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

Report from the virtual American Society of Hematology (ASH) Annual Meeting, December 5–8, 2020

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Preface

Dear Colleagues,

The ASH Annual Meeting and Exposition is the premier event for presentation of novel data on malignant and non-malignant hematologic diseases, attracting up to 30,000 specialists from all over the world. The 62nd ASH Annual Meeting was planned to be held on December 5–8, 2020 in San Diego, California, but due to the COVID-19 pandemic had been transformed to an all-virtual event. Attendees had access to thousands of scientific abstracts highlighting cutting-edge research in hematology. This publication summarizes work presented in the field of B-cell malignancies with a focus on targeted therapies.

Inhibition of the Bruton's tyrosine kinase (BTK) has been implemented as a mainstay of treatment in various types of hematologic malignancies, including Waldenström's macroglobulinemia, chronic lymphocytic leukemia, marginal zone lymphoma, and mantle cell lymphoma. Later-generation BTK inhibitors designed to achieve optimized selectivity offer advantages with respect to tolerability and efficacy compared to first-generation BTK inhibition. Benefits have been observed with these agents irrespective of factors such as pretreatment or cytogenetic risk.

Progress is also ongoing regarding other drug classes such as PI3Kδ inhibitors and anti-CD20 antibodies that complement the armamentarium available for the treatment of various B-cell malignancies. Immune checkpoint inhibition might also play a role in the future, although a variety of inhibitory receptors apart from PD-1 and PD-L1 are still awaiting investigation in terms of their clinical usefulness as targets for drug therapy.

Naturally, combinations are a major area of research given the importance of achieving deep remission that allows for long-lasting disease-free survival. The wide range of drugs already established in the field of hematologic diseases enables the assessment of new regimens that might represent a major step forward in terms of patient life expectancy and quality of life.

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What is new in Waldenström's macroglobulinemia?

Constitutive activation of the Bruton's tyrosine kinase (BTK) pathway has been shown to induce malignant cell survival in patients with Waldenström's macroglobulinemia (WM) [1, 2]. The disease is based on the accumulation of IgM-secreting clonal lymphoplasmacytic cells in the bone marrow and extramedullary sites [3]. *MYD88*^{L265P} mutations (> 90 % of cases) and *CXCR4*^{WHIM}-like mutations (approximately 27 % of cases) have been established as the pathologic hallmarks of WM [4-6].

iNNOVATE: ibrutinib plus rituximab

BTK inhibition with ibrutinib has dramatically changed the treatment landscape in WM. The phase III iNNOVATE study compared ibrutinib plus rituximab with placebo plus rituximab in WM patients who were either treatment-naïve or pretreated; the latter had to be rituximab-sensitive (i.e., not refractory to the last prior rituximab-based therapy and no treatment with rituximab within the last 12 months before the first study dose). Each arm included 75 individuals. After a median follow-up of 26.5 months, the primary analysis of iNNOVATE demonstrated superiority of the combination over rituximab monotherapy [7]. These data formed the basis for the approval of ibrutinib plus rituximab in the United States and Europe.

At ASH 2020, Buske et al. reported the final analysis of the study after an overall follow-up of 63 months [8]. The protocol permitted cross-over to single-agent ibrutinib after disease progression in the control arm. Indeed, 35 (47 %) of these patients crossed over. After study closure, 68 (45 %) remained on ibrutinib, as 32 enrolled in a treatment extension program and 36 continued to receive ibrutinib in a commercial setting.

Even 5 years after the initiation of the trial, median progression-free survival (PFS) had not been reached in the experimental arm. Compared to the median PFS of 20.3 months observed with placebo plus rituximab, this translated into a 75 % risk reduction (HR, 0.25; $p < 0.0001$; **Figure**). At 54 months, PFS rates were 68 % vs. 25 %. In both arms, the PFS benefit did not depend on the genotype (i.e., any combinations of *MYD88*^{L265P} or *MYD88* wildtype and *CXCR*^{WHIM} or *CXCR4* wildtype). Moreover, ibrutinib plus rituximab improved PFS irrespective of the prior treatment status; in both pretreated and not pretreated patients, PFS was superior in all prespecified subgroups that received the combination.

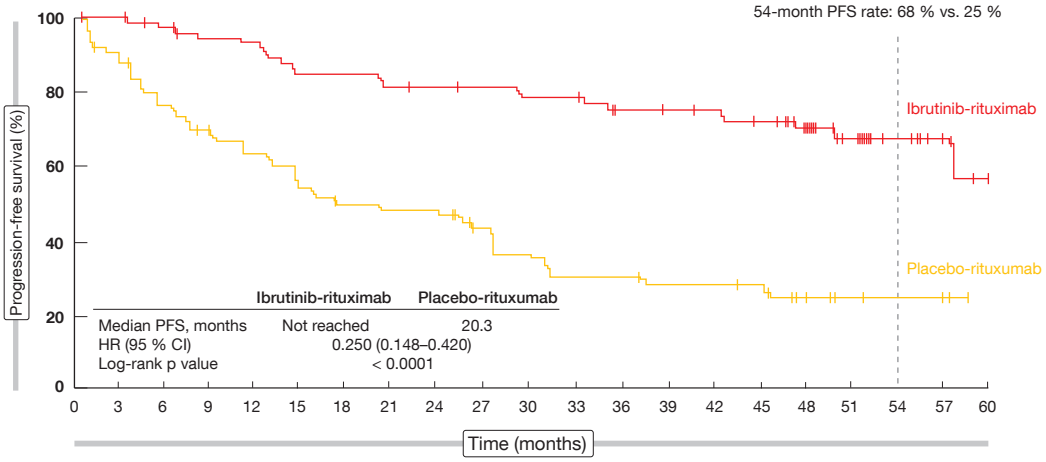

Figure: Progression-free survival benefit with ibrutinib plus rituximab vs. placebo plus rituximab

Rapid and sustained improvements

Responses occurred early on in the experimental arm, with median time to major response amounting to 3 months vs. 6 months in the control arm. Overall, the major response rates were 76 % vs. 31 % for the two arms. The proportion of patients experiencing very good partial responses increased over time with ibrutinib plus rituximab. Again, responses were largely independent of the genotype and prior treatment status.

IgM levels decreased rapidly during the first year of treatment. Maximum changes were -33.5 g/L for the combination at 56 months and -26.9 g/L for rituximab monotherapy at 57 months. Also, a larger fraction of patients treated in the experimental arm experienced sustained hemoglobin improvement, which was defined as increases of ≥ 20 g/L (or ≥ 5 g/L if baseline levels were ≤ 110 g/L) that persisted for ≥ 8 weeks without the need of blood transfusions or growth factors. This was the case for both the total group (77 % vs. 43 %; $p < 0.0001$) and the group with low baseline hemoglobin levels (95 % vs. 56 %; $p < 0.0001$). Median overall survival (OS) had not been reached yet in either treatment arm. The 54-month OS rates were 86 % vs. 84 %.

After 63 months of follow-up, the combination maintained a manageable safety profile, and no new safety signals emerged. The incidences of the main adverse events (AEs) including diarrhea, arthralgia and hypertension decreased over time. In year 4–5, AE-related ibrutinib dose reductions and treatment discontinuation became necessary in 5 % each. Eighty-eight percent of AEs that led to ibrutinib dose reductions subsequently resolved. In their conclusion, the authors noted that ibrutinib plus rituximab showed ongoing superiority across different clinical outcomes in patients with Waldenström's macroglobulinemia.

Phase II data for zanubrutinib

The selective, irreversible next-generation BTK inhibitor zanubrutinib has been designed to maximize BTK occupancy and minimize off-target inhibition of other kinases [9-11]. A pivotal, single-arm, open-label, multicenter phase II trial evaluated zanubrutinib 160 mg twice daily until progression in 44 Chinese patients with relapsed and refractory WM [12]. They had received ≥ 1 prior line of standard chemotherapy-containing treatment and had failed to achieve at least minor response or had progressed after response to the most recent regimen. The major response rate (MMR) was defined as the primary endpoint; this included complete, partial, and very good partial responses as assessed by an independent review committee. Seventy-five percent of patients had intermediate or high risk according to the WM prognostic score. A median of 2 prior systemic regimens had been administered. The study also enrolled *MYD88*-wildtype patients, who made up 15.9 % of the total population. Anemia (hemoglobin ≤ 110 g/L) was present at baseline in 75 %.

After a median follow-up of 18.6 months, zanubrutinib demonstrated pronounced and durable efficacy. Almost 70 % of patients developed MMR, with 32.6 % experiencing very good partial remission **(Table)**. Responses were achieved quickly; median time to overall response was 2.76 months. Neither median PFS nor the median duration of major response had been reached yet. At 12 months, 78.3 % of patients were progression-free, and 88.1 % showed ongoing major responses. The MMR benefit of zanubrutinib was generally consistent across subgroups. Treatment-related AEs mainly included neutropenia, thrombocytopenia, infections, and diarrhea. The safety and tolerability profiles of zanubrutinib corresponded to those reported previously in WM patients. Study drug discontinuation was required in 11.4 %.

These results have been submitted to the Chinese National Medical Product Administration for approval of zanubrutinib in patients with WM. The European approval in this indication based on the phase III ASPEN trial is expected for summer 2021 [13, 14].

Chinese real-world observation

A large, multicenter, retrospective study conducted in China assessed the clinical presentation, frontline treatment, outcome and prognosis of WM in patients diagnosed between January 2003 and December 2019 at 35 tertiary hospitals in 22 provinces [15]. Overall,

TABLE
Best overall response with zanubrutinib as assessed by independent review committee (IRC)

Efficacy per IRC	n = 43
Best overall response, n (%)	
- Complete response	0
- Very good partial response	14 (32.6)
- Partial response	16 (37.2)
- Minor response	4 (9.3)
- Stable disease	4 (9.3)
- Progressive disease	2 (4.7)
- Unknown	3 (7.0)
Complete + very good partial response rate, n (%)	14 (32.6)
Major response rate (partial response or better), n (%)	30 (69.8)
Overall response rate (minor response or better), n (%)	34 (79.1)

1,141 patients with a median age of 63 years were enrolled. Forty percent were older than 65 years. The male-to-female ratio was 2.7:1. According to the revised International Prognostic Scoring System (rIPSS), most of the patients had low (n = 342) and intermediate (n = 325) risk.

Documented treatment information was available for 734 patients. Due to the heterogeneous clinical presentations and the rarity of the disease, frontline treatment choices showed a considerable variety. Monotherapies such as chlorambucil, ibrutinib and rituximab represented 10.2 % of the total. Chemoimmunotherapy (e.g., rituximab/dexamethasone/cyclophosphamide, rituximab/prednisone/cyclophosphamide, R-COP, R-CHOP, rituximab/fludarabine/cyclophosphamide) accounted for 36.0 %. In 53.8 %, other combinations were used, with bortezomib-based regimens ranging first, followed by fludarabine/cyclophosphamide, CHOP and immunomodulatory agents plus dexamethasone.

After a median follow-up of 32 months, the estimated 3-year OS rate was 83 %. Most of the established prognostic factors according to rIPSS indicated worse prognosis in this population. These included LDH levels ≥ 250 IU/L, albumin levels < 3.5 g/dL, β-2 microglobulin ≥ 4 mg/L, and age > 65 years. The median OS of patients aged ≤ 65 years had not been reached yet, while this was 132 months and 61 months for those aged 66-75 years and > 75 years, respectively. Also, platelet counts ≤ 100 x 10^9/L constituted a prognostic factor. ■

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Management of CLL patients: BTK inhibition and beyond

BTK inhibitors, the Bcl-2 inhibitor venetoclax and anti-CD20 antibodies such as obinutuzumab have dramatically changed the therapeutic landscape of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). Ibrutinib, as the first-generation representative of the BTK inhibitor class, is a therapeutic mainstay, although it has notable shortcomings that led to the introduction of second-generation agents. Acalabrutinib has already received approval in the US and Europe for the treatment of patients with CLL, while zanubrutinib was approved in China in this indication in 2020. BTK-inhibitor–based doublets and triplets are being evaluated in clinical trials, particularly

with a view to achieving undetectable minimal residual disease that allows for fixed-duration therapy and treatment discontinuation. At the same time, new agents such as orelabrutinib and LOXO-305 are being tested in the clinical setting. Progress is also ongoing with respect to the expansion of PI3Kδ inhibitory options and the development of novel anti-CD20 antibodies.

Ibrutinib-based therapy

CAPTIVATE: ibrutinib plus venetoclax

To date, ibrutinib is the only targeted therapy to demonstrate significant OS benefit as a first-line treatment of patients with CLL included in randomized phase III studies [1, 2]. The international, phase II CAPTIVATE trial evaluated 12 cycles of ibrutinib plus venetoclax in the first-line setting to explore the question of whether deep remission can be achieved with 1-year fixed treatment duration to allow for treatment discontinuation. At ASH 2020, Wierda et al. presented the primary analysis for the minimal residual disease (MRD) cohort [3]. In this cohort (n = 149), treatment with ibrutinib plus venetoclax for 12 cycles after a 3-month lead-in with ibrutinib only was followed by randomization based on the MRD status. Patients with confirmed undetectable MRD (uMRD) received either placebo or ibrutinib in a double-blind manner, while those in whom uMRD was not confirmed underwent open-label randomization to either ibrutinib or ibrutinib plus venetoclax. The primary endpoint was the 1-year disease-free survival (DFS) rate in patients with confirmed uMRD randomized to placebo vs. ibrutinib.

Fifty-eight percent of patients in the MRD cohort achieved confirmed uMRD in the peripheral blood and bone marrow after 12 cycles of ibrutinib and venetoclax. Within this group, the 1-year DFS rates did not differ significantly between placebo and ibrutinib after a median follow-up of 16.6 months post-randomization (100 % vs. 95.3 % for ibrutinib and placebo, respectively; p = 0.1475). According to the authors, the 95 % rate in the placebo arm supports a fixed-duration treatment approach and discontinuation in patients who obtained confirmed uMRD. The overall median follow-up on the study was 31.3 months. At 30 months, the PFS rates were > 95 % across all four randomized arms. This compared favorably to other first-line fixed-duration regimens including rituximab, fludarabine and cyclophosphamide (3-year PFS, 73 %) [2] and venetoclax plus obinutuzumab (3-year PFS, 82 %) [4].

For patients who did not achieve confirmed uMRD at the end of 12 cycles of ibrutinib plus venetoclax, improvement in MRD status was observed with continued administration of the combination vs. single-agent ibrutinib. In the bone marrow, the additional randomized treatment led to a 34 % increase in uMRD in patients receiving ibrutinib plus venetoclax, whereas this was only 10 % in the ibrutinib-only arm **(Figure 1)**. The uMRD rate in the peripheral blood increased by 19 % in the combination arm vs. 0 % in the monotherapy arm. AEs generally lessened after the first 6 months of ibrutinib plus venetoclax treatment irrespective of the subsequent randomized regimen. Few patients required dose adjustment or discontinuation. Grade ≥ 3 AEs were uncommon. Based on these findings, the authors concluded that ibrutinib plus venetoclax is an all-oral, once-daily, chemotherapy-free, fixed-duration regimen that provided highly concordant, deep MRD remissions in bone marrow and blood in first-line CLL.

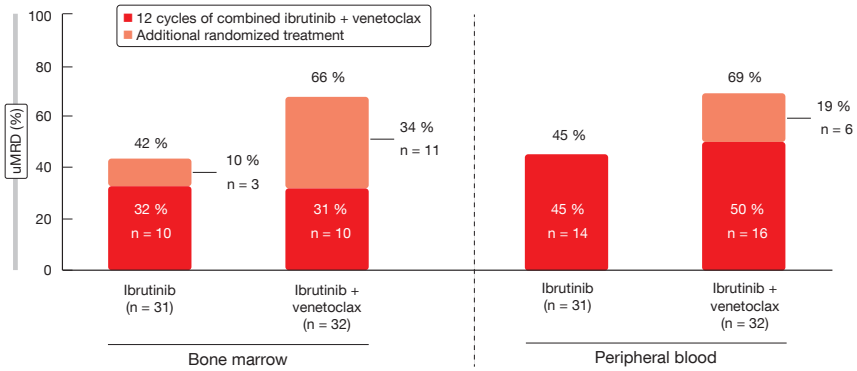


Figure 1: Increases in best overall uMRD rates with additional randomized treatment in the uMRD not confirmed population of the CAPTIVATE study

MRD-guided treatment intensification

A single-arm, phase II study including patients with relapsed/refractory (r/r) CLL who were naïve to BTK and Bcl-2 inhibitors investigated the efficacy of the addition of ibrutinib to venetoclax in terms of MRD [5]. Thirty-eight patients received venetoclax for 12 months; at that time, response and MRD status were evaluated. Those who had achieved complete response (CR)/partial response (PR) and uMRD stopped treatment, while those with CR/PR and detectable MRD continued venetoclax therapy and added ibrutinib. MRD was periodically evaluated, and patients who obtained uMRD in both peripheral blood and bone marrow at any time discontinued treatment. Patients with detectable MRD at the end of the 12-month combination period went on to receive single-agent ibrutinib.

This sequential MRD-guided approach proved to be feasible. uMRD was obtained by 45 % of patients after 12 months of venetoclax monotherapy. Among the remaining patients, 84 % achieved uMRD with venetoclax plus ibrutinib. In total, MRD was achieved in 87 % with either the monotherapy or the combination. Overall, 95 % of patients responded. Only 2 clinical relapses occurred after uMRD during the 27-month follow-up. The authors noted that responses to venetoclax retreatment remain to be established; also, the biological characteristics of patients with persistent MRD and early MRD relapse after treatment discontinuation will be investigated.

Obinutuzumab, ibrutinib & venetoclax

The fixed-duration triple combination of ibrutinib, venetoclax and obinutuzumab was tested in a phase II study enrolling patients with treatment-naïve

(n = 25) and r/r CLL (n = 25). Obinutuzumab was administered in cycles 1-8, ibrutinib in cycles 2-14, and venetoclax in cycles 3-14. Rogers et al. presented the 3-year update at the ASH 2020 Congress [6]. The CR rates with uMRD (i.e., the primary endpoint) were 28 % in both treatment-naïve and r/r patients. Fifty-six percent and 44 %, respectively, showed uMRD in both blood and bone marrow. Overall, 84 % and 88 %, respectively, achieved PR, CR or CR with incomplete marrow recovery (CRi). At 36 months, the PFS rate was 95 % in both groups, and OS rates amounted to 95 % and 100 % for treatment-naïve and r/r patients, respectively. These findings indicated durability of responses with the triplet therapy. Two cases of disease progression occurred in the r/r group, at 24 and 36 months.

This suggested that a time-limited treatment of 14 cycles with the three-drug combination can result in continued durable remissions. Additional follow-up is required to determine the median PFS and duration of benefit to patients. Ibrutinib plus venetoclax and obinutuzumab is currently being compared to ibrutinib plus obinutuzumab in two phase III cooperative group trials (NCT03701282 and NCT03737981).

Regimens including second-generation BTK inhibitors

Acalabrutinib: final results of ASCEND

At ASH 2020, Ghia et al. reported the final results of the ASCEND trial that compared the second-generation, highly selective, covalent BTK inhibitor acalabrutinib (n = 155) with idelalisib plus rituximab (IdR; n = 119) or bendamustine plus rituximab (BR; n = 36) according to investigator's choice in patients with r/r CLL [7]. After a median follow-up of 22 months, the results emphasized the favorable efficacy and safety of the BTK inhibitor compared to standard-of-care regimens. Median PFS had not been reached with acalabrutinib, while this was 16.2 months with IdR and 18.6 months with BR ($p < 0.0001$ for both comparisons; **Figure 2**). At 18 months, PFS rates were 82 % vs. 48 % for acalabrutinib and IdR/BR, respectively. PFS benefits were also observed in patients with high-risk genetic features including deletion 17p, *TP53* mutations and unmutated *IGHV* status. Median OS had not been reached yet in either treatment arm. The overall response rates (ORRs) did not differ (80 % vs. 84 %), although the median duration of response was longer with acalabrutinib than with IdR/BR (not reached vs. 18 months; HR, 0.19). At 18 months, 85.4 % vs. 49.4 % of patients responded.

Both acalabrutinib and BR showed higher tolerability than IdR. Compared to IdR, grade ≥ 3 AEs, treatment-related AEs and AEs leading to drug discontinuation or dose delays occurred less frequently with acalabrutinib and BR. As the authors summarized, these data support the use of acalabrutinib in patients with r/r CLL including those with high-risk features.

Triple acalabrutinib combinations: phase Ib

Acalabrutinib was tested in various combinations in the phase Ib ACE-CL-003 study. Woyach et al. presented data on two cohorts of the trial, namely cohort 3 evaluating acalabrutinib plus venetoclax and rituximab (AVR) in patients with r/r CLL and cohort 4 that assessed acalabrutinib plus venetoclax and obinutuzumab (AVO) in the treatment-naïve setting [8]. Each cohort contained 12 patients. With regard to safety, which was the primary endpoint, AEs turned out as expected based on each individual agent's safety profiles. One patient in either cohort discontinued treatment due to AEs. Headache, diarrhea and nausea were the most frequent AEs of all grades. Most AEs of interest including infections, hemorrhage, neutropenia, and hypertension were low-grade. No tumor lysis syndrome (TLS) occurred.

After 16 cycles, the ORRs were 92 % and 100 % for AVR and AVO, respectively. Half of patients in each cohort had achieved CR or CRi at the time of data cutoff. All of those with CR/CRi obtained uMRD in the blood at the time of CR/CRi or earlier. At cycle 10, only 1 of 12 patients (8 %) in each cohort remained MRD-positive in the blood. Six cycles later, none of the patients in the AVR cohort and one patient in the AVO cohort were MRD-positive. The overall uMRD rate was 71 % (67 % and 75 % in patients treated with AVR and AVO, respectively). Median duration of response, PFS, and OS had not been reached in either group.

The authors concluded that the triple combination therapy with acalabrutinib plus an anti-CD20 antibody and a Bcl-2 inhibitor is feasible based on tolerability and yielded high CR and uMRD rates in both r/r and treatment-naïve patients with CLL.

Phase II data on AVO in treatment-naïve patients

AVO as front-line CLL treatment is currently being assessed in a phase II trial. Acalabrutinib is administered for 15 cycles, obinutuzumab from cycle 2 to 8, and venetoclax from cycle 4 to 15. If CR with uMRD has been obtained after the 15th cycle, acalabrutinib and venetoclax

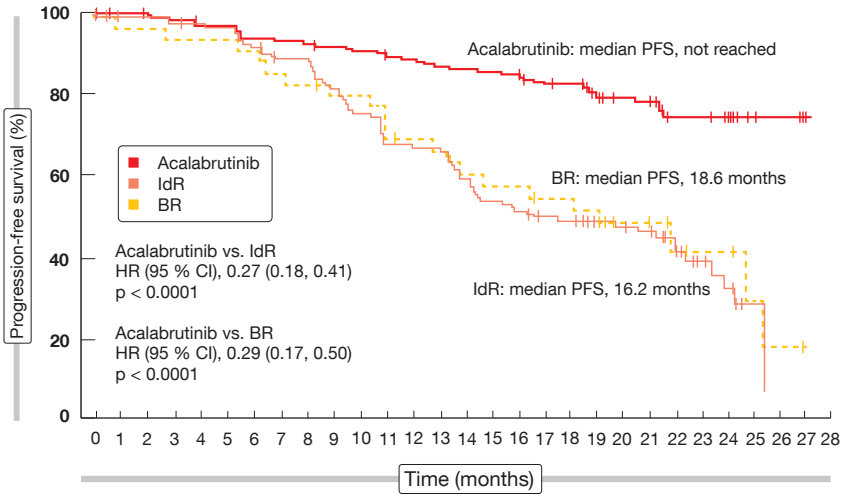


Figure 2: Superior progression-free survival for acalabrutinib *versus* bendamustin/rituximab (BR) and idelalisib/rituximab (IdR)

are discontinued but can be resumed upon MRD positivity. The MRD status is tested every 3 months. Patients who continue to show MRD-positive CR and/or PR after 15 cycles receive the doublet regimen for another 8 cycles. This is followed by a response reassessment and the same allocation, with acalabrutinib and venetoclax administered until progression in case of MRD positivity. Stable disease or progression prompt patient removal from the study. The study population is enriched for high-risk disease, with substantial proportions of patients showing unmutated *IGHV* status, *TP53* mutation, and other aberrations. A recent protocol amendment restricted additional enrollment to patients with *TP53*-aberrant disease in a new cohort.

The updated analysis reported at ASH 2020 yielded uMRD rates of 76.5 % and 83.9 % in bone marrow and blood, respectively, after 15 cycles of therapy in the overall cohort (n = 44) [9]. In patients with *TP53* aberrations (n = 17), these were 70 % and 90 %, respectively. After a median follow-up of 19 cycles, no patients had progressed or developed recurrent MRD. The depth of response increased over time. At cycle 16, CR/CRi rates were 44 % and 40 % in the total cohort and in the patients with *TP53* aberrations, respectively. AVO showed a favorable safety profile with low risk of grade ≥ 3 infections, atrial fibrillation, and infusion-related reactions (2 % each). The 3-cycle lead-in with acalabrutinib and obinutuzumab effectively reduced TLS risk at the time of venetoclax initiation **(Figure 3)**. No TLS event was observed due to venetoclax. A phase III trial of AVO vs. AV vs. chemoimmunotherapy is currently recruiting (NCT03836261).

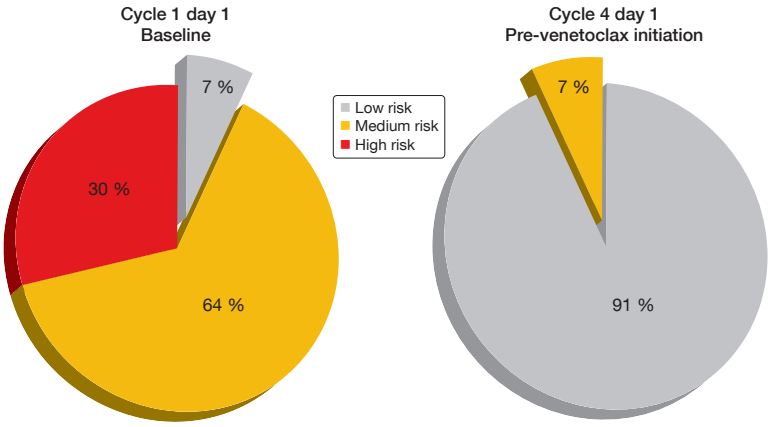


Figure 3: Reduction in tumor lysis syndrome risk based on the 3-cycle lead-in with acalabrutinib and obinutuzumab

Meta-analysis of time-limited vs. continuous agents

Molica et al. performed a systematic literature review and network meta-analysis to estimate the relative efficacy and safety of targeted agents approved by the FDA and/or EMA for upfront therapy of CLL (i.e., ibrutinib, acalabrutinib, and venetoclax) [10]. In particular, time-limited venetoclax-based regimens were compared with continuous BTK inhibitor-based therapy based on the following trials: ILLUMINATE (ibrutinib + obinutuzumab; IO), CLL14 (venetoclax + obinutuzumab; VO), and ELEVATE-TN (acalabrutinib monotherapy and acalabrutinib + obinutuzumab; AO). Data were available for a total population of 1,191 individuals.

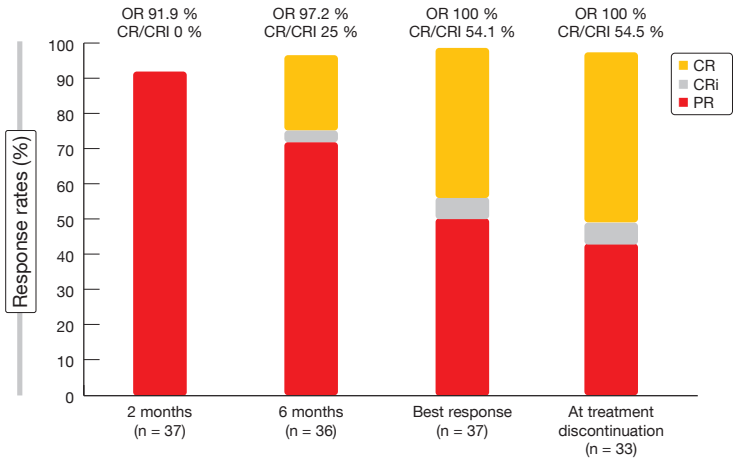
PFS did not differ between time-limited (VO) and continuous therapy (IO and acalabrutinib monotherapy). However, those treated with AO fared better with respect to PFS than the groups receiving IO and VO. A subgroup analysis focusing on patients with *TP53* aberrations demonstrated similar PFS outcomes irrespective of the targeted agent used. Also, the incidence of grade 3–4 AEs did not vary significantly across ibrutinib, acalabrutinib and venetoclax treatment. Ongoing studies will further delineate the position of different targeted therapies and schedule of administration in CLL therapy based on efficacy, availability, safety, cost, treatment objectives, and patient choice.

SEQUOIA: zanubrutinib in deletion 17p

Patients with CLL/SLL who harbor deletion 17p have an unfavorable prognosis and respond poorly to standard chemoimmunotherapy [11, 12]. BTK and Bcl-2 inhibitors have been shown to improve outcomes for patients with deletion 17p [13, 14]. However, the first-generation BTK inhibitor ibrutinib demonstrates limited efficacy in this population. Real-world data presented at ASH 2020 strengthen the evidence indicating inferior survival with first-line ibrutinib in deletion 17p-positive patients compared to those without deletion 17p, which reflects an ongoing need for more efficacious therapies [15].

The global, phase III, open-label, randomized SEQUOIA study aimed at evaluating first-line use of the second-generation BTK inhibitor zanubrutinib in CLL/SLL patients with and without deletion 17p. Zanubrutinib was designed to maximize BTK occupancy and minimize off-target inhibition of TEC and EGFR family kinases [16, 17]. Patients included in Arm C of the SEQUOIA trial had deletion 17p and received zanubrutinib monotherapy. Brown et al. presented the updated results for this group after a median follow-up of 22 months [18]. Among 109 enrolled patients, 95 were still on study treatment at the time of the analysis. Single-agent zanubrutinib gave rise to an ORR of 94.5 % and a CR/CRi rate of 6.4 % that had increased from the initial CR/CRi rate of 1.9 % estimated 1 year earlier [19]. Almost 88 % of patients showed ongoing responses for at least 18 months. The 18-month PFS and OS rates were 90.6 % and 95.4 %, respectively. PFS was analyzed by *IGHV* mutation and karyotype status. With limited follow-up, the findings appeared similar between patients with unmutated vs. mutated *IGHV* as well as between patients with complex vs. non-complex karyotype. The tolerability of zanubrutinib monotherapy was generally consistent with previous observations reported for patients with various B-cell malignancies [17, 20-22].

Based on the encouraging results obtained in Arm C, Arm D of the SEQUOIA study was devised to evaluate zanubrutinib plus venetoclax [23]. At present, patients are being recruited into this



CR: complete response; CRi: complete response with incomplete marrow recovery; PR: partial response

Figure 4: Response rates according to iwCLL criteria observed in the BOVen study

arm in 8 countries worldwide, with planned enrollment of approximately 50 individuals. After 3 months of zanubrutinib monotherapy, venetoclax is added for 12-24 cycles. Restaging and MRD measurements are performed regularly at 3-monthly intervals. Patients who achieve confirmed uMRD in blood and bone marrow are allowed to discontinue zanubrutinib and venetoclax therapy after a minimum of 27 and 12 cycles, respectively.

Zanubrutinib, obinutuzumab, and venetoclax: BOVen

Ibrutinib plus venetoclax doublets as well as triplets with obinutuzumab are active but associated with characteristic toxicities. The BOVen study was conducted based on the hypothesis that first-line treatment with zanubrutinib, obinutuzumab, and venetoclax (BOVen) will achieve frequent uMRD, and MRD-driven treatment discontinuation will allow for durable responses off treatment [24]. Venetoclax was introduced in cycle 3 after a 2-month lead-in with zanubrutinib and obinutuzumab. Patients completed 8 cycles of obinutuzumab and 6 cycles of the triple combination. Thereafter, the management was determined by pre-specified MRD endpoints with a minimum and maximum duration of therapy of 8 and 24 months, respectively. If uMRD according to flow cytometry ($< 10^{-4}$) was present, the patients received 2 additional cycles. In case of ongoing confirmed uMRD at the time of the next blood MRD test, they discontinued therapy with the option for retreatment at progression. The frequency of uMRD confirmed in blood and marrow constituted the primary outcome.

In 89.2 % of 37 evaluable patients, uMRD was achieved in both blood and marrow, and the treatment was discontinued after a median of 10 months. All of the patients responded, with 54.5 % achieving CR/CRi at the time of treatment discontinuation **(Figure 4)**. BOVen was well tolerated; only few grade ≥ 3 treatment-emergent AEs occurred. Among 34 patients who achieved uMRD in peripheral blood by flow cytometry, 97 % obtained uMRD according to immunosequencing at a cutoff of $< 10^{-5}$. Rapid clearance with a ≥ 400-fold decrease within 6 cycles of starting the BOVen triplet was highly predictive of uMRD and might thus identify a favorable patient group.

Early vs. late use of zanubrutinib

Pooled data from two phase I studies (NCT02343120 and NCT03189524) and one phase II study (NCT03206918) investigating zanubrutinib monotherapy in CLL/SLL patients showed that superior outcomes can be obtained with this agent in earlier lines [25]. Treatment-naïve patients had a significantly higher ORR than those with relapsed/refractory disease (100 % vs. 90.6 %; $p < 0.001$), and median PFS was numerically longer (HR, 0.32; $p = 0.14$). For OS, the comparison revealed no difference. In general, treatment-naïve patients showed a better exposure-adjusted safety profile that those with r/r CLL, particularly regarding AEs of special interest such as diarrhea, hypertension and atrial fibrillation/flutter.

Another comparison across patients with 1 prior line of treatment and those after ≥ 2 prior lines yielded similar results. Here, the ORR was numerically higher in the early lines (97 % vs. 88.3 %; $p = 0.05$), while median PFS was significantly longer (HR, 0.13; $p < 0.001$). The 24-month PFS rates amounted to 95 % and 75.3 %, respectively. Again, OS did not differ. Exposure-adjusted safety profiles were generally similar for both groups, although patients after only 1 treatment line showed lower rates of AEs of special interest.

Emerging BTK-inhibiting agents

Robust results for orelabrutinib

The ongoing, multicenter, open-label, single-arm, phase II ICP-CL-00103 study is evaluating the novel, highly selective, irreversible BTK inhibitor orelabrutinib in 80 patients with r/r CLL. According to the update provided by Xu et al. at the ASH 2020 Congress, the results confirmed the efficacy of orelabrutinib [26]. At a median follow-up of 14.3 months, the ORR according to independent review was 91.3 %, and CR/CRi was obtained in 10 %. Disease control resulted in 95 %. Over time, the CR rates increased significantly. Also, very high ORRs occurred in cytogenetic high-risk subgroups (deletion 17p, 100 %; *TP53* mutation, 100 %; deletion 11q, 94.7 %; unmutated *IGHV*, 93.9 %).

Neither median PFS nor median duration of response had been reached at the time of data cutoff. At 12 months, the PFS rate was 81.1 %, and 77.1 % of patients responded. Orelabrutinib showed a robust safety profile and was found to be well tolerated with low rates of off-target side effects. Neutropenia, thrombocytopenia and upper respiratory tract infection occurred most commonly. No events were reported regarding atrial fibrillation/flutter and grade ≥ 3 hypertension. Grade ≥ 3 diarrhea occurred in one case, and major hemorrhage was seen in 2 cases.

LOXO-305: BRUIN

The phase I/II BRUIN study demonstrated promising efficacy of the novel,

non-covalent BTK inhibitor LOXO-305 in CLL/SLL patients previously treated with all classes of available therapy [27]. BRUIN included 170 patients whose number of prior lines of systemic therapy ranged from 1 to 11. Eighty-six percent had already received BTK inhibition, with progressive disease representing the most common reason for treatment discontinuation (67 %). High-risk molecular features were present in considerable percentages of patients.

The safety and tolerability of LOXO-305 were favorable and consistent with the design of this agent as a highly selective and non-covalent BTK inhibitor. No dose-limited toxicities occurred, and only 1.5 % of patients discontinued LOXO-305 due to treatment-related AEs. A daily dose of 200 mg was selected as the recommended phase II dose.

LOXO-305 showed efficacy regardless of BTK pretreatment and use of other prior agents, the reason for BTK inhibition discontinuation (i.e., progression vs. intolerance), and the presence of the *BTK C481* mutation status. In the total population and the BTK-pretreated group, the ORRs were 63 % and 62 %, respectively **(Table)**. Responses increased over time and were ongoing in 94 % of responders after a median follow-up of 6 months. Median PFS had not been reached yet.

TABLE
BRUIN study: responses obtained with LOXO-305 in all patients and in the BTK-inhibitor–pretreated group

All CLL/SLL patients	**n = 139**
Overall response rate, % (95 % CI)	63 (55-71)
Best response	
- Complete response, n (%)	0
- Partial response, n (%)	69 (50)
- Partial response with lymphocytosis, n (%)	19 (14)
- Stable disease	45 (32)
BTK-pretreated CLL/SLL patients	**n = 121**
Overall response rate, % (95 % CI)	62 (53-71)
Best response	
- Complete response, n (%)	0
- Partial response, n (%)	57 (47)
- Partial response with lymphocytosis, n (%)	18 (15)
- Stable disease, n (%)	41 (34)

Novel agents targeting PI3Kδ and CD20

UNITY-CLL

As not all patients are ideal candidates for BTK and Bcl-2 inhibitors, other agents such as phosphatidylinositol-3-kinase-delta (PI3Kδ) inhibitors with distinct mechanisms of action have been evaluated. However, studies of previous generations of PI3Kδ inhibitors in treatment-naïve CLL patients have shown substantial toxicity [28, 29]. Umbralisib, an oral dual inhibitor of PI3Kδ and casein kinase-1ε, exhibits improved selectivity for the delta isoform of PI3K, with low rates of immune-mediated toxicities and discontinuations due to AEs [30, 31]. The combination of umbralisib and ublituximab, which is a novel anti-CD20 monoclonal antibody offering enhanced antibody-dependent cellular cytotoxicity, has demonstrated promising activity in heavily pretreated CLL patients [32].

The UNITY-CLL study compared umbralisib plus ublituximab (U2; n = 210) with chemoimmunotherapy consisting of obinutuzumab and chlorambucil (n = 211) in patients with treatment-naïve or r/r CLL [33]. PFS according to independent review committee was defined as the primary endpoint. In both arms, 57 % and 43 % of patients were treatment-naïve and pretreated, respectively. The median numbers of prior therapies were 2 and 1 for U2 and obinutuzumab plus chlorambucil, respectively.

Durable responses regardless of subgroup

In terms of the primary endpoint, the novel combination was superior to obinutuzumab plus chlorambucil in the ITT population, with a median PFS of 31.9 vs. 17.9 months (HR, 0.546;

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p < 0.0001; **Figure 5**). At 2 years, the PFS rates were 60.8 % vs. 40.4 %. The treatment-naïve population derived greater PFS benefits in both arms (38.5 vs. 26.1 months; HR, 0.482; p < 0.001) than the pretreated population (19.5 vs. 12.9 months; HR, 0.601; p < 0.01), although the differences between the regimens were significant for both groups.

Moreover, the ORR observed with U2 exceeded the response rate achieved in the control arm (83.3 % vs. 68.7 %; p < 0.001); this also applied to the proportions of patients with CR/CRi (5 % vs. 1 %). ORRs favored the novel regimen in both treatment-naïve and previously treated patients. In the population who had received prior BTK inhibition, those in the U2 arm fared comparatively better (ORR, 57 % vs. 25 %). Also, responses were durable, with 62 % still responding at 2 years. Disease control resulted in 93 %. Grade ≥ 3 AEs occurred more commonly with the novel combination (82 % vs. 66 %), which might be explained by the fact that median exposure was more than 4 times longer than in the control arm (21 vs. 5 months). The most common AEs observed in the experimental arm included diarrhea, nausea, and infusion-related reactions. At the grade 3/4 level, only neutropenia and diarrhea showed substantial rates (13 % and 12 %, respectively). While diarrhea occurred more frequently in the treatment-naïve population than in the previously treated patients, the opposite was true for neutropenia.

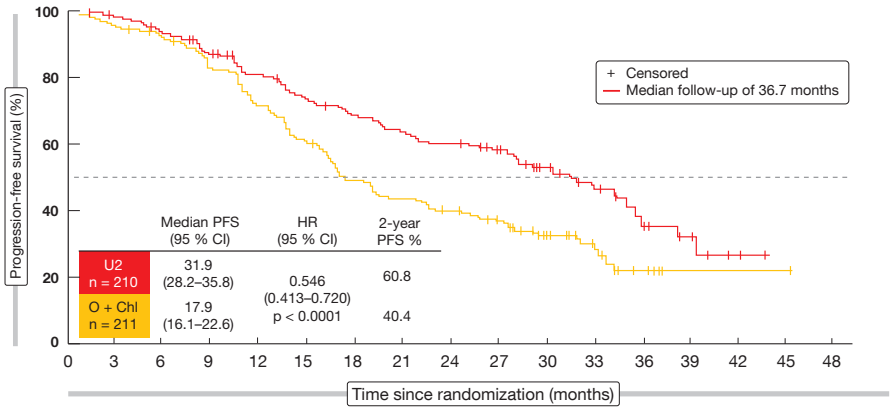

Figure 5: UNITY-CLL: progression-free survival with umbralisib plus ublituximab compared to obinutuzumab plus chlorambucil

In their conclusion, the authors noted that UNITY-CLL is the first randomized trial of a PI3Kδ inhibitor in treatment-naïve CLL, thus establishing a new mechanism of action in this setting. The non-chemotherapy U2 regimen is highly active in CLL patients and is being explored as a backbone for triplets including combinations with venetoclax and BTK inhibitors.

U2 followed by venetoclax

Based on the observation that targeting of PI3K might prevent drug resistance to Bcl-2 inhibition [34, 35], a multicenter, phase I/II, dose-escalation trial investigated U2 in combination with venetoclax [36]. Patients with r/r CLL received a fixed dose of ublituximab (900 mg) and two dose levels of umbralisib (600 mg and 800 mg) for 3 cycles

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(induction/debulking period). This was followed by the consolidation period encompassing 9 cycles of venetoclax at the standard dose of 400 mg after a 5-week ramp up. The protocol was amended to add ublixitumab infusions on day 1 of cycle 4, 5 and 6, which coincided with the venetoclax treatment period. After the total 12-cycle treatment period, patients underwent full response assessment including MRD testing of their blood and marrow. Treatment was stopped in patients with uMRD, whereas those with detectable MRD continued on single-agent umbralisib. Forty-three and 39 patients were evaluable for safety and efficacy, respectively. The primary objective of the trial was the safety of the venetoclax addition after U2 induction.

U2 and venetoclax were shown to be well tolerated at the phase II doses. Only 7 % of patients discontinued the regimen prior to cycle 12. Also, U2 induction mitigated the TLS risk; after the induction phase, this risk showed an 81 % relative reduction. No patient developed clinical or laboratory TLS during the venetoclax ramp up. The regimen demonstrated encouraging efficacy in the patient cohort including those who were refractory to prior BTK inhibition (i.e., 52 % of the total population). All of the patients responded, and the CR rate at cycle 12 was 41 %. At that time, MRD was undetectable in 96 % and 77 % in the blood and bone marrow, respectively.

To date, only 1 patient has progressed 10 months after achieving uMRD in the blood and marrow and the discontinuation of therapy. Retreatment strategies are being investigated. The regimen is further explored in the setting of Richter's transformation and in mantle cell lymphoma. Also, a phase II study assessing U2 plus venetoclax is ongoing in treatment-naïve and r/r CLL patients. ■

Insights from early clinical trials on targeted treatment in B-cell malignancies

DTRM-555: fixed-dose combination

Richter's transformation (RT), which describes transformation of CLL/SLL to diffuse large B-cell lymphoma (DLBCL) or Hodgkin lymphoma, is a rare event occurring in approximately 5–7 % of CLL cases [1]. However, defined standards of care are lacking, and outcomes are generally poor once patients are refractory to rituximab plus chemotherapy. A new strategy is the synthetic lethality approach that describes simultaneous inhibition of multiple pathways leading to cell death. Both the primary aberrant pathway and compensatory pathways are inhibited.

Analyses using an independent, iterative screening and optimization process were used to assess combinations of targeted agents based on DTRM-12, a novel, covalent, selective BTK inhibitor that has been specifically designed as a backbone for combination therapies [2]. After *in vitro* and *in vivo* screening, the best candidate triplet was selected for clinical trials. Preclinical studies showed that concurrent BTK inhibition, mTOR inhibition and the use of an immunomodulating agent at low doses can synergistically kill malignant B cells. The DTRM-555 regimen was designed as an oral, once-daily, triplet combination consisting of DTRM-12, the mTOR inhibitor everolimus, and the immunomodulating agent pomalidomide.

A phase I clinical trial was conducted to test this concept in patients with B-cell non-Hodgkin lymphomas (NHLs) or CLL for whom no standard therapies were available. In stage 1 of the trial, DTRM-12 doses were escalated between 50 and 300 mg/d. Stage 2 was devoted to testing DTRM-12 in escalating doses plus everolimus 5 mg/d. Finally, in stage 3, the combination of DTRM-12 in escalating doses plus everolimus 5 mg/d and pomalidomide 2 mg/d on 21 out of 28 days was examined. The ultimate goal of the phase II was the production of a single, fixed-dose combination tablet.

Viable regimen in RT and DLBCL

At ASH 2020, Mato et al. presented the data on patients enrolled in phase I with a diagnosis of RT (n = 13) or *de novo* DLBCL (n = 11) [2]. All patients were pretreated with an anti-CD20 antibody, and all DLBCL patients had received R-CHOP, as had 69 % of RT patients. BTK inhibitors and the Bcl-2 inhibitor venetoclax had also been used in substantial proportions prior to study entry.

DTRM-12 200 mg/d, everolimus 5 mg/d and pomalidomide 2 mg/d were established as the recommended phase II dose of the DTRM-555 regimen. This combination had an acceptable safety profile, which meant that the primary endpoint of the study was met. The main safety findings were expected and manageable. Mostly, hematologic AEs occurred, with grade 3/4 neutropenia and grade 3/4 thrombocytopenia emerging in 54 % and 37 %, respectively. No patient discontinued combination therapy due to an AE. Pharmacokinetic analyses demonstrated that plasma concentrations of DTRM-12 were linear and unaffected by the coadministration of everolimus and pomalidomide. The pharmacokinetic data supported the once-daily dosing of DTRM-12, with an estimated half-life of 5–9 hours.

Best overall responses were 46 % and 45 % for patients with RT and DLBCL, respectively. In the RT population, 1 and 4 patients achieved CR and PR, respectively. For the DLBCL group, this applied to 2 and 3 individuals, respectively. Overall, 43 % of patients had ≥ 50 % reductions in the sum of the products of the greatest diameters of lymph nodes **(Figure)**. Even patients with 10 prior treatment lines experienced durable responses. Overall, the

triple fixed-dose combination tablet DTRM-555 showed encouraging clinical activity in a high-risk, heavily pretreated RT/DLBCL population. The tablet is currently in the final stage of development. Once-daily, oral dosing provides a convenient treatment schedule for patients and might therefore improve adherence to therapy.

Safety of zanubrutinib after ibrutinib/acalabrutinib

A multicenter, single-arm, open-label phase II study evaluated the next-generation BTK inhibitor zanubrutinib in 60 patients with previously treated B-cell malignancies who had discontinued ibrutinib and/or acalabrutinib due to AEs [3]. Tolerability issues are a common cause of treatment discontinuation with respect to these two agents [4, 5]. The primary objective was the assessment of the safety of zanubrutinib compared with the ibrutinib and/or acalabrutinib intolerance AE profile. Due to its improved selectivity, zanubrutinib was assumed to provide greater tolerability with reduced recurrence and severity of BTK-inhibitor–emergent AEs. The population included 25 patients with CLL/SLL, two with mantle cell lymphoma (MCL), and five with Waldenström's macroglobulinemia (WM).

According to the analysis, zanubrutinib was tolerable and effective. Intolerable AEs experienced on ibrutinib and/or acalabrutinib were unlikely to recur while on zanubrutinib; no recurrence was noted for 88 % of ibrutinib-intolerant events and 50 % of acalabrutinib-intolerant events. Among the events that did recur, 88 % of ibrutinib events and 50 % of acalabrutinib events showed lower severity. None of the grade 4 intolerant events recurred on zanubrutinib. Out of 25 grade 3 events, only 2 recurred. No serious AEs were observed, and no patient discontinued treatment due to adverse events.

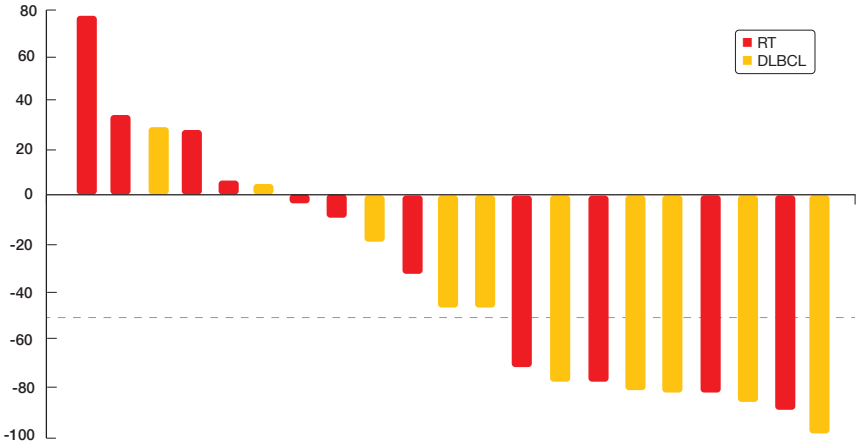

Figure: Depth of nodal response observed with DTRM-555 treatment in patients who had Richter's transformation or *de novo* DLBCL

Compared with prior BTK inhibitor treatment, zanubrutinib maintained responses (44.4 %) or improved them (50 %). At a median follow-up of 3.5 months, 96.9 % of patients remained on study. As the authors noted, these data suggest that zanubrutinib might provide a therapeutic option in patients intolerant to other BTK inhibitors.

LOXO-305: durable responses in MCL

The highly potent and selective non-covalent BTK inhibitor LOXO-305 was assessed in 323 patients with CLL/SLL, MCL, WM, and other NHLs participating in the phase I/II BRUIN study. At ASH 2020, Wang et al. presented the efficacy results for 61 patients with MCL, 26 with WM and 66 with other NHLs, and safety results for all 323 patients [6].

In the efficacy population, all patients were pretreated. The median numbers of prior lines of systemic therapies were 3, 3, and 4 for those with MCL, WM and other NHLs. Previous treatments included all available classes of therapy including BTK inhibition, chemotherapy, anti-CD20 antibodies, CAR-T cell therapy, and stem cell transplantation. Progressive disease was the reason for discontinuation of BTK inhibitor pretreatment in 67–79 % of cases.

The pharmacokinetic analysis was conducted within a dose range from 25 to 300 mg/d. Here, plasma exposures of LOXO-305 were shown to be dose-dependent and linear. They exceeded BTK IC_{90} throughout dosing intervals at doses ≥ 100 mg/d. LOXO-305 showed a favorable safety profile consistent with its design as a highly selective and non-covalent BTK inhibitor. No dose-limiting toxicities were reported, and no maximum tolerated dose was identified. LOXO-305 200 mg/d was selected as the recommended phase II dose. Rates of AEs of special interest such as bruising, rash, arthralgia and hemorrhage were low. Among 323 patients, only 5 (1.5 %) discontinued LOXO-305 due to treatment-related AEs.

LOXO-305 demonstrated promising efficacy independent of prior therapy. ORRs were 52 % and 68 % for patients with MCL and WM, respectively. In the group with other NHLs, they ranged

TABLE
Responses elicited with LOXO-305 treatment in patients with various non-Hodgkin lymphomas

	Richter's transformation (n = 8)	Follicular lymphoma (n = 8)	Marginal zone lymphoma (n = 9)	DLBCL (n = 25)
Overall response rate, % (95 % CI)	75 (35-97)	50 (16-84)	22 (3-60)	24 (9-45)
Best Response				
- Complete response, n (%)	0	2 (25)	0	4 (16)
- Partial response, n (%)	6 (75)	2 (25)	2 (22)	2 (8)
- Stable disease, n (%)	1 (13)	1 (13)	7 (78)	2 (8)

from 22 % for marginal zone lymphoma to 75 % for Richter's transformation **(Table)**. Notably, LOXO-305 led to durable responses in BTK-pretreated patients with MCL in whom outcomes are generally poor following progression on covalent BTK inhibitors such as ibrutinib [7, 8]. BTK-pretreated MCL patients achieved complete remissions in 25 %, and 83 % of responders were still responding and on treatment at 6 months. Overall, the analysis showed that LOXO-305 is well tolerated and exhibits promising efficacy in heavily pretreated patients with various NHLs. A longer follow-up is required to better understand the safety profile associated with chronic administration.

TG-1701 as single agent and in combination with U2

Another investigational next-generation BTK inhibitor is TG-1701, a once-daily, covalently bound agent. Compared with ibrutinib, it was shown to exhibit superior selectivity [9]. The triple combination of TG-1701 with the dual PI3Kδ/CK-1ε inhibitor umbralisib and ublituximab, a glycoengineered anti-CD20 antibody, demonstrated inhibition of tumor growth in BTK-resistant xenograft models [10]. Cheah et al. reported phase I study results for TG-1701 as monotherapy and in combination with umbralisib and ublituximab (U2) in patients with B-cell lymphoma or CLL that warranted systemic therapy [11]. Parallel dose escalation was conducted in both monotherapy (n = 25; 100–400 mg/d) and combination cohorts (n = 16; 100–300 mg/d). Disease-specific cohorts were expanded at 200 mg and 300 mg of single-agent TG-1701 for patients with CLL (n = 20), MCL (n = 21), and WM (n = 20). All patients in the dose escalation phase had relapsed and refractory disease, while several individuals in each disease-specific cohort were treatment-naïve.

The safety profile was generally favorable, and no patient discontinued therapy due to AEs. For both TG-1701 monotherapy and the triplet combination, grade ≥ 3 AEs were infrequently observed. Regarding efficacy, monotherapy at doses of 100–400 mg gave rise to an ORR of 52 %. In the disease-specific cohorts treated with TG-1701 200 mg, ORRs for patients with CLL, MCL and WM were 95 %, 50 %, and 95 %, respectively. For the dose-escalation triplet combination consisting of TG-1701 and U2, the ORR was 79 %, including complete remissions in 22 %. At the time of the analysis, most patients were still on study.

Overall, TG-1701 exhibited an encouraging safety profile, with clinical and pharmacodynamic activity at all evaluated dose levels that support once-daily dosing. The maximum tolerated dose had not been reached in the monotherapy arm. Also, the combination with U2 was well tolerated, and dose escalation continues. Combination treatment was associated with encouraging clinical activity, including early complete responses. This study continues enrollment, and future registrations trials are being planned. ■

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Approaching marginal zone lymphoma from various angles

Approximately 10 % of Non-Hodgkin lymphomas are classified as marginal zone lymphoma (MZL) [1]. This is a heterogeneous malignancy with three main subtypes (i.e., extranodal, nodal, splenic) arising from memory B cells in the marginal zone of secondary lymphoid follicles [2, 3]. Due to its rarity and heterogeneous nature, the optimal therapeutic strategies for patients with MZL have been difficult to define. Advanced disease is largely considered incurable, with continuing patterns of relapse and remission. However, phase II data presented at the ASH 2020 Congress showed that emerging treatment options such as the BTK inhibitor zanubrutinib and the PI3Kδ inhibitor parsaclisib have the potential to change the course of disease in a considerable proportion of patients.

MAGNOLIA: patients with high-risk features

BTK inhibition has been hypothesized to work in MZL patients based on the ob-

servation that B-cell-receptor–mediated signaling is a critical step in the pathogenesis of this disease [4]. Indeed, the first-generation BTK inhibitor ibrutinib was shown to be active in the relapsed/refractory (r/r) setting [5] and has been granted accelerated approval by the FDA as monotherapy in patients pretreated with ≤ 1 anti-CD20-based regimen.

In an early-phase study, the next-generation BTK inhibitor zanubrutinib induced an 80 % ORR in 20 patients with r/r MZL [6]. Therefore, the multicenter, open-label, single-arm, phase II MAGNOLIA study investigated single-agent zanubrutinib 160 mg twice daily in 68 patients with r/r MZL who had received ≤ 1 prior line of CD20-directed therapy. ORR by independent review committee (IRC) using the Lugano classification was defined as the primary outcome. At ASH 2020, Opat et al. reported the response findings according to investigator assessment after a median follow-up of 10.7 months, while the blinded response assessment by IRC was ongoing [7].

MAGNOLIA generally enrolled patients with high-risk features. Sixty percent were aged ≥ 65 years, and 28 % were even 75 years or older. Two thirds and one third had relapsed and refractory disease, respectively. All subtypes of MZL were included, with 38.2 % showing the nodal subtype that conveys a poorer prognosis than the extranodal subtype. Lymphoma involvement in bone marrow was present in 42.6 %. A median of 2 lines of systemic therapy had been administered prior to study inclusion. At the time of the analysis, 44 patients remained on treatment.

Clinical benefit of almost 90 %

Zanubrutinib proved to be highly active in this population. Overall, 74.2 % of patients responded, with complete remissions resulting in 24.2 % (**Table**). Clinical benefit (complete and partial responses plus stable disease) was observed in 89.4 %. Median time to response was short at 2.8 months. The majority of patients developed reductions in their tumor burden. Responses were generally consistent across subgroups with respect to MZL subtype, age, number of prior lines of systemic therapy and nature of prior treatment, among others. The ORRs were 89 % in patients aged ≥ 75 years, 65 % in those after ≥ 3 treatment lines, and 71 % in those with refractory disease. Almost 80 % of the entire group were still responding at 6 months.

TABLE
Best overall response by investigator observed with zanubrutinib in the MAGNOLIA study

Best response	n = 66
ORR (complete or partial response), n (%) 95 % CI	49 (74.2) (61.99, 84.22)
- Complete response	16 (24.2)
- Partial response	33 (50.0)
- Stable disease	10 (15.2)
- Progressive disease	5 (7.6)
- Disease control rate	59 (89.4)
- Discontinued prior to first assessment/missing	2 (2.9)
Time to response (months), median (range)	2.8 (1.7-11.1)
Study follow-up (months), median (range)	10.7 (1.6-16.7)

Median PFS and OS had not been reached yet. At 9 months, 67 % of patients were progression-free, and at 12 months, 94 % were alive. Zanubrutinib showed a favorable AE profile and was generally well tolerated, which is also mirrored by the 99.6 % median relative dose intensity. Grade ≥ 3 treatment-emergent AEs (TEAEs) occurred in 38.2 %. In 23.5 %, dose interruptions were performed, while no patient required dose reductions. Only 2.9 % discontinued treatment due to TEAEs. Among TEAEs of interest, infection, hemorrhage, diarrhea and neutropenia prevailed. One patient each developed atrial fibrillation and atrial flutter. No major hemorrhages and no cases of hypertension were observed.

Preliminary results from CITADEL-204

The potent, highly selective, next-generation PI3Kδ inhibitor parsaclisib has shown promising clinical activity in r/r B-cell lymphomas including MZL in early trials [8]. Therefore, the open-label, phase II CITADEL-204 study assessed two parsaclisib treatment schedules in patients with r/r MZL who had received ≥ 1 prior systemic therapy including ≥ 1 anti-CD20 antibody as monotherapy or chemoimmunotherapy combination.

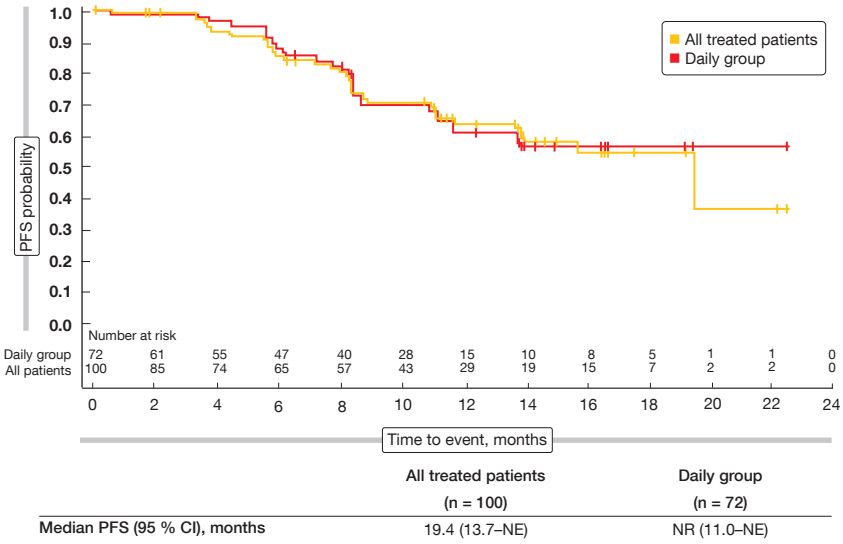

Figure: Progression-free survival in all patients treated with parsaclisib and in the cohort receiving continuous daily parsaclisib doses

The study was designed to include a BTK-inhibitor–naïve and an ibrutinib-experienced cohort. However, the latter was eventually terminated due to slower-than-expected enrollment.

Patients enrolled in the study were initially allocated to either parsaclisib 20 mg daily for 8 weeks followed by 20 mg once weekly (weekly group) or parsaclisib 20 mg daily for 8 weeks followed by 2.5 mg daily continuously (daily group). The daily group regimen was selected as the preferred regimen during the study, and all subsequent patients were enrolled into this group. ORR constituted the primary endpoint. At ASH 2020, Phillips et al. presented preliminary efficacy and safety data from the BTK inhibitor-naïve cohort for all treated patients (n = 100) and the daily group (n = 72) [9]. At data cutoff, the median duration of follow-up was 16.7 and 14.9 months, for all treated patients and the daily group, respectively.

Rapid and durable responses

The ORR by independent review was 57.0 % and 56.9 % in all patients and the daily group, respectively. Complete remission resulted in 6.0 % and 5.6 %, respectively. ORRs did not differ significantly across patients with nodal, extranodal and splenic MZL; this also applied to the groups who were refractory to prior therapy and those who had relapsed on it. Sixty-seven percent of responders had either complete or partial responses already at the time of the first assessment. Median time to first response was 8.1 weeks. In the total group, median duration of response and median PFS were 12.0 months and 19.4 months (**Figure**), respectively. In the daily group, neither median duration of response nor median PFS (**Figure**) had been reached yet.

Parsaclisib showed a manageable safety profile. Diarrhea, cough and rash were observed as the most common AEs. The most common grade ≥ 3 AEs were diarrhea and neutropenia. Among serious TEAEs, pneumonia (7 %), colitis (5 %), diarrhea (5 %) and febrile neutropenia (5 %) showed the highest incidence. A total of 27 patients discontinued treatment due to TEAEs, with diarrhea or colitis events occurring in 14 individuals. The median time to onset of grade ≥ 3 diarrhea/colitis events was 5.3 months, and the median time to improvement to grade ≤ 2 was 12.0 days. In their conclusion, the authors noted that parsaclisib represents a potential new treatment option and first-in-class PI3Kδ inhibitor for MZL patients. ■

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Advancing treatment in patients with mantle cell lymphoma

Update on acalabrutinib monotherapy

High relapse rates after standard-of-care regimens in the frontline setting are typical of mantle cell lymphoma (MCL), which is an aggressive, rare, B-cell Non-Hodgkin lymphoma [1-4]. The second-generation, highly selective BTK inhibitor acalabrutinib has been approved in the US for the treatment of patients with MCL after ≥ 1 prior therapy based on the single-arm, open-label, multicenter, phase II ACE-LY-004 study [5]. At ASH 2020, Wang et al. reported updated efficacy and safety results from this trial after an additional year of follow-up [6]. A total of 124 patients with r/r MCL were enrolled. At a median follow-up of 38.1 months, 55 (44 %) remained on study, with 24 (19 %) still receiving acalabrutinib.

According to the updated findings, treatment efficacy was largely maintained. The ORR was 81 %, as it had been after the 26-month follow-up at the time of the primary analysis **(Table)** [5]. Complete responses had increased from 43 % to 48 %. Median duration of response amounted to 28.6 months. At 36 months, 41.9 % of patients responded, and 37.2 % were progression-free. Median PFS was 22.0 months. Median OS had not been reached yet, and the 36-month OS rate was 60.5 %. Six of 30 patients (20 %) with available samples maintained complete remission and undetectable minimal residual disease at the last assessment.

Moreover, the extended follow-up conveyed no new safety concerns. The AE profile was basically unchanged, with infections and bleeding events occurring as the most common toxicities. More than half of patients with any bleeding event were receiving anticoagulant medication. AEs led to dose delays in 50 patients (40 %) and dose modifications in 2 (2 %). There were 57 deaths (46 %), most commonly due to disease progression (n = 38; 31 %). Overall, these

TABLE
Updated response rates with acalabrutinib monotherapy for the treatment of relapsed/refractory mantle cell lymphoma

	All patients (n = 124)	
	26-month follow-up n (%)	38-month follow-up n (%)
Overall response rate (complete + partial response)	100 (81)	101 (81)
Best response		
- Complete response	53 (43)	59 (48)
- Partial response	47 (38)	42 (84)
- Stable disease	11 (9)	10 (8)
- Progressive disease	10 (8)	10 (8)
- Not evaluable	3 (2)	3 (2)

data confirmed the safety and efficacy of acalabrutinib in patients with r/r MCL.

Frontline ibrutinib + rituximab in the elderly

Many elderly patients suffering from MCL are transplant-ineligible and not suitable for intensive chemoimmunotherapy due to comorbidities. The combined use of ibrutinib and rituximab was tested in a single-center, phase II study containing 50 previously untreated MCL patients aged ≥ 65 years with ECOG performance status ≤ 2 and normal organ function [7]. Their median age was 71 years. Bone marrow involvement was present in 94 %. Twenty-five percent had a Ki-67 index ≥ 30-50 %.

Overall, 90 % of patients responded to the treatment, with 62 % and 28 % achieving complete and partial remissions, respectively. MRD negativity at the time of the best response was 87 %. Median PFS and OS had not been reached yet at a median follow-up of 43 months. Out of 4 patients who progressed, 3 showed transformation to the blastoid/pleomorphic variant. Two had Ki-67 ≥ 30 %, one was *TP53*-mutated, and another had *FAT1* and *SF3B1* mutations. Five patients died off study; in 3 cases, this was due to progression, and in 2, the etiology was unknown. Among AEs, fatigue, diarrhea and myalgia occurred most frequently. Seventeen patients (34 %) developed atrial fibrillation. Median time to onset from the start of treatment was 9.4 months.

The authors noted that ibrutinib plus rituximab is a highly effective, easily administered, chemotherapy-free option for transplant-ineligible elderly patients with non-blastoid (Ki-67 < 50 %) MCL. The increased incidence of arrhythmia observed in the study was likely due to the high number of cardiovascular risk factors in this population. This suggested that baseline cardiac evaluation and cardiovascular risk factor modification should be performed in the context of treatment with ibrutinib and rituximab. The long-term follow-up will reveal the impact of the combined treatment on safety and relapse patterns.

Orelabrutinib gives rise to high CR rates

A multicenter, open-label, phase II study tested the efficacy and safety of the novel, highly selective, irreversible BTK inhibitor orelabrutinib as monotherapy in Chinese patients with r/r MCL [8]. The safety population comprised 106 patients, and 99 made up the efficacy population. Orelabrutinib was administered at doses of 100 mg twice daily (n = 20) and 150 mg/d (n = 86).

The treatment gave rise to marked responses and durable remissions. At 16.4 months, the ORR was 87.9 %, with a CR rate of 34.3 % by CT-based imaging. These results represented slight increases compared to the ORR and CR of 85.9 % and 30.3 %, respectively, observed at 10.5 months. Complete responses according to PET-CT had even been achieved in 42.9 %. The disease control rate added up to 93.9 %. At 12 months, 70.8 % of patients were progression-free, and 88.7 % were alive. Median PFS and duration of response had not been reached yet at the time of the analysis.

Orelabrutinib showed a favorable safety profile. Treatment-related AEs leading to dose reductions and study drug discontinuation occurred in 6.6 % and 2.8 %, respectively. Thrombocytopenia, neutropenia and upper respiratory tract infections were most commonly reported. Among AEs of special interest, hemorrhage was most common but was restricted to grade 1 and 2. Moreover, no grade ≥ 3 atrial fibrillation/flutter or grade ≥ 3 diarrhea occurred. Grade ≥ 3 infections were observed in 12.3 %. As the authors noted in their conclusion, the pronounced efficacy and improved safety of orelabrutinib resulting from its high target selectivity, combined with the convenience of daily dosing, mark this agent as a preferable option for the treatment of patients with B-cell malignancies.

Parsaclisib in BTK-inhibitor–pretreated patients…

The CITADEL-205 study evaluated the highly selective, next-generation PI3Kδ inhibitor parsaclisib in the setting of r/r MCL. Cohort 1 of the study contained patients who had previously received BTK inhibition, while those in Cohort 2 were BTK-inhibitor–naïve. In both groups, 1–3 prior lines of systemic therapy had been administered. Parsaclisib 20 mg for 8 weeks was followed by either 20 mg once weekly (weekly group) or 2.5 mg once daily continuously (daily group). During the study, the daily group dose was selected as the preferred dosing regimen, and patients in the weekly group were allowed to switch to the daily group. The findings for the overall and daily groups were reported at ASH 2020 for Cohorts 1 and 2 separately.

Zinzani et al. presented the results for the BTK-inhibitor–pretreated Cohort 1 which consisted of a total of 53 patients, with 41 treated in the daily group [9]. The ORRs according to independent review were 25 % and 29 % **(Figure)** for the overall and daily groups, respectively. CRs resulted in 2 % each, and PRs and 23 % and 27 %, respectively. Forty-seven percent of all treated patients and 51 % of those in the daily group had regression of target lesions. Median duration of response

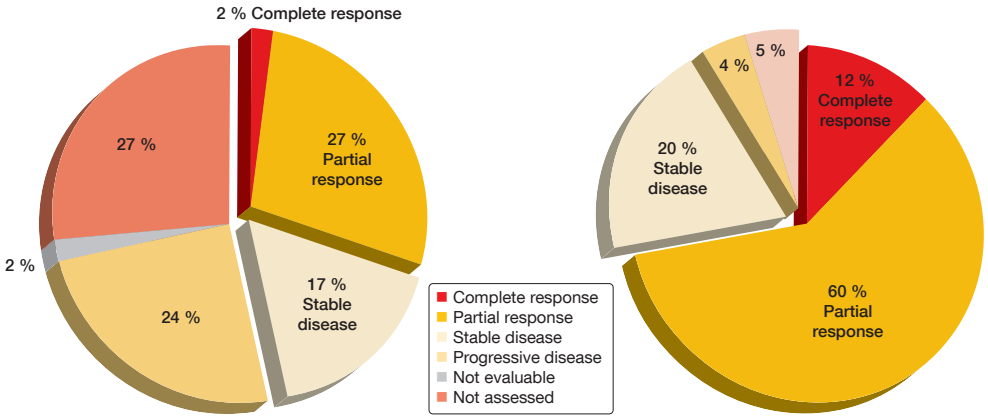

Figure: CITADEL-205: responses obtained with parsaclisib in BTK-inhibitor–pretreated patients (left) and not pretreated patients (right; daily dosing groups)

amounted to 3.7 months in both groups; likewise, median PFS was 3.7 across all patients. Median OS was 11.2 in both the total cohort and the daily group. Estimated survival rates at 18 months were 32 % and 37 %, respectively.

… and those without BTK inhibitor pretreatment

For Cohort 2 that contained BTK-inhibitor–naïve patients, Mehta et al. reported the findings [10]. Here, 108 and 77 individuals made up the total and daily groups, respectively. Responses were observed in 70 % and 71 %, respectively, with 15 % and 12 % obtaining CR, respectively **(Figure)**. Partial responses occurred in 56 % and 60 %, respectively. Eighty-four percent and 87 %, respectively, developed regression of their target lesions. Median duration of response was 14.7 and 9.0 months, respectively, and median PFS was 11.1 months in both groups. Median OS had not been reached yet in either group. At 18 months, 69 % and 68 % of patients, respectively, were alive.

Overall, parsaclisib showed clinical activity in both cohorts with r/r MCL. The efficacy of treatment was deemed excellent in the BTK-inhibitor–naïve setting. Here, the authors concluded that parsaclisib represents a potential new option and is a first-in-class PI3Kδ inhibitor in the setting of MCL. In both Cohort 1 and 2, the new agent demonstrated an acceptable safety profile and was generally well tolerated. ■

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Interview: Stephen Opat, MD, School of Clinical Sciences at Monash Health, Monash University, Melbourne, Australia

Finding the way among a multitude of targets and regimens

Under which conditions might patients with chronic lymphocytic leukemia achieve long-term treatment-free remission?

I would like to address two factors here. The first one relates to favorable disease biology. Patients who have mutated immunoglobulin genes or lack *TP53* mutations or 17p loss are more likely to experience treatment-free remission. The other main factor is treatment capable of inducing deep remission, which is usually combination therapy. Historically, the fludarabine/cyclophosphamide/rituximab regimen was the gold standard with which patients could achieve deep remissions. However, we have several fixed-duration options. The CLL14 study investigated venetoclax plus obinutuzumab, while CAPTIVATE assessed ibrutinib plus venetoclax. Also, the combination of acalabrutinib, venetoclax and obinutuzumab was tested. These combinations achieved undetectable minimal residual disease in large proportions of patients [1-4], which correlates with long treatment-free remissions.

Where do you see BTK inhibition in the management of B-cell malignancies 3 years from now?

This is a very difficult question. If you look at the data, you see that in the RESONATE-2 trial investigating first-line ibrutinib in patients with CLL/SLL, 70 % of patients were progression-free at the time of the 5-year update that was recently published [5]. However, only 60 % were still receiving the study drug. The follow-up is still relatively short. I think single-agent BTK inhibitors will be a good option for several patients, particularly for those with comorbidities. It is being said that combinations tend to have more side effects; for instance, the rates of neutropenia are higher if you combine venetoclax with other drugs. Some of the newer BTK inhibitors have a favorable safety profile and might thus be more suited to long-term usage. A number of long-term toxicities have not been elucidated yet. There is a risk of infection, hypertension and arrhythmias, and there is also a question about second primary malignancies. Continuously administered BTK inhibitors are one option and combination time-limited therapy is another; it is really hard to say which one will win out. However, many patients have been on BTK inhibitor therapy for several years and have achieved great disease control.

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What are the strengths and limitations of immune checkpoint inhibition in B-cell malignancies from the current point of view?

This area is still emerging. We have seen very good responses in primary mediastinal lymphoma and Hodgkin's disease [6-8]. However, most studies to date have involved the PD-1 and PD-L1 checkpoints, although there are many other inhibitory receptors such as CTLA-4, TIM-3, TIGIT, and BTLA that can be explored. This also includes the agonist receptors 4-1BB, LAG-3, OX40 and CD27, the macrophage checkpoint CD47, and NK ligands. The main problem with these drugs is induction of autoimmunity, which can involve any organ system. Immune-related toxicities include rash, colitis, pneumonitis, or even endocrine insufficiency.

This entire area of immune checkpoint inhibition is a fantastic emerging area. However, our knowledge is early, and we still have a long way to go. Some patients are already deriving benefit, and I think there will be many more once we have worked out what the best combinations are and in which patients they should be used. ■

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PD-1 inhibition and (Non-)Hodgkin lymphoma: promising outcomes in an emerging field

Nivolumab plus BV for MGZL treatment

Mediastinal gray zone lymphoma (MGZL) is an extremely rare type of Non-Hodgkin lymphoma with a predominance in young men [1]. This disease exhibits transitional features between nodular sclerosis classical Hodgkin lymphoma (cHL) and primary mediastinal B-cell lymphoma (PMBL) [2, 3]. However, compared to PMBL, survival of patients with MGZL is inferior after conventional chemotherapy [4]. The phase II Checkmate 436 trial has established high response rates for the anti-PD-L1 antibody nivolumab in combination with the antibody-drug conjugate brentuximab vedotin (BV) in adult patients with r/r PMBL [5]. Similarly, nivolumab plus BV conferred favorable results in patients with r/r cHL treated in the phase I/II setting [6].

In a separate cohort of the CheckMate 436 study, patients with r/r MGZL received nivolumab 240 mg plus BV 1.8 mg/kg 3-weekly until disease progression. The primary efficacy and safety analysis for the MGZL cohort (n = 10) was reported at ASH 2020 [7]. Refractory disease was present in 7 patients (70 %), and the median number of prior systemic cancer therapies was 2. None of the patients had undergone autologous stem cell transplantation (ASCT).

Findings that favor bridging

At database lock, all patients had discontinued treatment. The reasons included disease progression (n = 5), maximum clinical benefit (n = 3), allogeneic SCT (n = 1) and ASCT (n = 1). All of those with maximum clinical benefit had achieved complete remission and proceeded to allogeneic SCT. The ORR obtained in the total group was high at 70 %; complete and partial responses occurred in 50 % and 20 %, respectively. Also, time to CR was short (1.2–4.8 months). As the authors noted, these findings were consistent with the results reported for nivolumab plus BV in r/r PMBL and r/r cHL [5, 6, 8]. All patients who achieved CR were bridged to hematopoietic cell transplantation (i.e., 4 to allogeneic SCTs and 1 to ASCT).

Median OS had not been reached yet; at 6 months, 80 % of patients were alive. Duration of response and PFS could not be estimated reliably due to earlier censoring of patients who received subsequent therapies. The safety profile of the combination was tolerable and consistent with previous reports [5, 6, 8]. Cytopenia, paresthesia and peripheral sensory neuropathy occurred. No grade 4 AEs were observed. One patient was diagnosed with grade 3 febrile neutropenia, and another developed rash that was the only reported immune-mediated AE and resolved without systemic steroids. Based on these findings, the authors concluded that nivolumab plus BV represents a potential option for bridging to stem cell transplant in patients with chemotherapy-refractory MGZL.

TABLE
KEYNOTE-204: progression-free survival with pembrolizumab vs. brentuximab vedotin (BV) according to the number of prior treatment lines

	1 prior line of therapy		≥ 2 prior lines of therapy	
Primary analysis (including clinical and imaging data following ASCT or allogeneic SCT)				
	Pembrolizumab	**BV**	**Pembrolizumab**	**BV**
Median PFS (months)	16.4	8.4	12.6	8.2
12-month PFS rates (%)	58.9	37.4	52.8	35.3
Hazard ratio	0.70		0.66	
Secondary analysis (excluding clinical and imaging data following ASCT or allogeneic SCT)				
	Pembrolizumab	**BV**	**Pembrolizumab**	**BV**
Median PFS (months)	11.7	8.3	12.6	8.2
12-month PFS rates (%)	49.5	28.3	50.5	34.1
Hazard ratio	0.62		0.63	

cHL: pembrolizumab vs. BV

Prognosis is poor for patients with relapsed/refractory cHL who have failed ASCT, have primary refractory disease or are ineligible for ASCT [9-13]. The open-label, international, randomized, phase III KEYNOTE-204 study tested the PD-1 inhibitor pembrolizumab as monotherapy (n = 151) against the antibody-drug conjugate brentuximab vedotin (BV; n = 153) in patients with r/r cHL. Treatment was administered for up to 35 cycles in both arms. The primary analysis presented at ASCO 2020 already showed a statistically significant and clinically meaningful PFS benefit for pembrolizumab compared to BV (13.2 vs. 8.3 months; HR, 0.65; p = 0.00271) [14]. At ASH 2020, Kuruvilla et al. presented a post-hoc exploratory analysis of the study that assessed the outcomes according to the number of prior lines of therapy [15]. Within the group of 55 patients who had previously been treated with one line, 27 and 28 had received pembrolizumab and BV, respectively. The cohort of patients after ≥ 2 treatment lines (n = 249) comprised 124 and 125 individuals randomized to the checkpoint inhibitor and BV, respectively.

Single-agent pembrolizumab was shown to improve clinical outcomes compared with BV regardless of the number of prior therapies. This held true irrespective of whether patients who went on to receive consolidative ASCT or allogeneic SCT were included in the data set or not **(Table)**. Risk re-

ductions ranged between 30 % and 38 %. Overall, these results were consistent with the primary analysis [14]. Likewise, ORRs were similar regardless of the treatment line. After one line, 66.7 % vs. 53.6 % of patients responded, and after ≥ 2 lines, this was true for 65.3 % vs. 54.4 %. Reponses lasted for a median of 20.7 vs. 14.1 months and 20.5 vs. 11.2 months, respectively. The safety profiles of both agents were generally similar across the subgroups. No unexpected safety signals occurred.

Also, subsequent ASCT was assessed by prior line of therapy. In the group of patients after one line, 25.9 % and 33.3 % of patients in the pembrolizumab and BV groups, respectively, underwent ASCT. For those with ≥ 2 pretreatment lines, this applied to 19.0 % and 20.0%, respectively. As the authors noted in their conclusion, these findings confirm that patients with r/r cHL after only one prior line of therapy who are ineligible for ASCT appear to benefit from pembrolizumab monotherapy.

Effect of TME on tislelizumab efficacy

Histologically, cHL has been shown to be characterized by low tumor cellularity (1–5 %) and a dominant tumor microenvironment (TME) composed of macrophages, T cells and other immune cells [16]. Limited efficacy of anti-PD-1 antibodies with a wild-type Fc region such as nivolumab and pembrolizumab might be due to binding to FcγR on macrophages, as this compromises the agents' antitumor activity through activation of antibody-dependent macrophage-mediated killing of T effector cells [17, 18]. The anti-PD-1 antibody tislelizumab has been specifically engineered to minimize binding to FcγR on macrophages.

Preclinical data showed that in macrophage- and T-cell–enriched conditions, tislelizumab did not induce antibody-dependent cellular phagocytosis (ADCP), and thus its anti-tumor activity was not compromised [19]. A pivotal phase II trial investigating tislelizumab in Chinese patients with cHL that had failed or were no candidates for high-dose chemotherapy/ASCT revealed an ORR of 87.1 %, with a CR rate of 62.9 % [20]. The study reported at ASH 2020 explored whether FcγR expression on macrophages in the cHL TME impacts the efficacy of tislelizumab [21]. Moreover, additional biomarkers associated with CRs were assessed. Multiplex immunohistochemistry (mIHC) and gene expression profiling (GEP) were used to

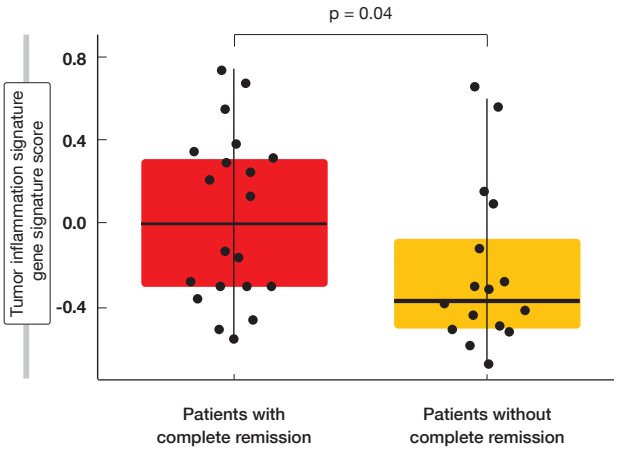

Figure: Significantly increased inflammation of the tumor microenvironment in patients who developed complete response on tislelizumab treatment

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analyze samples from 70 patients included the BGB-A317-203 trial. Among these, 41 and 36 were mIHC- and GEP-evaluable, respectively.

In accordance with the characteristics of tislelizumab, the agent demonstrated high CR rates regardless of FcγR expression levels on macrophages in the CD8+ T-cell–high TME where ADCP-induced effector T-cell clearance is more likely. The CR rates were 86.6 % vs. 85.7 % for high and low numbers of FcγR1+ macrophages, respectively. Multiple biomarkers were identified that correlated with complete responses to tislelizumab treatment. Higher CD8+ T-cell infiltration according to mIHC and tumor inflammation signature gene signatures in the TME by GEP corresponded with higher CR rates **(Figure)**. Moreover, mixed cellularity and nodal sclerosis histological subtypes showed specific gene signatures associated with complete response. ■

Bone marrow microenvironment: culprit and target

Apart from factors such as genetic events that contribute to the malignant transformation in Waldenström's macroglobulinemia (WM), the bone marrow microenvironment has been identified as a crucial player in WM disease progression [1]. Similarly, it appears to be essential for the emergence and progression of multiple myeloma (MM) and constitutes a significant reason why MM patients are not amenable to cure but inevitably develop relapses [2]. Delineation of malignant cell growth in the context of the bone marrow microenvironment has therefore moved into the focus of research approximately 15 years ago as it might enable the design of more efficient therapeutic strategies for both MM and WM.

According to our understanding, immunomodulatory agents such as thalidomide and lenalidomide that are being used to treat MM patients exert effects by modifying the microenvironment. Likewise, I believe that ibrutinib, when used in patients with WM, not only works by inhibiting BTK, which is an important aspect, but also regulates the microenvironment to some degree. Observations we make in clinical routine support this assumption. For example, we would

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treat a patient with WM and 80 % infiltration of the bone marrow who is very anemic because the marrow does not provide sufficient space to produce an appropriate quantity of red cells. Three to 6 months into therapy, the patient's hemoglobin is back to normal or much improved, and the IgM levels have decreased by 50 % or 70 %. However, when we perform another bone marrow biopsy on this patient, we find that the degree of infiltration is still 80 %. Therefore, we believe that a mechanism within the malignant cell uses the microenvironment to achieve a survival advantage. I feel that ibrutinib and many other medications work by suppressing the disease's impact on the microenvironment.

Much research is going on concerning the possibility of targeting the disease by targeting the microenvironment. From my perspective, this specific approach has been more successful in MM than it has been in WM, but I believe that we are on our way to identifying agents that can potentially help in this scenario. Hopefully, we can combine these with BTK inhibitors, Bcl-2 inhibitors and other agents to achieve more profound and long-lasting responses.

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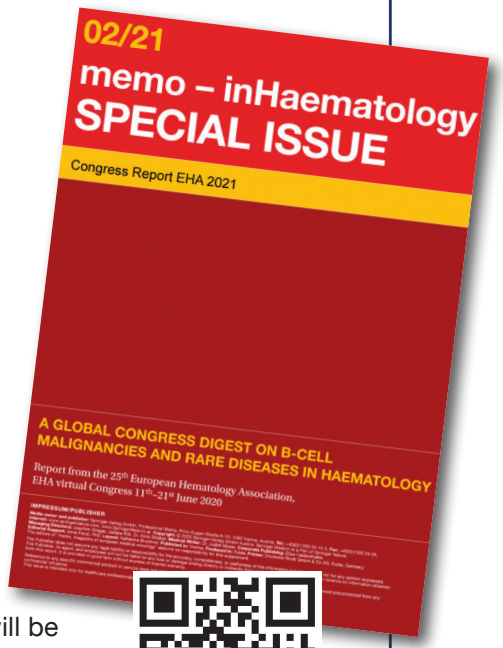
Steven P. Treon, MD, explains about innovative approaches in the treatment of Waldenström's macroglobulinemia, future aspects and the successful use of BTK inhibition within niche groups of patients with WM, and potential benefits of BTK inhibitors regarding COVID-19 complications.

Alessandra Tedeschi, MD, summarizes the results from the MAGNOLIA and iNNOVATE trials, relates to recent advances in the management of marginal zone lymphoma and discusses the effect of the introduction of BTK inhibition on the prognosis of patients with Waldenström's macroglobulinemia.

Stephen Opat, MD, discusses the requirements for treatment-free long-term remission in the setting of CLL and talks about the future of BTK inhibitors and promising combinations in B-cell malignancies in general, as well as the strengths and limitations of immune checkpoint inhibitors.

Jorge Castillo, MD, relates to recent developments with respect to follicular lymphoma, multiple myeloma and Waldenström's macroglobulinemia, current insights into CAR-T cell therapy in the setting of multiple myeloma, and the future of anti-CD38 antibody treatment in patients with Waldenström's macroglobulinemia.



Forthcoming Special Issue

This special issue will be offering a synopsis from the EHA 2021 that will be held in June 2021. The report promises to make for stimulating reading, as the EHA Congress itself draws on the input from a number of partner organizations, representing a multidisciplinary approach to cancer treatment and care. Stay tuned for the latest news in hematology and its subspecialties.

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