discontinuation and switches were statistically significant predictors of more frequent inpatient admissions and increased length of hospital stay.

In their summary, the authors noted that these real-world data demonstrated significant clinical and economic burden associated with CLL/SLL among the US veterans. The suboptimal adherence, as reported by the high treatment discontinuation rates, and its impact on costs and healthcare resource use, highlights the real-world unmet needs of CLL/SLL management in the veteran population. ■

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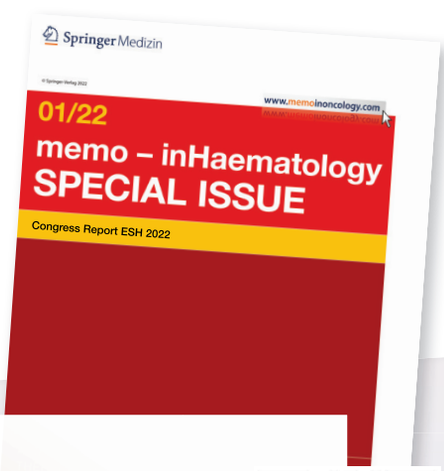
Expert interviews at ASH 2021

Paolo Ghia highlights what modern targeted agents can achieve in terms of undetectable minimal residual disease in the management of patients with CLL and important methodological recommendations to ensure correct assessment of TP53 and IGHV mutational status. He explains how the three epigenetic subgroups (m-CLL, n-CLL, i-CLL) are related, what effect a thorough immunogenetic analysis has on the risk stratification of patients with CLL and gives an overview about the most interesting findings on the management of pretreated CLL patients.

Alessandra Tedeschi depicts her personal highlights reported at ASH 2021 and explains the results obtained in treatment-naïve CLL patients with a deletion of 17p in the SEQUOIA study. The influence of age, fitness, and concomitant medications on the management and outcomes of patients with CLL treated with targeted agents, the most notable progress in B-cell malignancies over the last years and the role of BTK inhibitors in the treatment of patients with Waldenström's macroglobulinemia are summarized, too.

Constantine Tam gives an overview of the results obtained by the SEQUOIA trial, the advantages and disadvantages of BTKi and BCL2i 1L therapy versus their drawbacks and explains which CLL-patients might benefit from BTK inhibitor monotherapy and who might be better off receiving combination treatment including a BTK inhibitor and how novel BCL2 inhibitors improve CLL treatment compared to the standard agent venetoclax.

Jennifer A. Woyach explains which factors need to be considered when choosing the frontline regimen for patients with early-stage CLL, how resistance to BTK inhibition can be tackled in later lines, if chemoimmunotherapy still has a role in the treatment of CLL and highlights the most interesting findings on the management of treatment-naïve CLL patients.



Forthcoming Special Issue

This special issue will be offering a synopsis from the ESH 2022 that will be held in March 2022. The report promises to make for stimulating reading, as the ESH Congress itself draws on the input from a number of partner organizations, representing a multidiscplinary approach to cancer treatment and care. Stay tuned for the latest news in hematology and its subspecialties.

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