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

Report from the virtual American Society of Clinical Oncology (ASCO) Annual Meeting, 4th-8th June 2021, the 26th European Hematology Association (EHA) 2021 Virtual Congress, 9th-17th June 2021, and the virtual 17th International Conference on Malignant Lymphoma, 18th-22nd June 2021
Table of Contents

3 Preface
3 CLL/SLL: current perspectives across a range of potent agents
10 Waldenström’s macroglobulinemia: outcome optimization via combinations
12 Successful inhibition of PI3K, BTK, BCL2 and other targets in various B-cell malignancies
16 Extending anti-PD-1-based options in the setting of Hodgkin lymphoma
19 Mantle cell lymphoma: improving outcomes in difficult-to-treat patient populations
22 Zanubrutinib in relapsed/refractory marginal zone lymphoma: MAGNOLIA
22 Novel bispecific antibodies in CD20-positive B-cell non-Hodgkin lymphomas

Editorial Board:

Othman Al-Sawaf, MD, University Hospital, Cologne, Germany
Véronique Leblond, MD, Paris, France
Heinz Ludwig, MD, Wilhelminen Hospital, Vienna, Austria
Shirley D’Sa, MD, University College London Hospital, London, UK

Lecture Board for this issue:

Othman Al-Sawaf, MD,
Stephen M. Ansell, MD, PhD
Jorge Castillo, MD
Chan Cheah, MBBS
Martin Hutchings, MD, PhD
Véronique Leblond, MD
Jeff Sharman, MD

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

Dear Colleagues,

As virtual scientific conferences are becoming part of our daily routine as clinicians and researchers, information in individual areas of interest is easily accessible across different congresses. This publication summarizes studies investigating targeted and immune-directed treatment of B-cell malignancies that were presented at the European Hematology Association (EHA) Annual Congress, 9th-17th June, the 16th International Conference on Malignant Lymphoma (ICML), 18th-22nd June, and the 2021 Annual Meeting of the American Society of Clinical Oncology (ASCO), 4th-8th June 2021.

Chemotherapy-free regimens that can induce deep responses to the point of undetectability of minimal residual disease are generally gaining momentum and have already been established as cornerstones of treatment in various settings. A broad range of clinical trials is exploring effective and tolerable combinations with and without chemotherapeutic agents, as well as potent targeted drugs that show effectiveness as monotherapies. BTK inhibition represents an important pillar in the management of diseases such as chronic lymphocytic leukemia, Waldenström's macroglobulinemia, and marginal zone lymphoma. Trial results have demonstrated that patient outcomes can be improved with the use of new-generation agents, while yet newer BTK inhibitors are being developed. Likewise, novel BCL2- and PI3K-targeted agents are being designed with optimized features such as increased selectivity. Novel bispecific antibodies appear to offer substantial activity across a range of hematologic entities.

Moreover, the use of drugs that enhance anti-tumor immunity is an attractive approach, both in the single-agent and combination therapy settings. Checkpoint inhibition has been tested successfully in patients with non-Hodgkin lymphoma and classical Hodgkin lymphoma. As for solid tumors, durable responses are being observed in a certain percentage of patients. The development of innovative checkpoint inhibitors, which are expected to provide improved outcomes, is ongoing.

Véronique Leblond, MD
Department of Hematology, Pitié Salpêtrière Hospital
Paris, France

CLL/SLL: current perspectives across a range of potent agents

ALPINE: zanubrutinib vs. ibrutinib

The introduction of effective inhibitors of B-cell receptor signaling such as the BTK inhibitor ibrutinib has transformed the treatment of patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). The irreversible, potent, next-generation BTK inhibitor zanubrutinib has been designed to maximize BTK occupancy and minimize off-target inhibition of other kinases [1]. Based on the assumption that zanubrutinib might offer advantages over ibrutinib in terms of toxicity and efficacy, the randomized, phase III head-to-head ALPINE study was conducted at 129 centers in 15 countries to compare zanubrutinib 160 mg twice daily (n = 207) with ibrutinib 420 mg/d (n = 208) in patients with relapsed/refractory CLL or SLL after ≥ 1 prior systemic therapy. Approximately 20 % in both arms had deletion 17p and/or mutant TP53, and deletion 11q was present in 29.5 % and 26.4 %, respectively. Overall response rate (ORR, i.e., partial plus complete responses) non-inferiority and superiority as assessed by the investigator constituted the primary endpoint. At EHA 2021, Hillmen et al. presented the pre-planned interim analysis for the first 415 patients [2].

Indeed, zanubrutinib, as compared to ibrutinib, was shown to confer superior response, as well as other improvements. The ORR was 78.3 % and 62.5 % for zanubrutinib and ibrutinib, respectively (p = 0.0006; Table 1). Complete responses (CRs) and complete responses with incomplete bone marrow recovery (CRi) resulted in 1.9 % vs. 1.4 %. For the group that included patients with partial response and lymphocytosis in addition to those with CR and PR, the ORR was 88.4 % vs. 81.3 %. Likewise, patients with deletion 17p benefited from the new BTK inhibitor. According to the subgroup analysis, the ORR results for all key patient subgroups favored zanubrutinib.

Significant reduction in atrial fibrillation

With respect to progression-free survival (PFS), the patients treated in the experimental arm experienced a 60 % reduction in the risk of progression and
Responses obtained for zanubrutinib vs. ibrutinib in the ALPINE trial

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Responses obtained for zanubrutinib vs. ibrutinib in the ALPINE trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zanubrutinib (n = 207), n (%)</td>
</tr>
<tr>
<td></td>
<td>Ibrutinib (n = 206), n (%)</td>
</tr>
<tr>
<td>Overall response rate (partial and complete responses)</td>
<td>162 (78.3)</td>
</tr>
<tr>
<td></td>
<td>p = 0.0006</td>
</tr>
<tr>
<td>Complete response/complete response with incomplete bone marrow recovery</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>Nodular partial response</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Partial response</td>
<td>157 (75.8)</td>
</tr>
<tr>
<td>Overall response rate (partial and complete responses + partial response with lymphocytosis)</td>
<td>183 (88.4)</td>
</tr>
<tr>
<td>Partial response with lymphocytosis</td>
<td>21 (10.1)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>17 (8.2)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Discontinued or new therapy prior to first assessment</td>
<td>6 (2.9)</td>
</tr>
</tbody>
</table>

Deletion 17p (n = 24), n (%) Deletion 17p (n = 26), n (%)

| Overall response rate (partial and complete responses) | 20 (83.3) | 14 (53.8) |

The once-daily, all-oral, fixed-duration regimen of ibrutinib and the BCL2 inhibitor venetoclax has been shown to effectively induce tumor debunking in patients with CLL and to reduce the risk of tumor lysis syndrome (TLS) due to high tumor burden [5, 6]. In the first-line setting, the international, phase II CAPTIVATE trial is evaluating three cycles of ibrutinib lead-in followed by twelve cycles of ibrutinib/venetoclax. CAPTIVATE comprises the fixed-duration (FD) cohort and the minimal residual disease (MRD) cohort, which received MRD-guided randomization to either placebo vs. ibrutinib or ibrutinib vs. ibrutinib/venetoclax after the fixed-duration schedule. Results from the MRD cohort demonstrated undetectable MRD (uMRD) in more than two thirds of patients after 12 cycles of ibrutinib/venetoclax and 30-month PFS rates of ≥ 95% irrespective of subsequent MRD-guided randomized treatment [6]. At EHA 2021, Allan et al. presented the primary analysis results for the FD cohort after a median follow-up of 14.0 months post completion of treatment [7].

The FD cohort contained 159 patients aged ≤ 70 years with previously untreated CLL/SLL and ECOG performance status of 0–2. High-risk features including unmutated IGHV, deletion 17p/TP53 mutation and complex karyotype were present in 56%, 17%, and 19%, respectively. Bulky disease was found in 30%. The primary endpoint was the CR/CRI rate per investigator assessment in patients without deletion 17p; this cohort included 136 individuals.

Fixed-duration treatment with ibrutinib/venetoclax was shown to induce deep and durable responses. With a 56% CR/CRI rate, the primary endpoint was met (Figure 1). This provided a meaningful improvement over the 40% rate obtained with the historical comparator of fludarabine, cyclophosphamide and rituximab (FCR) in the CLL10 study [8]. Best overall response amounted to 96% both in patients without deletion 17p (i.e., those included in the primary endpoint analysis) and in monly. Two thirds of patients were still benefiting from continuous zanubrutinib treatment at the time of data cutoff.

### Long-term findings from BGB-3111-205

The single-arm, multicenter, phase II BGB-3111-205 study has already demonstrated efficacy and tolerability of zanubrutinib 160 mg twice daily in relapsed/refractory CLL/SLL after ≥1 prior therapy [3]. According to the long-term results reported at EHA 2021 for 91 patients after a 34-month follow-up, responses deepened over time [4]. The updated ORR was 87.9%, with 6.6% of patients achieving CR. All subgroups analyzed responded to treatment including those with high-risk cytogenetics. Patients with deletion 17p/TP53 mutation and deletion 11q achieved high response rates of 91% and 100%, respectively.

The safety data were consistent with those previously reported. AEs led to treatment discontinuation in 15.4%, and dose interruptions became necessary in 46.2%. Among AEs of special interest, infections, neutropenia, and hemorrhage were observed most commonly. Two thirds of patients were still benefiting from continuous zanubrutinib treatment at the time of data cutoff.
all patients treated in the FD cohort (Figure 1). Complete responses lasted for ≥ 12 cycles in 87 % and 89 %, respectively. High CR/CRi rates were observed in almost all treated patients, including those with high-risk features. An exception was the group with bulky disease that showed a 31 % CR rate (vs. 66 % in patients without bulky disease).

Deep and durable responses

As many as 76 % and 77 % of patients in the two cohorts achieved uMRD in the peripheral blood as best uMRD response; for the bone marrow, this was 62 % and 60 %, respectively. Despite the divergence of CR rates between patients with and without bulky disease, uMRD rates were similar across these groups. On the other hand, those with unmutated IGHV had higher uMRD rates than those with mutated IGHV. At 24 months, 98 % of patients in both groups were alive, and 96 % and 95 % among those without deletion 17p and all treated patients, respectively, showed freedom from progression. PFS rates at 24 months were high for patients with both deletion 17p and in the total treated population

remissions, and in two patients, response evaluation was pending at the time of data presentation. The fixed-duration regimen proved tolerable. Ninety-two percent of patients completed the full schedule. Three cycles of ibrutinib were shown to provide effective tumor debulking; no clinical TLS occurred, and no patient had laboratory TLS per Howard criteria. Diarrhea (62 %), nausea (43 %), neutropenia (42 %), and arthralgia (33 %) emerged as the most common AEs. Any-grade atrial fibrillation and major hemorrhage were seen in 4 % and 2 %, respectively. Ibrutinib/venetoclax was well tolerated with concomitant medications including antihypertensive agents, acid-reducing drugs, antiplatelet agents, and anticoagulants. AEs leading to dose reduction occurred in 21 %; here, 88 % of patients had resolution of these AEs at the time of the analysis. The treatment was discontinued due to AEs in 5 %.

In their conclusions, the researchers noted that the results from the FD cohort are largely consistent with the MRD cohort [6] and support fixed-duration treatment with ibrutinib and venetoclax as an all-oral, once-daily, chemotheraphy-free regimen that drives deep and durable responses.

GLOW study: ibrutinib/venetoclax in the elderly

The randomized, phase III GLOW study was specifically designed to assess the efficacy and safety of ibrutinib/venetoclax compared to chlorambucil/obinutuzumab in older or unfit patients with previously untreated CLL. These were ≥ 65 years of age or < 65 years with a CIRS (Cumulative Illness Rating Scale) score > 6 or creatinine clearance < 70 mL/min. No deletion 17p or known TP53 mutation were present. In the experimental arm, 106 patients received ibrutinib/venetoclax for twelve cycles after a 3-cycle lead-in with ibrutinib. Patients in the control arm (n = 105) were treated with chlorambucil for six cycles plus obinutuzumab in cycles 2-6. The median age of the total patient population was 71 years, with one third in both arms being 75 years of age or older. CIRS scores > 6 were present in 69.8 % and 58.1 % in the experimental and control arms, respectively. Kater et al. reported the primary results of the GLOW study at EHA 2021 [9].

![Figure 1: CAPTIVATE: best overall responses for fixed-duration ibrutinib/venetoclax in patients without deletion 17p and in the total treated population](image)

![Figure 2: Progression-free survival advantage for ibrutinib/venetoclax vs. chlorambucil/obinutuzumab in older and comorbid patients treated in GLOW](image)
PFS by independent review committee (IRC) was defined as the primary endpoint. After a median follow-up of 27.7 months, ibrutinib/venetoclax, as compared to chlorambucil/obinutuzumab, gave rise to a 78 % reduction in the risk of progression and death (median PFS, not reached vs. 21.0 months; HR, 0.216; p < 0.0001; Figure 2). PFS improvement was consistent across the pre-specified subgroups. Ibrutinib/venetoclax induced significantly higher CR/CRi rates (38.7 % vs. 11.4 %; p = 0.0259). With respect to best uMRD rates by flow cytometry, patients treated with the BTK-inhibitor–based regimen fared better. This applied to both bone marrow (51.9 % vs. 17.1 %; p < 0.0001), but also in the peripheral blood (54.7 % vs. 39.0 %; p = 0.0029).

Tripling of uMRD rate in the marrow

Three months after the end of treatment, the uMRD rate was significantly higher for ibrutinib/venetoclax vs. chlorambucil/obinutuzumab, particularly in the bone marrow (51.9 % vs. 17.1 %; p < 0.0001), but also in the peripheral blood (54.7 % vs. 39.0 %; p = 0.0029). With respect to best uMRD rates by flow cytometry, patients treated with the BTK-inhibitor–based regimen fared better. This applied to both bone marrow (67.9 % vs. 22.9 %) and peripheral blood (80.2 % vs. 46.7 %). Also, the marrow/blood uMRD concordance rate was comparatively higher in the experimental arm (92.9 % vs. 43.6 %), and the majority of ibrutinib-treated patients sustained uMRD in the peripheral blood 12 months after treatment cessation (84.5 %), while this was 29.3 % with the comparator regimen. Time to next treatment was substantially prolonged in the experimental arm. Ibrutinib/venetoclax reduced the risk of requiring second-line therapy by 86 % (HR, 0.143).

The tolerability profiles for both regimens were consistent with the observations in the setting of CLL treatment in elderly comorbid patients. Serious AEs that occurred in ≥ 5 % of cases included infections (12.3 % vs. 8.6 %) and atrial fibrillation (6.6 % vs. 0 %). Two patients in the experimental arm (1.9 %) discontinued ibrutinib due to atrial fibrillation. After three cycles of ibrutinib lead-in, less than 2 % of patients remained at risk for TLS based on high tumor burden. Causes of death were generally similar across the arms, with infections and cardiac events being most common. As the authors noted in their conclusions, the results of the GLOW study support the positive clinical profile of all-oral, once-daily, fixed-duration ibrutinib/venetoclax as first-line treatment for older patients with CLL.

CLL14: 4-year update

Patients with previously untreated CLL and coexisting medical conditions (CIRS > 6 and/or creatinine clearance < 70 mL/min) were enrolled in the CLL14 study that compared venetoclax/obinutuzumab with chlorambucil/obinutuzumab for six cycles. After the combination phase, venetoclax and chlorambucil as monotherapies were administered for another six cycles in the experimental and control arms, respectively. Each arm contained 216 patients. The median total CIRS scores were 9 and 8 for venetoclax/obinutuzumab and chlorambucil/obinutuzumab, respectively. Approximately 60 % of patients across the groups had an unmutated IGHV status, and 12 % each showed TP53 deletions and/or mutations. Al-Sawaf et al. reported the 4-year update of the CLL14 study at the EHA 2021 congress [10].

According to this, very low rates of grade ≥ 3 AEs resulted after cessation of treatment in both arms. No long-term or late-onset AEs emerged, which suggests benefits due to lower risk of toxicity and drug-drug interactions based on the fixed-duration approach. Similar proportions of patients developed at least one secondary primary malignancy (14 % vs. 18.9 %). PFS was defined as the primary endpoint of the study. After the prolonged follow-up, median PFS had not been reached with venetoclax/obinutuzumab and was 36.4 months with chlorambucil/obinutuzumab (HR, 0.33; p < 0.0001). Three years after treatment cessation, 74.0 % vs. 35.4 % of patients remained progression-free.

PFS assessment according to TP53 and IGHV status showed substantial benefit from venetoclax treatment in patients with TP53 deletions/mutations and unmutated IGHV, although PFS was still shorter than in those without TP53 deletions/mutations and with mutated IGHV. This demonstrates that patient outcomes can be improved with venetoclax/obinutuzumab in the presence of high-risk features, although these cannot be overcome. Head-to-head comparisons with continuous treatment regimens are called for to elucidate the optimal strategy in these subgroups.

Figure 3: Time to MRD conversion from > 10^{-4} at the end of treatment with venetoclax/obinutuzumab vs. chlorambucil/obinutuzumab
**MRD dynamics favor venetoclax/obinutuzumab**

Time to next treatment had not been reached in either arm at the time of the analysis; at 4 years, the rates were 81.08 % vs. 59.9 % (HR, 0.46; p < 0.0001). Considerably fewer subsequent anti-leukemic therapies were administered in the venetoclax/obinutuzumab-treated group (17 vs. 70). No overall survival difference has been noted to date (4-year OS rates, 85.3 % vs. 83.1 %). CLL-related deaths occurred only in seven patients in the experimental arm, which indicates that the treatment is able to mitigate the disease-inherent risk. MRD was maintained more effectively with venetoclax/obinutuzumab according to longitudinal assessments, although the data are not mature here. Loss of uMRD response occurred after a median of 21 months after discontinuation of treatment with the venetoclax-based therapy, while this was 6 months for chlorambucil/obinutuzumab (Figure 3).

A population-based MRD model was conducted to evaluate growth dynamics in the CLL14 study as this enables description of differential MRD growth trajectories [11]. The findings showed that MRD doubling time was significantly longer with venetoclax/obinutuzumab than with chlorambucil/obinutuzumab (80 vs. 69 days; p < 0.0039), as was time to MRD 10^–2 (1,259 vs. 233 days; p < 2e-16). In addition to other factors such as genetic aberrations, disease burden and risk according to the international prognostic index, the regimens themselves were identified as factors affecting the length of MRD doubling time and time to MRD 10^–2. In their conclusions, the authors noted that MRD eradication is significantly more effective with venetoclax/obinutuzumab than with chlorambucil/obinutuzumab, and MRD regrowth is significantly slower after cessation of the venetoclax-based regimen. This translated into a sustained and significant PFS benefit for patients with MRD doubling time > 76 days vs. those with MRD doubling time < 76 days.

**Impact of genetic markers in CLL14**

Another analysis explored the impact of genetic markers on patient outcomes observed in the CLL14 study [12]. This confirmed the IGHV status as a prognostic marker, as patients with unmutated IGHV experienced shorter PFS in both arms, although the impact was less pronounced with the venetoclax-based treatment (HRs, 2.14 vs. 3.07). Overall, the experimental treatment was superior in patients with both unmutated and mutated IGHV (HRs, 0.25 and 0.36, respectively). The same was true for deletion 17p that adversely affected PFS in both arms (HRs, 3.19 and 3.15, respectively), while venetoclax/obinutuzumab was superior to the chlorambucil-based regimen independent of the presence of 17p deletion.

Chlorambucil-treated patients with deletion 11q experienced shorter PFS compared to those without deletion 11q (HR, 1.84), whereas no difference was observed for those on venetoclax/obinutuzumab therapy. This also applied to BIRC3 mutations. Acquisition of deletion 17p or 11q after therapy occurred more frequently in the control arm, while patients in the experimental arm mainly showed decreasing deletion 17p and 11p fractions.

For TP53 and BIRC3 mutations, the variant allele frequency basically decreased with venetoclax/obinutuzumab over time but remained stable or increased with chlorambucil/obinutuzumab. In the absence of deletion 17p, TP53 major and minor mutations had no impact on PFS. The researchers also performed an analysis of resistance mutations in 113 relapse samples. Here, venetoclax-treated patients showed no acquired mutations in BCL2, BIM, BAX, BCL-XL or MCL1, which indicated that resistance to venetoclax is unlikely to occur in a fixed-duration setting. At the same time, new high-risk mutations such as TP53, BIRC3, SF3B1 and ATM occurred more frequently with chlorambucil.

**ELEVATE-RR: acalabrutinib vs. ibrutinib**

The next-generation, potent, highly selective BTK inhibitor acalabrutinib offers decreased alternative-target activity compared to ibrutinib in vitro, which potentially confers an improved tolerability profile [13, 14]. ELEVATE-RR is the first head-to-head trial to compare acalabrutinib with ibrutinib in patients with previously treated CLL and deletion 17p or deletion 11q. This open-label, phase III study was conducted at 124 centers in 15 countries. Overall, 533 patients were randomized to either acalabrutinib 100 mg twice daily (n = 268) or ibrutinib 420 mg/d (n = 265). Non-inferiority of IRC-assessed PFS constituted the primary outcome. According to the findings presented at EHA 2021, the trial met its primary endpoint, with median PFS of 38.4 months in both arms (HR, 1.00) [15]. IRC-assessed PFS was comparable across prespecified subgroups. A key secondary endpoint related to the incidence of any-grade atrial fibrillation or flutter. Here, acalabrutinib demonstrated significantly improved results with an absolute reduction of 6.6 % in any-grade incidence rates (Table 2). Markedly fewer patients in the experimental arm who had no prior history of atrial fibrillation or flutter experienced new events. No differences were observed for grade ≥ 3 infection (30.8 % vs. 30.0 %) and Richter’s transformation (3.8 % vs. 4.9 %). Median OS had not been reached in either arm; the mortality risk was 18 % lower with acalabrutinib (HR, 0.82).

Compared to ibrutinib, acalabrutinib demonstrated lower rates of grade ≥ 3 atrial fibrillation/flutter with acalabrutinib vs. ibrutinib

<table>
<thead>
<tr>
<th><strong>Table 2: Significant reduction in any-grade atrial fibrillation/flutter with acalabrutinib vs. ibrutinib</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrial fibrillation/flutter (any grade), n (%)</strong></td>
</tr>
<tr>
<td>Events/100 person-months</td>
</tr>
<tr>
<td>Median time to onset, months (range)</td>
</tr>
<tr>
<td>Events leading to treatment discontinuation, n (%)</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter among patients without a history of atrial fibrillation/flutter, n (%)</td>
</tr>
</tbody>
</table>

© Springer-Verlag
AEs (68.8 % vs. 74.9 %), serious AEs (53.8 % vs. 58.6 %) and treatment discontinuation due to AEs (14.7 % vs. 21.3 %). While headache and cough occurred more commonly with acalabrutinib, ibrutinib showed higher rates of diarrhea, arthralgia, and hypertension. Bleeding events occurred in 38.0 % vs. 51.3 % and interstitial lung disease/pneumonitis in 2.6 % vs. 6.5 %. Cumulative incidences of any-grade atrial fibrillation/flutter and hypertension over time were lower for acalabrutinib with HRs of 0.52 and 0.34, respectively. This also applied to bleeding events, diarrhea, and arthralgia (HRs, 0.63, 0.61 and 0.61, respectively). The authors stated in their summary that acalabrutinib is better tolerated and has similar efficacy compared to ibrutinib in patients with previously treated CLL.

Four-year data from ELEVATE-TN

The pivotal phase III ELEVATE-TN study investigated the combination of acalabrutinib and obinutuzumab (A+O; n = 179), as well as acalabrutinib monotherapy (A; n = 179), in treatment-naive patients aged ≥ 65 years or 18-64 years with comorbidities (i.e., creatinine clearance 30-69 mL/min or CIRS-G score > 6). Patients in the control arm (n = 179) received obinutuzumab plus chlorambucil (O+Clb). Early results at a median follow-up of 28.3 months demonstrated superior efficacy of acalabrutinib ± obinutuzumab with an acceptable tolerability profile [16]. At EHA 2021, Sharman et al. reported 4-year update [17]. According to this analysis, the efficacy and safety of the acalabrutinib-based therapy was maintained relative to O+Clb. At a follow-up of 46.9 months, treatment was ongoing in 74.9 % and 69.3 % of patients in the A+O and A arms, respectively, but in none in the O+Clb arm. Median PFS was significantly longer for A+O vs. O+Clb (HR, 0.10; p < 0.0001) and A vs. O+Clb (HR, 0.19; p = 0.0001; Figure 4). Median PFS had not been reached in the acalabrutinib arm and was 27.8 months for obinutuzumab/chlorambucil. The PFS rates at 48 months amounted to 87 %, 78 % and 25 %, respectively; here, the analysis revealed a trend in favor of A+O over A.

The PFS findings were consistent across high-risk genetic subgroups. Patients with deletion 17p/TP53 mutation showed 48-month PFS rates of 76 % (HR, 0.17 vs. O+Clb; p = 0.0001), 75 % (HR, 0.18 vs. O+Clb; p < 0.0001), and 18 %, respectively. In the group with unmutated IGHV, this was 86 % (HR, 0.06 vs. O+Clb; p < 0.0001), and 18 %, respectively. For OS, the findings yielded a trend in favor of A+O as compared to O+Clb (HR, 0.10; p < 0.0001). In the A+O arm, 93 % of patients were alive at 48 months, while this applied to 88 % in the other groups.

The safety of both acalabrutinib-based regimens was consistent with the interim findings, including low incidences of cardiovascular events such as atrial fibrillation and hypertension, and low rates of treatment discontinuation despite longer treatment exposure. Grade ≥ 3 infections occurred more frequently with A+O than with A monotherapy (23.6 % and 16.2 %, respectively). According to the authors, acalabrutinib with or without obinutuzumab demonstrated durable disease control, tolerability, and flexibility to tailor treatment as monotherapy or combination therapy in treatment-naive CLL patients.

CLL2-BAAG: bendamustine, VenG & acalabrutinib

In the CLL2-BAAG trial, bendamustine followed by obinutuzumab and venetoclax induced ORR and uMRD rates of 95 % and 87 %, respectively [18]. As a relevant proportion of patients retained residual lymphadenopathy and only achieved partial remission, it was decided to add a BTK inhibitor in the next phase II study. At EHA 2021, Cramer et al. reported results from the ongoing CLL2-BAAG trial that is evaluating bendamustine followed by obinutuzumab, acalabrutinib and venetoclax [19].

Debulking with two cycles of bendamustine is recommended for patients with high tumor burden prior to induction that contains obinutuzumab monotherapy in the first cycle and obinutuzumab plus acalabrutinib in cycles 2-6. Venetoclax is administered at the full dose in cycles 4-6 after the ramp-up in cycle 3. The uMRD rate at the end of the six induction cycles constitutes the primary endpoint of the CLL2-BAAG trial. Maintenance is open to responders and includes daily acalabrutinib and venetoclax plus 3-monthly obinutuzumab for a maximum of eight cycles. Forty-five patients with relapsed/refractory CLL were enrolled. Among these, 32 % had 17p deletion/TP53 mutation, and in 30 %, a complex karyotype was
present. Forty-seven percent had already received targeted agents, such as ibrutinib, venetoclax, or both.

**uMRD rate of 76 %**

All patients responded to treatment. At the end of the induction phase, the CR/CRi rate was 18 %, and partial remission had been obtained in 82 % (Table 3). An uMRD rate of 76 % was found in the peripheral blood. This fell slightly short of the study assumption based on the 83 % uMRD rate observed in the relapsed/refractory population of the CLL2-BAAG trial [18]. Therefore, the primary endpoint of CLL2-BAAG was not met. Nevertheless, considering the adverse genetic setup in one third of the population and pretreatment with targeted agents in half of the cases, the authors deemed this outcome impressive. Moreover, a redistribution phenomenon caused by the BTK inhibitor might be responsible for the lower rate, and improvement with continued follow-up can be expected.

Until data cutoff, maintenance treatment had been started in 32 patients (71 %). Twelve of these have discontinued, among them 9 (28 %) who stopped treatment due to uMRD. The regimen of bendamustine followed by obinutuzumab, acalabrutinib and venetoclax did not give rise to cumulative or unexpected toxicity. Overall, these findings are in accordance with other phase II trials investigating the triple combination. Phase III studies are ongoing.

**Promising results for pirtobrutinib**

The highly potent and selective non-covalent BTK inhibitor pirtobrutinib (LOXO-305) is being investigated in patients with previously treated advanced B-cell malignancies in the phase I/II BRUIN study. Roeker et al. presented the results from the CLL/SLL cohort at EHA 2021 [20]. The safety and efficacy populations included 170 and 139 patients, respectively. They had previously been treated with all classes of available therapies including anti-CD20 antibodies, BTK inhibitors, chemotherapy, BCL2 inhibitors and PI3K inhibitors. The median number of prior lines of therapy was 3.

**REFERENCES**

1 Tam CS et al., Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. Blood 2019; 134(1): 851-859
2 Hillmen P et al., First interim analysis of ALPINE study: results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. EHA 2021, LB1900
4 Xu W et al., Zanubrutinib monotherapy in patients with relapsed or refractory chronic lymphocytic leukemia: 34-month follow-up results. EHA 2021, EP639
6 Wierda WG et al., Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma: 1-year disease-free survival results from the MRD cohort of the phase 2 CAPTIVATE study. ASH 2020, 123
7 Allan JN et al., Primary analysis of the fixed-duration cohort from the phase 2 CAPTIVATE study of first-line ibrutinib + venetoclax for chronic lymphocytic leukemia/small lymphocytic lymphoma. EHA 2021, S147
9 Kater AP et al., Fixed-durUeron ibrutinib plus venetoclax versus chlorambucil plus obinutuzumab for first-line treatment of chronic lymphocytic leukemia: primary analysis of the phase 3 GLOW study. EHA 2021, LB1902
10 Al-Sawaf O et al., Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 4-year follow-up analysis of the randomised CLL14 study. EHA 2021, S146
11 Al-Sawaf O et al., Venetoclax-obinutuzumab modulates clonal growth: results of a population-based minimal residual disease model from the randomized CLL14 study. JCI Clin Investig 2021, 101
12 Tausch E et al., Genetic markers and outcome with front-line obinutuzumab plus either chlorambucil or venetoclax – updated analysis of the CLL14 trial. EHA 2021, S144
15 Hillmen P et al., First results of a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia. EHA 2021, S145
17 Sharman JP et al., Acalabrutinib ± obinutuzumab vs obinutuzumab + chlorambucil in treatment-naive chronic lymphocytic leukemia: ELEVATE-TN 4-year follow-up. EHA 2021, S148
18 Cramer P et al., Bendamustine followed by obinutuzumab and venetoclax in chronic lymphocytic leukemia (CLL2-BAG): primary endpoint analysis of a multicentre, open-label, phase 2 trial. Lancet Oncol 2018; 19(9): 1215-1228
19 Cramer P et al., CLL2-BAAG, a prospective, open-label, multicenter phase II trial to evaluate the efficacy and safety of a sequential regimen of bendamustine followed by obinutuzumab, acalabrutinib and venetoclax in patients with relapsed/refractory CLL. JCI Clin Investig 2021, 101
20 Roeker L et al., Pirtobrutinib (LOXO-305), a next generation, highly selective, non-covalent BTK inhibitor in previously treated CLL/SLL: results from the phase 1/2 BRUIN study. EHA 2021, EP033

---

**TABLE 3**

<table>
<thead>
<tr>
<th>Responses, n (%)</th>
<th>CLL2-BAAG (all patients; n = 45)</th>
<th>CLL2-BAAG (relapsed/refractory patients; n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response/complete response with incomplete bone marrow recovery</td>
<td>8 (18)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Partial response</td>
<td>37 (82)</td>
<td>22 (83)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>-</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>45 (100)</td>
<td>26 (90)</td>
</tr>
</tbody>
</table>

**MRD in the peripheral blood, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>CLL2-BAAG (all patients; n = 45)</th>
<th>CLL2-BAAG (relapsed/refractory patients; n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable (&lt; 10^{-4})</td>
<td>34 (76)</td>
<td>24 (83)</td>
</tr>
<tr>
<td>Intermediate (≥ 10^{-3} and &lt; 10^{-2})</td>
<td>8 (18)</td>
<td>-</td>
</tr>
<tr>
<td>Positive (≥ 10^{-2})</td>
<td>2 (4)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (2)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

© Springer-Verlag
In terms of pharmacokinetics, plasma exposures were shown to be dose-dependent and linear. A daily dose of 200 mg was selected as the recommended phase II dose. Responses were observed across all dose levels and irrespective of BTK C481 mutation status, the reason for prior BTK inhibitor discontinuation (i.e., progression vs. intolerance), or other classes of prior therapies including covalent BTK inhibitors, BCL2 inhibitors, and PI3Kδ inhibitors. The evaluable CLL/SLL population (n = 139) achieved an ORR of 63 %. In the BTK-pretreated cohort (n = 121), this was 62 %. ORR increased over time. At ≥ 10 months since the start of treatment, the rate had risen to 86 %. Only five responders discontinued treatment, which was due to disease progression in four cases and the decision to perform transplantation in one patient who was in partial remission.

The researchers demonstrated that notable covalent BTK-inhibitor-associated toxicities were only rarely observed, which was consistent with the design of pirtobrutinib as a highly selective and non-covalent BTK inhibitor. Longer follow-up is needed to better understand the safety profile of the agent in the setting of chronic administration. Overall, pirtobrutinib appeared well tolerated and exhibited promising efficacy in heavily pretreated CLL/SLL patients.

## Waldenström’s macroglobulinemia: outcome optimization via combinations

### Final analysis of iNNOVATE

Ibrutinib is the only once-daily BTK inhibitor approved as a single agent or in combination with rituximab for patients with Waldenström’s macroglobulinemia (WM) across all lines of therapy. In the international, double-blind, randomized, phase III iNNOVATE trial, ibrutinib plus rituximab was tested against placebo plus rituximab in patients with rituximab-sensitive WM. Each arm contained 75 individuals. Crossover to single-agent ibrutinib was allowed in the control arm after disease progression. The primary analysis after a median follow-up of 26.5 months yielded improved progression-free survival (PFS) in the experimental arm [1]. At 33.4 months, the combination continued to show superiority regardless of the genomic subtype [2]. Infusion-related reactions and immunoglobulin M flares occurred less frequently with ibrutinib/rituximab than with placebo/rituximab.

The final analysis of the iNNOVATE study for the randomized arms was presented at EHA 2021 after an overall follow-up of 63 months [3]. Here, ibrutinib/rituximab demonstrated ongoing superiority over placebo/rituximab across clinical outcomes. PFS in the ITT population had not been reached in the experimental arm and was 20.3 months in the control arm (HR, 0.250; p < 0.0001). At 54 months, 68 % vs. 25 % of patients were progression-free. The PFS benefit was independent of the genotype, i.e., the presence of MYD88 and/or CXCR4 mutations. Moreover, previously treated and untreated patients derived similar PFS benefits from ibrutinib/rituximab. In contrast, in the control arm, the previously untreated group had better results than the treated group, with both of them showing inferior outcomes compared to the patients in the experimental arm. Ibrutinib/rituximab significantly improved PFS across all prespecified subgroups within the previously treated population and within most of the subgroups in the previously untreated population.

### Sustained improvements

Major responses (i.e., complete, very good partial and partial remissions) deepened and were sustained over time in the experimental arm, with superior results compared to rituximab alone (Figure). The combination induced higher responses irrespective of the genotype or prior treatment status. IgM levels decreased rapidly during the first year and continued to decrease in patients treated with ibrutinib/rituximab, whereas IgM levels in the control arm tended to fluctuate over time and were generally higher. The maximum changes across the two arms amounted to -33.5 g/L vs. -26.9 g/L. Similarly, a significantly greater proportion of patients receiving ibrutinib/rituximab had sustained improvement in hemoglobin levels (77 % vs. 43 %; p < 0.0001). Among those with baseline levels ≤ 110 g/L, 95 % vs. 56 % experienced persistent improvement (p < 0.0001). Median overall survival had not been reached in either arm, with 54-month OS rates of 86 % vs. 84 % (HR, 0.81).

The combination maintained a manageable safety profile. No new safety signals occurred with long-term ibrutinib treatment for over five years. The prevalence of grade ≥ 3 adverse events (AEs) of clinical interest, such as infections, neutropenia, atrial fibrillation and hypertension, generally decreased over time. Eighty-eight percent of AEs that happened, which was consistent with the design of pirtobrutinib as a highly selective and non-covalent BTK inhibitor. Longer follow-up is needed to better understand the safety profile of the agent in the setting of chronic administration. Overall, pirtobrutinib appeared well tolerated and exhibited promising efficacy in heavily pretreated CLL/SLL patients.

### Mavrorixafor/ibrutinib in MYD88/CXCR4 co-mutation

The presence of the CXCR4mut mutation, which is found in 30–40 % of patients with WM, is associated with higher disease burden and reduced re-
sponse to BTK inhibitors, as manifested by delayed response, inferior depth of response, and/or shorter PFS [4–6]. Inhibition of CXCR4 has been demonstrated to sensitize CXCR4Wt/WT, expressing cells to ibrutinib [7, 8], thus providing a rationale for combination therapy. The oral small-molecule CXCR4 antagonist mavorixafor inhibits CXCL12 binding as well as extracellular signal-regulated kinase and protein kinase B (AKT) hyperactivation for many CXCR4 mutations in vitro [9]. Mavorixafor was well tolerated and active in combination with standard-of-care treatment in clinical studies for other solid malignancies [10, 11].

An ongoing, phase Ib, open-label, multicenter, single-arm study is assessing intra-patient dose escalation, safety, pharmacokinetics and pharmacodynamics of mavorixafor plus ibrutinib in patients with both MYD88L265P and CXCR4 mutations after 0–3 prior therapies. Three cohorts (A–C) are initiated on mavorixafor 200 mg and ibrutinib 420 mg daily. In the absence of dose-limiting toxicities (DLTs), mavorixafor is escalated to 400 mg after 28 days and then again to 600 mg if 400 mg is deemed tolerable (< 2/6 DLTs). The cohorts differ with respect to the steps taken if DLTs occur (i.e., withdrawal of the patient, de-escalation). Treon et al. reported preliminary clinical data for eight patients included in Cohorts A and B at EHA 2021 [12].

Rapid and clinically relevant benefits

At the time of the analysis, all patients had completed the low- and mid-dose levels. Mavorixafor and ibrutinib exposures were shown to be consistent with previous single-agent studies, which suggests no drug-drug interactions. Mavorixafor exposures tracked with increases in key white blood counts in all patients. The combination was well tolerated, with 77 % of AEs rated as grade 1. AEs related to use of mavorixafor only occurred in two patients; these were grade 1 or 2 and included nausea, acid reflux, constipation, elevated white blood cell count, and worsening pain/numbness in the shoulder/hands/wrists.

All patients experienced reductions in IgM levels, and none progressed while on treatment. Median absolute serum IgM levels decreased from pre-treatment levels of 23.56 g/L to 9.93 g/L at 6 months. At the same time, patients with decreased baseline hemoglobin levels showed increases toward normal. In those on treatment for six cycles, median hemoglobin increased by > 20 g/L. The authors noted in their conclusions that further follow-up will help define the potential of mavorixafor plus ibrutinib to improve clinical response to BTK inhibition in patients with MYD88 and CXCR4 mutations.

**REFERENCES**

2 Buske C et al., Ibrutinib treatment in Waldenström’s macroglobulinemia: follow-up efficacy and safety from the INNOMATE study. Blood 2018; 132(suppl 1): 149
3 García-Sanz R et al., Ibrutinib monotherapy in symptomatic, previously treatment-naïve patients with Waldenström macroglobulinemia. J Clin Oncol 2018; 36(2): 2755-2761
4 Teun SP et al., Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenström macroglobulinemia. Blood 2014; 123(18): 2791-2796
6 Teun SP et al., Ibrutinib monotherapy in symptomatic, treatment-naïve patients with Waldenström macroglobulinemia. J Clin Oncol 2018; 36(2): 2755-2761
8 Cao Y et al., The WHIM-like CXCR4(S338X) somatic mutation activates AKT and ERK and promotes resistance to ibrutinib and other agents used in the treatment of Waldenström's macroglobulinemia. Leukemia 2015; 29(1): 169-176
9 X4 Pharmaceuticals. Data on File
12 Treon SP et al., Preliminary clinical data from a phase 1b study of mavorixafor and ibrutinib in patients with Waldenström’s macroglobulinemia with MYD88 and CXCR4 mutations. EHA 2021, EP784
Successful inhibition of PI3K, BTK, BCL2 and other targets in various B-cell malignancies

CHRONOS-3: copanlisib plus rituximab

Rituximab monotherapy is a recognized standard of care in patients with relapsed indolent non-Hodgkin lymphoma (iNHL) who have had long remissions after rituximab-based therapy or who are unwilling or unfit to be treated with chemotherapy. However, the clinical benefit conferred by rituximab can be limited due to drug resistance. Based on the assumption that a combined strategy might improve patient outcomes, the phase III CHRONOS-3 trial investigated the combination of rituximab with the selective, potent, pan-class I PI3K inhibitor copanlisib that shows predominant on-target activity against the PI3K-α and PI3K-δ isoforms [1, 2].

CHRONOS-3 recruited patients with relapsed CD20-positive indolent B-cell lymphoma including follicular lymphoma (FL) grades 1-3a, marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), and Waldenström’s macroglobulinemia (WM). Their disease had relapsed following regimens containing rituximab or anti-CD20 antibodies. Eligible patients had to be progression- and treatment-free for ≥ 12 months since the last rituximab-containing regimen or for ≥ 6 months and unwilling or unfit to receive chemotherapy. The study treatment consisted of copanlisib 60 mg i.v. on days 1, 8 and 15 of a 28-day cycle plus rituximab (n = 307), or placebo plus rituximab (n = 151). Median time since the last systemic therapy was 25.1 months in both arms; approximately half of patients had received ≥ 2 prior lines of anti-cancer treatment. Progression-free survival (PFS) by central review was defined as the primary endpoint. The primary analysis of the study was reported at EHA 2021 by Zinzani et al. [3].

Benefits across all subtypes

CHRONOS-3 met its primary endpoint. Compared to rituximab alone, copanlisib/rituximab induced a 48 % reduction in the risk of progression or death, with a median PFS of 21.5 vs. 13.8 months (HR, 0.52; p < 0.0001). PFS benefits were observed across all iNHL subtypes and in all pre-specified subgroups pertaining to patient and disease characteristics. In the total study population, objective responses occurred in 81 % vs. 48 % (p < 0.0001; Figure 1). Complete responses (CRs) resulted in 34 % vs. 15 %. Objective response rates (ORRs) and CR rates were improved in the experimental arm compared to the control arm across all histologic subtypes. Reductions in target lesion size were observed in 98 % of evaluable patients with copanlisib/rituximab and in 86 % with placebo/rituximab. The trend towards greater tumor shrinkage in the experimental arm was consistent across histologic subtypes.

Patient-reported outcomes constituted a secondary endpoint. These were reported as the time to deterioration or improvement in ≥ 3 points in patient-reported disease-related physical symptoms according to the FLymSI-18 questionnaire. Here, the analysis revealed no significant differences across the two treatment arms regarding time to deterioration (5.5 months each; HR, 1.060; p = 0.69) and time to improvement (not estimable in either arm; HR, 0.996; p = 0.51).

Copanlisib plus rituximab demonstrated a manageable safety profile that was consistent with previous reports of both agents as monotherapies. Hyperglycemia was the most frequently reported treatment-emergent adverse event (AE) in both arms (69.4 % vs. 23.3 %), followed by hypertension.
Zandelisib plus zanubrutinib

Dual inhibition of the PI3Kδ and BTK pathways is considered capable of overcoming monotherapy resistance, although tolerability can be an issue. Therefore, a multicohort phase 1b study explored the combination of the PI3K inhibitor zandelisib, which offers an innovative dose schedule based on optimized pharmaceutical properties, and the BTK inhibitor zanubrutinib to improve tolerability of the dual targeted approach and to provide deeper and longer responses.

Patients after failure of ≥ 1 prior therapy for B-cell malignancies were treated until progression with one of two dose schedules. Group A received zandelisib 60 mg/d for 8 weeks followed by days 1–7 of each subsequent 28-day cycle, plus zanubrutinib 160 mg twice daily (n = 7). In Group B, zandelisib 60 mg was taken daily on days 1–7 of each 28-day cycle starting in cycle 1 in addition to zanubrutinib 80 mg twice daily (n = 13). At EHA 2021, Soumerai et al. reported on 20 patients in the completed safety dose-finding cohort [4].

Disease-specific expansion cohorts were created (FL, CLL/SLL, MZL, mantle cell lymphoma [MCL], diffuse large B-cell lymphoma [DLBCL]/high-grade B-cell lymphoma [HGBCL]) that received the Group B dose schedule. Across these cohorts, 18 individuals were evaluable. All of them responded to zandelisib 60 mg on an intermittent schedule from cycle 1 plus zanubrutinib 80 mg twice daily except for two patients with DLBCL/HGBCL (Figure 2). Complete remissions with and without incomplete bone marrow recovery occurred in 25 % and 40 % of FL and CLL patients, respectively. The combination was generally well tolerated and did not result in additive toxicity compared to each agent alone. Neutropenia, thrombocytopenia, transaminase elevations, diarrhea, rash, hyperkalemia and fatigue represented the most common AEs. Patients are currently enrolled in expansion cohorts for FL and MCL with the regimen identified in Group B.

Another zandelisib-based combination is currently being tested in the setting of relapsed iNHL by the randomized, open-label, controlled, multicenter phase III COASTAL study [5]. Here, patients with FL or MZL after ≥ 1 prior line of therapy are receiving either zandelisib plus rituximab or standard immunochemotherapy. Pretreatment must include an anti-CD20 antibody in combination with chemotherapy or lenalidomide. Zandelisib is limited by AEs [6, 7]. The next-generation BTK inhibitor zanubrutinib, which has been optimized for BTK selectivity and occupancy, has shown increased tolerability compared to ibritinib in patients with WM treated in the ASPEN trial [8]. Lower rates of AEs leading to death (1 % vs. 4.1 %), discontinuation (4 % vs. 9.2 %), dose reductions (13.9 % vs. 23.5 %) and dose holds (46.5 % vs. 56.1 %) were observed, as well as a lower rate of atrial fibrillation or flutter (2 % vs. 15.3 %).

The multicenter, single-arm, open-label phase II BGB-3111-215 study investigated the safety and efficacy of zanubrutinib in patients with pretreated B-cell malignancies who were intolerant to ibritinib and/or acalabrutinib, compared with their ibritinib and/or acalabrutinib intolerance as assessed by the recurrence and change in severity of AEs. Patients with previously treated CLL/SLL, WM, MCL, or MZL were divided in those intolerant to ibritinib (Cohort 1) and those intolerant to acalabrutinib alone or to both agents (Cohort 2). They were treated with zanubrutinib 160 mg twice daily or 320 mg per day.

The analysis reported at EHA 2021 related to 57 and 7 patients included in Cohort 1 and 2, respectively [9]. Most of them had received prior ibritinib...
monotherapy. The median time on the most recent prior BTK inhibitor was 9.2 months in the total cohort. Overall, 75 % of ibrutinib and acalabrutinib intolerance events did not recur on zanubrutinib. Among the intolerance events that recurred, 90 % and 33 % of ibrutinib and acalabrutinib intolerance events, respectively, occurred at a lower severity, while 10 % and 67 %, respectively, occurred at the same severity. No intolerance events occurred at a higher grade.

Zanubrutinib itself proved effective, with ORR and disease control rates of 50.0 % and 89.6 %, respectively, in the total population. At data cutoff, 87.7 % and 100 % of patients in Cohorts 1 and 2, respectively, remained on treatment. AEs were the reason for zanubrutinib treatment discontinuation in three cases; none of these were due to recurrence of a prior intolerance event. The authors emphasized that zanubrutinib might provide a therapeutic option in patients intolerant to other BTK inhibitors across hematologic malignancies.

**Broad efficacy of pirtobrutinib**

Non-covalent BTK inhibition might offer advantages over covalent inhibitors that have been demonstrated to elicit limited OS benefits in patients with MCL and other lymphomas [10, 11]. The highly potent and selective non-covalent BTK inhibitor pirtobrutinib (LOXO-305) is being assessed in the phase I/II BRUIN trial in patients with previously treated advanced B-cell malignancies who have received all classes of available therapy.

According to the analysis presented at EHA 2021, pirtobrutinib showed promising efficacy with responses across all dose levels and clinical activity independent of prior therapy [12]. MCL patients (n = 56) demonstrated a 52 % ORR, with CRs emerging in 25 %, which also applied to BTK-pretreated MCL patients (n = 52; Table). Those with other NHLs showed response rates ranging from 22 % (MZL) to 75 % (Richter’s transformation; Table). After a median follow-up of 6 months for the efficacy-evaluable population, 83 % of responding MCL patients were ongoing and in response. Given the poor outcomes with existing options for the treatment of MCL, these results are particularly notable. Also, 77 % and 83 % of responders in the groups with WM and Richter’s transformation were ongoing and in response. The favorable safety and tolerability were consistent with the design of pirtobrutinib as a highly selective and non-covalent BTK inhibitor. No dose-limiting toxicities occurred, and the maximum tolerated dose was not reached. Pirtobrutinib 200 mg/d was selected as the recommended phase II dose. Only 1.5 % of patients discontinued treatment due to treatment-related AEs. Notable covalent BTK-inhibitor-associated toxicities were rarely observed. The authors concluded that pirtobrutinib is well tolerated and exhibits promising efficacy in heavily pretreated patients with MCL and other NHLs. Longer follow-up is required to better understand the safety profile associated with chronic administration.

**TG-1701 ± U2**

An emerging BTK inhibitor with favorable characteristics is the covalently bound agent TG-1701 that has shown superior selectivity compared to ibrutinib [13]. Data have indicated increased inhibition of TG-1701 in combination with the PI3Kδ inhibitor umbralisib and the anti-CD20 antibody ublituximab (U2) in a BTK-resistant cell model [14]. A phase I/II dose escalation trial presented at ASCO 2021 evaluated TG-1701 as monotherapy and combined with U2 in dose escalation cohorts and disease-specific cohorts [15]. The patients included had relapsed/refractory disease to prior standard therapy; in addition, the disease-specific cohorts enrolled treatment-naive patients who were unsuitable for standard front-line chemoimmunotherapy. TG-1701 doses were escalated across a range of 100-400 mg/d as monotherapy and 100-300 mg/d as part of the combination regimen.

TG-1701 exhibited an encouraging safety profile with clinical and pharmacodynamic activity at all dose levels that supported once-daily dosing. The maximum tolerated dose was not achieved in the monotherapy arm. Respiratory tract infections, constipation, bruising, neutropenia and ALT elevations were seen most frequently, with the majority of AEs rated as grade 1/2. Patients on the triplet regimen developed most commonly diarrhea, infusion-related reactions, and bruising (47 % each) among grade 3 laboratory AEs, ALT and AST prevailed (16 % each). Dose escalation continues.

Single-agent TG-1701 100–400 mg gave rise to an ORR of 57 % across a range of histologic subtypes including CLL, SLL, MCL, FL, MZL, and WM, while patients with DLBCL did not respond. In the disease-specific cohorts, the ORRs with TG-1701 monotherapy at a dose of 200 mg were 95 %, 65 % and 95 % for CLL, MCL, and WM, respectively. All patients treated in the CLL cohort with TG-1701 300 mg achieved objective responses. For the triplet combination, the ORR was 79 %, with a
CR rate of 21%, across all subtypes (Figure 3). After a median follow-up of 15.6 months, most patients remained on treatment. The study continues enrollment, and future registration trials are being planned.

**Atezolizumab-based triple combination**

Combining targeted therapies with agents that enhance anti-tumor immunity represents an attractive treatment paradigm. A multicenter phase II trial evaluated the PD-L1 inhibitor atezolizumab in combination with the anti-CD20 antibody obinutuzumab and the BCL2 inhibitor venetoclax in patients with relapsed/refractory FL and MZL who had failed ≥ 1 line of therapy. Induction included eight 3-weekly cycles of obinutuzumab. Venetoclax was started on day 8 of cycle 1 and was administered until the end of maintenance or until progression. Atezolizumab was given on day 2 of each cycle. ORR at the end of induction after eight cycles of the three drugs or at premature treatment discontinuation constituted the primary endpoint.

Herbaux et al. presented the results for the FL and MZL cohorts at EHA 2021 [16]. The FL cohort comprised 58 patients, 85.7% of whom had Ann Arbor stage III/IV disease. High risk according to the Follicular Lymphoma International Prognostic Index was present in 47.3%. One third of patients had been treated with > 2 lines of previous therapy, and 30.4% had undergone autologous stem cell transplantation. In this group, 63% of patients received the full induction treatment. The ORR according to PET scan at the end of induction was 53.6%, with complete molecular remissions in 30.4%.

In the MZL cohort, 20 patients were enrolled. Thirteen, five and two had nodular, extra-nodular and splenic MZL, respectively. All of them were in Ann Arbor stage IV, 38.9% showed bone marrow infiltration, and 50% had ≥ 2 extra-nodal sites. In 22.2%, > 2 prior lines of treatment had been administered. Eleven patients (55%) received the full induction treatment. According to CT assessment at the end of induction, 66.76% of patients demonstrated objective responses, which included complete and partial remissions in 16.7% and 50.0%, respectively. At the time of the analysis, responses in the two cohorts appeared to be durable, with only 21.4% of responders experiencing relapses or progression.

In 70.5% of the total study cohort, grade 3/4 AEs occurred, and one patient experienced an AE that led to discontinuation of treatment. Grade 3/4 AEs were mainly cytopenias, with only one case of febrile neutropenia (1.3%). Three patients developed immune-related AEs classified as grade 2 or 3. No tumor lysis syndrome occurred. Overall, the combination appeared to be well tolerated, with no unexpected toxicity. The authors concluded that the ORR results were comparable to the findings seen for other innovative regimens in this setting.

**Novel BCL2 inhibitor BGB-11417**

Cheah et al. provided the initial clinical report of the first-in-human trial investigating the potent and highly selective BCL2 inhibitor BGB-11417 at EHA 2021 [17]. In vitro evaluation has shown that BGB-11416 is > 10-fold more potent than venetoclax at inhibiting BCL2 (IC50, 0.014 vs. 0.20 nM) [18]. Moreover, the potency of BGB-11417 for inhibiting the BCL2-G101V mutant protein, which can induce resistance to venetoclax on continued treatment, was > 50-fold higher than that of venetoclax. BGB-11417 demonstrated ≥ 2,000-fold selectivity for BCL2 compared to BCL-xL, BCL-W, MCL-1, and BCL2A1 in vitro, which illustrates its selectivity. Various xenograft models including acute lymphoblastic leukemia, MCL and DLBCL revealed superior anti-tumor activity of BGB-11417 vs. venetoclax. The novel BCL2 inhibitor exhibits a favorable pharmacokinetic profile with low plasma clearance and an encouraging safety profile [19].

The first-in-human phase 1/Ib study is being conducted in patients with relapsed and refractory B-cell malignancies including NHL (i.e., FL, DLBCL, MZL, transformed NHL), CLL/SLL, MCL, and WM. Dose escalation (Part 1) is performed in independent cohorts categorized by disease type. These cohorts will continue until a recommended phase II dose is identified, which is then used in corresponding expansion cohorts (Part 2). The study will also include dose escalation and expansion cohorts for the combination of BGB-11417 and the BTK inhibitor zanubrutinib in patients with CLL/SLL and mantle cell lymphoma.

At the time of the first analysis, seven patients with relapsed/refractory NHL were treated in Cohort 1A, and two patients with relapsed/refractory CLL were treated in Cohort 1B. According to the results, BGB-11417 is tolerable at the dose levels tested, with no dose-limiting toxicities observed across two dose levels. Grade ≥ 3 AEs were infrequent and manageable. Two patients experienced neutropenia, and only one instance of laboratory TLS was recorded in a patient with high TLS risk. Preliminary activity will be assessed with increased enrollment and follow-up. Although enrollment of patients with relapsed/refractory CLL has only recently started, decreases in absolute lymphocyte counts were already seen at the initial ramp-up dose of 1 mg.
Anti-CD19-based approach: ongoing study

The anti-CD19 antibody tafasitamab has been licensed by the US FDA for use in the indication of relapsed/refractory DLBCL. In patients with relapsed/re-
fractory FL or MZL, tafasitamab plus lenalidomide/rituximab is being evalu-
ated versus lenalidomide/rituximab alone in the randomized, double-blind, placebo-controlled, phase III immIND study [20]. PFS in the FL cohort has been defined as the primary endpoint of the trial. At present, recruitment is on-
going in centers across Europe, Asia Pa-
cific and North America. The planned enrollment comprises 528 patients with relapsed/refractory FL and 60–90 pa-
tients with relapsed/refractory MZL.

REFERENCES

1 Liu N et al., BAY 80-6946 is a highly selective intravenous PI3K inhibitor with potent p110δ and p110α activities in tumor cell lines and xenograft models. Mol Cancer Ther 2013; 12(11): 2319-2330
2 Morschhauser F et al., On-Target Pharmacodynamic Activity of the PI3K Inhibitor Copanlisib in Paired Biopsies from Patients with Malignant Lymphoma and Advanced Solid Tumors. Mol Cancer Ther 2020; 19(2): 468-478
3 Zinzani P et al., CHRONOS-3: randomized phase III study of copanlisib plus rituximab vs rituximab/placebo in relapsed indolent non-Hodgkin lymphoma. EHA 2021; S211
4 Soumerai JD et al., Combination of PI3Kδ inhibitor zandelisib with rituximab versus immunotherapy in patients with relapsed indolent non-Hodgkin lymphoma. EHA 2021, S214
5 Jurczak W et al., COSITAL: A phase 3 study of the PI3Kδ inhibitor zandelisib with rituximab versus immunotherapy in patients with relapsed indolent non-Hodgkin’s lymphoma. EHA 2021, PB1569
6 Mato AR et al., Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. Haematologica 2018; 103(5): 874-879
7 Yacoby MS et al., Toxicities and outcomes of acalabrutinib-treated patients with chronic lym-
phocytic leukemia: a retrospective analysis of real world patients. Blood 2019; 134(Suppl 1, abstr 4311)
8 Dimopoulos MA et al., ASPIEN: results of a phase 3 randomized trial of lenalidomide versus ibrutinib for patients with Waldenström macroglobulinemia. EHA 2020; S225
9 Shadman M et al., Preliminary results of a phase 2 study of zandelisib in patients with previously treated B cell malignancies intolerant to ibrutinib/acalabrutinib. EHA 2021, EP642
10 Cheah CY et al., Patients with mantle cell lymphoma failing ibrutinib are unlikely to respond to salvage chemotherapy and have poor outcomes. Ann Oncol 2015; 26(8): 1175-1179
12 Shah NN et al., Pirtobrutinib (LOXO-305), a next generation highly selective non-covalent Bruton’s tyrosine kinase inhibitor in previously treated mantle cell lymphoma and other non-Hodgkin lymphomas: results from the phase 1/2 BRUINJ study. EHA 2021, EP503
13 Normant E et al., TG-1710 a novel, orally available, and covalently-bound BTK inhibitor. EHA 2018, PF628
14 Ribeiro M et al., TG-1701, a novel irreversible Bruton’s kinase inhibitor, cooperates with ublitux-
imab-driven ADCC and ADCP in in vitro and in vivo models of ibrutinib-resistant mantle cell lymphoma. AACR 2020, 2205
15 Cheah CY et al., Updated results of the sele-
ctive Bruton tyrosine kinase inhibitor TG-1701, as monotherapy and in combination with ublituxi-
mab and umbralisib in patients with B-cell malignan-
cies. J Clin Oncol 39, 2021 (suppl 15; abstr 7529)
16 Herbaux C et al., Atezolizumab + obinutu-
zumab + venetoclax in patients with relapsed or refractory indolent non-Hodgkin’s lymphoma: pri-
mary analysis of a phase 2 trial from LYSA. EHA 2021, S212
17 Cheah CY et al., Preliminary safety data from patients with relapsed/refractory B-cell malignan-
cies treated with the novel B-cell lymphoma in-
hibitor BGB-11417. EHA 2021, EP525
18 Hu N et al., Preclinical characterization of BGB-11417, a potent and selective Bcl-2 inhibi-
tor with superior antitumor activities in haemato-
logical tumor models. AACC 2020, abstract 3077
19 Data on file
20 Scholz C et al., Phase 3 study of tafasitamab + lenalidomide and rituximab vs placebo + lena-
lidomide and rituximab in patients with relapsed/refractory follicular lymphoma or marginal zone lymphomas. immIND. EHA 2021, PB1572

Extending anti-PD-1–based options in the setting of Hodgkin lymphoma

Patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed high-dose chemotherapy and autologous stem cell transplantation (HDT/ASCT) have poor prognosis, which also applies to those with chemother-

ty-resistant disease who are ineligible for HDT/ASCT [1-4]. The presence of chromosome 9p24.1 alterations in cHL provides a rationale for immune checkpoint inhibition as this leads to overexpression of the PD-L1 ligands [5-7]. Anti-PD-1 antibodies including nivolumab, pembrolizumab, tisleli-
zumab, camrelizumab and sintilimab have changed the treatment paradigm of adults with relapsed/refractory cHL [8-14]. Data presented at ASCO, EHA and ICML 2021 demonstrated efficacy of new agents and established PD-1 in-
hibitors over extended periods of time.

CheckMate 205

The pivotal, multicenter, single-arm, phase II CheckMate 205 trial evaluated the PD-1 inhibitor nivolumab at a dose of 3 mg/kg 2-weekly in patients with relapsed/refractory cHL after ASCT failure in three cohorts. Cohort A included 63 brentuximab vedotin(BV)-naïve pa-
tients; those in Cohort B (n = 80) had received BV after ASCT, while those in Co-
hort C (n = 100) had been treated with BV before and/or after ASCT. Objective response rate (ORR) by independent re-
view committee (IRC) was defined as the primary endpoint. In Cohort C, pa-
tients who achieved complete remis-
sion (CR) for ≥ 1 year could discontinue treatment and receive re-treatment if re-

lapses occurred within two years. At the time of the 33-month follow-
up presented at the ASH 2018 Congress, the ORR was 71 %, with 21 % of patients obtaining CR [15]. Ansell et al. reported updated results from CheckMate 265 with a median follow-up of 58 months at ICML 2021 [16]. Median duration of treatment was 14 months in the entire cohort. In 24 %, patients had been able to receive subsequent hematopoietic stem cell transplant based on the bene-
fit from the study treatment.
serious treatment-related AEs (TRAEs) occurred in 15 %, and the treatment was discontinued due to TRAEs in 11 %. Immune-related AEs (irAEs) were mainly classified as grade 1 or 2. Rash occurred most frequently (12 %), followed by hepatitis (6 %), and pneumonitis (6 %). Overall, these proportions were relatively modest despite the patients being on treatment for a long time.

In Cohort C, 12 patients out of 100 discontinued nivolumab therapy after they had maintained CR for ≥ 1 year. Among these, six remained in CR with no additional intervention. Four of the other six patients experienced disease progression. Three were re-treated per protocol, with one continuing on treatment and being in remission at the time of the analysis. In their summary, the authors pointed out that it appears feasible to stop nivolumab therapy after one year of CR and to re-initiate treatment upon disease progression.

BGB-A317-203: tislelizumab

Optimized efficacy can be expected from the PD-1 inhibitor tislelizumab that was engineered to minimize binding to FcγR on macrophages, which compromises anti-tumor activity of PD-1 antibodies through activation of antibody-dependent macrophage-mediated killing of effector T cells [17, 18]. The pivotal, multicenter, single-arm, phase II BGB-A317-203 trial tested tislelizumab 200 mg i. v. every 3 weeks in 70 patients with relapsed/refractory cHL who were ineligible for intensive treatment after ≥ 2 lines of systemic therapy or had achieved no response or progressed after HDT/ASCT. All patients had received chemotherapy; immunotherapy and BV had been administered in 21.4 % and 5.7 %, respectively. Nineteen percent had undergone ASCT, while the remaining patients were no candidates for transplant. The ORR by IRC constituted the primary endpoint. Song et al. presented long-term data at EHA 2021 [19]. After a follow-up of 33.8 months, tislelizumab proved highly active. Objective responses occurred in 87.1 %, and CRs were achieved by 67.1 % of patients. Complete remissions emerged irrespective of the number of prior treatment lines and pretreatment with ASCT or BV (Table 1). The median time to response was 12 weeks, with 72 % of complete re-

Response-related outcome improvements

The 5-year follow-up confirmed the efficacy and safety of nivolumab in patients with cHL who have progressed or relapsed after ASCT. ORRs were 65 %, 71 % and 75 % for Cohorts A, B and C, respectively. Complete remissions resulted in 32 %, 14 % and 21 %, respectively. The CR rate in the total population had increased from 16 % at 33 months to 21 % at 58 months. Remissions proved durable, particularly in patients who had obtained CR; here, the median duration of response was 30.3 months compared to 13.5 months in the group with partial remission (PR). Favorable overall survival (OS) results were observed over time. At 5 years, 71.4 % of all patients were alive, and median OS had not been reached in the groups with CR, PR, and stable disease, with those in the CR cohort showing the best survival outcome (Figure). Even in the group that progressed during the study and received salvage therapies, many patients survived.

The 5-year progression-free survival (PFS) rate in the total population amounted to 18 %, with median PFS of 15.1 months. Median PFS was longest in the CR cohort (37.4 months); this was more than double the result seen for patients with PR (15.2 months).

The adverse event (AE) profile resembled the findings reported previously. No new safety signals or increases in toxicity were noted over time. Any-grade
sponders obtaining CR at the first post-baseline tumor assessment. Median PFS was 31.5 months. At the time of the 36-month landmark analysis, 40.8 % of patients remained progression-free. Patients who had achieved CR fared better in terms of PFS compared to those with PR and stable disease (not reached vs. 13.2 months). The OS results were immature; at 36 months, 84.8 % of patients lived, which is favorable considering the relapsed/refractory disease setting.

Grade ≥ 3 TRAEs occurred in 31.4 %, and in 8.6 %, AEs necessitated treatment discontinuation. irAEs were observed in 45.7 % and mainly included hypothyroidism (28.6 %), skin reactions (8.6 %), and pneumonitis (7.1 %). No new safety concerns were identified. In their summary, the authors noted that tislelizumab conferred a favorable benefit-risk profile and might represent an important treatment option for patients with relapsed or refractory chHL. A confirmatory phase III study is ongoing.

Update on camrelizumab

Camrelizumab has been approved in China based on the primary results of a multicenter, phase II trial in 75 patients with relapsed/refractory chHL in whom ASCT had failed to induce (lasting) remission in whom ASCT had failed to induce (lasting) remission. Camrelizumab has been approved in China based on the primary results of a multicenter, phase II trial in 75 patients with relapsed/refractory chHL in whom ASCT had failed to induce (lasting) remission in whom ASCT had failed to induce (lasting) remission. At the time of the analysis, 50.0 % of patients showed an objective response, with 6.7 % of patients experiencing CR [20]. Overall, 94.7 % achieved disease control. More than half showed ongoing responses at the time of the analysis. Median duration of response and median PFS were 31.7 and 22.5 months, respectively. Median OS had not been reached yet; at 36 months, 82.7 % of patients were alive.

The most common AE was cutaneous reactive capillary endothelial proliferation (RCEP) that occurred in almost all patients but was classified exclusively as grade 1 or 2. Complete resolution of RCEP lesions occurred in 67.1 %, with median time to complete resolution of 8.2 months. Most of the RCEP lesions regressed spontaneously, and none required systemic corticosteroids. At 12 and 24 months, the recurrence rates were 19.0 % and 6.3 %, respectively. No new toxicities emerged during the prolonged follow-up. AEs led to treatment interruption and discontinuation in 40.0 % and 6.7 %, respectively. The authors concluded that camrelizumab monotherapy continued to provide robust and durable responses as well as favorable survival and a manageable safety profile.

Chidamide in addition to decitabine/camrelizumab

The combination of the anti-PD-1 antibody camrelizumab with the DNA-de-methylating agent decitabine was evaluated in the clinical trial setting based on the observation that inhibition of de novo methylation can increase T-cell responses and tumor control during PD-1 inhibitor therapy in mice [21, 22]. Indeed, in a randomized phase II trial, camrelizumab plus decitabine elicited CRs in 79 % of patients with relapsed/refractory chHL, compared to 32 % with camrelizumab alone (p = 0.001) [23]. However, effective options have been lacking for patients who progressed on this regimen. A phase II study therefore tested a combined approach encompassing the histone deacetylase inhibitor chidamide in patients with relapsed/refractory chHL who had progressed or relapsed on camrelizumab/decitabine. Nineteen patients were treated with chidamide 10 mg (days 1–4) and 20 mg (days 5, 8, 11, 15, 18) plus decitabine 10 mg (days 1–5) and camrelizumab 200 mg (day 6) every 3 weeks. According to preliminary results reported at ASCO 2021, the triple combination induced pronounced responses and showed an acceptable safety profile [24]. Among 14 patients who completed the response evaluation, 13 (93 %) experienced objective responses, including CRs in six cases (43 %). The most common AEs were leukopenia (58 %; grade 3, 16 %), nausea (53 %) and hypertriglyceridemia (26 %). No irAEs occurred.

Promising results for pembrolizumab

Pembrolizumab is a novel IgG1 anti-PD-1 antibody engineered to eliminate bind-

REFERENCES

16. Ansell SM et al., Nivolumab for relapsed or refractory classical Hodgkin lymphoma after autologous transplantation: 5-year overall survival from the phase 2 CheckMate 205 study. JCOIL 2021; 1074.
ing to FcγRIa and FcγRIIIa receptors with the aim to avoid or reduce antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and antibody-dependent cytokine release. A multicenter, single-arm, open-label, phase 1/II study investi-
gated penpulimab 200 mg i. v. 2-weekly in patients with relapsed/refractory CHL following ASCT or ≥ 2 lines of chemo-
therapy. Updated phase II findings from the trial were presented at ASCO 2021 for 94 and 85 patients included in the safety and full analysis sets, respectively [25]. Almost 65 % of patients in the full analysis set had stage IV disease, and ≥ 3 prior lines of therapy had been adminis-
tered in more than half of cases. Among 85 evaluable patients, ORR with penpulimab was 89.4 %, and 47.1 % achieved CR (Table 2). The ORR benefit prevailed in all evaluated subgroups. Median duration of response had not been reached, which also applied to median PFS and median OS. All pa-
tients were alive at 18 months. The most frequent TRAEs included hypothyroidism (31.9 %), upper respiratory tract infection (25.5 %), fever (24.5 %) and alanine aminotransferase elevations (23.4 %). Grade 3 TRAEs were observed in 26.6 %, and treatment was discontin-
ued in 5.3 %. Penpulimab showed a favorably immune-related safety profile. Grade 3 events occurred in 4.3 %, and no patient developed grade 4/5 events.

**REFERENCES**

19 Song Y et al., Tislelizumab (BGB-A317) for relapsed/refractory classical Hodgkin lymphoma: long-term follow-up efficacy and safety results from a phase 2 study. EHA 2021, S207
20 Wu J et al., Camrelizumab for relapsed or refractory classical Hodgkin lymphoma: three-year outcome of a multicenter, phase 2 study. EHA 2021, S206
21 Ghoneim HE et al., De novo epigenetic programs inhibit PD-1 blockade-mediated T cell re-
22 Pauken KE et al., Epigenetic stability of ex-
haustrated T cells limits durability of reinvigoration by PD-1 blockade. Science 2016; 354(6316): 1160-1165
24 Wang C et al., Safety and efficacy of chidamab in combination with decitabine plus anti-
PD-1 camrelizumab after relapse or progression on decitabine-plus-camrelizumab in classical Hodgkin lymphoma. J Clin Oncol 39, 2021 (suppl 15; abstr e19515)
25 Song Y et al., A phase II study of penpuli-
mab, an anti-PD-1 antibody, in patients with re-
lapsed or refractory classic Hodgkin lymphoma (cHL). J Clin Oncol 39, 2021 (suppl 15; abstr 7529)

**Mantle cell lymphoma: improving outcomes in difficult-to-
treat patient populations**

**Updated results from MAGNIFY**

Mantle cell lymphoma (MCL) accounts for approximately 3-10 % of non-Hodg-
kin lymphomas and shows one of the poorest survival rates among the lymph-
omas [1, 2]. The combination of lenalidomide and rituximab (R²) has demon-
strated activity in MCL patients in the frontline and relapsed/refractory set-
tings, with overall response rates (ORRs) of 92 % and 57 %, respectively [3-5]. R² is being explored in the multicenter, random-
ized, phase III MAGNIFY trial as in-
itial and extended treatment in patients with relapsed/refractory NHL (i.e., follic-
ular lymphoma grades 1-3b, transformed follicular lymphoma, marginal zone lymphoma, or MCL) after ≥ 1 prior therapy. Induction treatment consists of twelve 28-day cycles of lenalidomide 20 mg/d on day 1-21 and rituximab 375 mg/m² weekly in cycle 1 followed by administra-
tion on day 1 of every other cycle. Subse-
quently, patients who have achieved complete or unconfirmed complete re-
response (CR, CRu), partial remission, or disease stabilization, are randomized to either lenalidomide plus rituximab maintenance or rituximab maintenance for 18 cycles. Progression-free survival (PFS) follow-
ing randomization to R² or rituxi-
amab monotherapy maintenance is the primary endpoint of the study. The first report in patients with relapsed/refrac-
tory MCL (n = 56) has revealed an ORR of 54 % [6]. Updated findings from the pre-randomization period of the study that assessed the combination only were presented at ICML 2021 by Shar-
aman et al. [7].

**TABLE 2**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n = 85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate, n (%)</td>
<td>76 (89.4)</td>
</tr>
<tr>
<td>Complete response, n (%)</td>
<td>40 (47.1)</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>36 (42.4)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>6 (7.1)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>Disease control rate, n (%)</td>
<td>82 (96.5)</td>
</tr>
<tr>
<td>Duration of response, months</td>
<td>Not reached</td>
</tr>
<tr>
<td>12-month PFS rate, %</td>
<td>72.1</td>
</tr>
</tbody>
</table>

**REFERENCES**

19 Song Y et al., Tislelizumab (BGB-A317) for relapsed/refractory classical Hodgkin lymphoma: long-term follow-up efficacy and safety results from a phase 2 study. EHA 2021, S207
20 Wu J et al., Camrelizumab for relapsed or refractory classical Hodgkin lymphoma: three-year outcome of a multicenter, phase 2 study. EHA 2021, S206
25 Song Y et al., A phase II study of penpulimab, an anti-PD-1 antibody, in patients with relapsed or refractory classic Hodgkin lymphoma (cHL). J Clin Oncol 39, 2021 (suppl 15; abstr 7529)
Responses irrespective of rituximab sensitivity

The MCL population included in this analysis comprised 73 patients who had received a median of two prior systemic therapies. All of them had been exposed to rituximab, and 34 % were rituximab-refractory. In the entire MCL group, initial treatment elicited an ORR of 51 %, with 34 % of patients achieving CR/CRu. These findings were similar across the rituximab-refractory and rituximab-sensitive groups (Figure 1). Median time to response was 2.8 months, and the majority of patients experienced tumor size reductions of > 50 %. In the cohort that obtained CR or PR, the median duration of response was 31.6 months; for rituximab-refractory and rituximab-sensitive patients, this was 31.6 and 28.4 months, respectively. Median duration of complete response had not been reached in any subgroup. After a median follow-up of 31.7 months, the total group showed a median PFS of 28.0 months (14.7 and 30.1 months for rituximab-refractory and rituximab-sensitive patients, respectively).

The safety profile observed in the MCL cohort was consistent with previous reports of the overall MAGNIFY population. Neutropenia emerged most frequently (51 %), with 46 % of patients experiencing grade 3/4 events, followed by fatigue (44 %), diarrhea (32 %), constipation (28 %), and cough (28 %). Although neutropenia was common, grade 3/4 febrile neutropenia occurred only in seven patients (10 %). In their conclusions, the authors noted that R2 is an active and tolerated regimen with durable responses among patients with relapsed/refractory MCL. The trial is ongoing to compare R2 with rituximab extended treatment.

Venetoclax, lenalidomide & rituximab

Based on observations suggesting efficacy of venetoclax [8] and lenalidomide plus rituximab [9] in MCL patients, as well as synergistic effects of venetoclax plus lenalidomide [10], it was hypothesized that the chemotherapy-free combination of venetoclax, lenalidomide and rituximab would be safe with the potential to improve outcomes and induce minimal residual disease (MRD) negativity in this setting. At ICML 2021, Phillips et al. presented the results of a study that evaluated the triple regimen in patients with untreated MCL [11]. The induction phase included twelve cycles of lenalidomide 20 mg/d on day 1–21 every 28 days, venetoclax 400 mg/d after ramp-up, and rituximab 375 mg/m² weekly in cycle 1 and every other month thereafter. Response assessment was performed during and after induction using PET/CT scan and MRD testing in peripheral blood. Patients who achieved radiographic CR and MRD negativity, as well as those without disease progression who were not eligible for transplant or declined it, went on to receive maintenance. Here, the lenalidomide dose was reduced by half of the induction dose and continued for 24 months, while venetoclax was continued for 12 months and rituximab was given every other cycle for 36 months.

Activity in high-risk patients

Overall, 28 patients were treated, with 19 (68 %) completing induction and transitioning to maintenance. At the time of the analysis, 23 patients (82 %) remained on treatment. Three and two patients, respectively, left the study due to progressive disease or other medical conditions. This was a poor-prognosis population; high risk according to the MIPI score was present in 88 %, and 14 % and 7 % of patients had the blastoid/blastic and pleomorphic variants, respectively.

Nevertheless, these early preliminary data indicated efficacy of the regimen. Radiographic assessment revealed CR in 67 % of 28 patients after 3 months and in all patients (n = 12) at 12 months. Likewise, the percentage for undetectable MRD rose from 63 % at 3 months (n = 27) to 92 % at 12 months (n = 12). The 12-month PFS rate was 86 %. No patient who had obtained undetectable MRD had relapsed until cutoff. Three patients experienced disease progression, with all of them harboring p53 mutations.

Dose reductions or delays were necessary in 53 %. No dose-limiting toxicities occurred, and all patients were able to safely escalate venetoclax to 400 mg/d. The most common AEs included neutropenia, thrombocytopenia, diarrhea, and anemia, which were also the most common grade 3/4 AEs. Two secondary cancers (i.e., adenocarcinoma of unknown primary, cutaneous squamous cell carcinoma) emerged on study, and two disease-related deaths occurred. Future plans include the expansion of the original study to enroll another 50 patients who do not harbor the p53 mutation. However, this patient group will also be addressed as modification of the regimen to specifically target the p53 mutation and other high-risk features is planned.

Real-world data on rituximab maintenance

Randomized clinical studies have yielded improved survival with rituximab maintenance (MR) following frontline rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in both young and older MCL patients [12, 13]. Guidelines
therefore recommend MR after first-line treatment [14, 15]. To date, however, real-world evidence regarding the use of MR in routine clinical practice has been limited. In particular, the benefits of MR after first-line bendamustine plus rituximab (BR) are not well established. At EHA 2021, Salles et al. reported a retrospective analysis evaluating real-world patterns and outcomes of MR after first-line BR or R-CHOP in a large US MCL cohort using the nationwide Flatiron Health database [16].

The MR-eligible cohort included 1,621 patients; by definition, they had received first-line induction combined with rituximab, and rituximab had been continued as monotherapy for ≥ 28 days. This population was subdivided into four groups: those treated with BR only (n = 728; 44.9 %), BR plus MR (n = 458; 28.3 %), R-CHOP only (n = 255; 15.7 %), and R-CHOP plus MR (n = 180; 11.1 %). To date, this is the largest real-world cohort of patients with MCL treated mostly in community-based US practices.

**MR as independent predictor**

The use of MR in addition to both BR and R-CHOP conferred significantly improved outcomes. Median real-world time to next treatment was 37.0 months and 21.7 months, respectively, with BR and R-CHOP alone, while this had not been reached for either BR + MR or R-CHOP + MR (Figure 2). These differences were significant (p < 0.001 for both BR vs. BR + MR and R-CHOP vs. R-CHOP + MR). BR + MR performed relatively better than R-CHOP + MR. The real-world OS rates at 36 months amounted to 76 % vs. 85 % for BR vs. BR + MR (p = 0.001), and to 77 % vs. 88 % for R-CHOP vs. R-CHOP + MR (p = 0.030).

According to multivariate analyses, MR was an independent predictor of superior real-world time to next treatment and OS. Patient and disease characteristics associated with significantly worse outcomes included age ≥ 65 years, LDH/ULN ≥ 1, bulky disease, and blastoid/pleomorphic morphology. The authors pointed out that these results need to be interpreted in the context of evidence provided by randomized studies assessing MR in MCL as selection biases are inherent in real-world analyses. At present, the phase III SHINE trial is evaluating whether PFS can be improved with the addition of ibrutinib to BR followed by MR in older patients with previously untreated MCL.

**REFERENCES**

7 Shorman JP et al., Induction R2 followed by maintenance in patients with relapsed/refractory mantle cell lymphoma: interim analysis from the phase 3b MAGNIFY study. JCO 2013; 31(11): 1835-1844
9 Yamshon S et al., Initial treatment with lenalidomide plus rituximab for mantle cell lymphoma: 7-year analysis from a multicenter phase III study. ASH 2020, 704
10 Paulus A et al., AT-101 downregulates BCL2 and MCL1 and potentiates the cytotoxic effects of lenalidomide and dexamethasone in preclinical models of multiple myeloma and Waldenström macroglobulinemia. Br J Haematol 2014; 164(3): 352-365
11 Phillips TJ et al., The combination of venetoclax, lenalidomide and rituximab in patients with newly diagnosed mantle cell lymphoma induces high response rates and MRD undetectability. ICML 2021, 061
14 NCCN Clinical Practice Guidelines in Oncology B-Cell Lymphoma, version 4-2021-February 16, 2021
16 Salles G et al., Role of maintenance rituximab after first-line bendamustine plus rituximab or R-CHOP in patients with mantle cell lymphoma form a large US real-world cohort. EHA 2021, EP785
Zanubrutinib in relapsed/refractory marginal zone lymphoma: MAGNOLIA

B-cell receptor-mediated signaling has been identified as a critical step in marginal zone lymphoma (MZL) pathogenesis [1]. Accordingly, BTK inhibition is effective in the management of patients with relapsed/refractory MZL, as shown for the first-generation BTK inhibitor ibrutinib [2]. The multicenter, single-arm, phase II MAGNOLIA study is evaluating the next-generation BTK inhibitor zanubrutinib 160 mg twice daily in patients with relapsed/refractory MZL including splenic, nodal and extra-nodal subtypes after pretreatment with ≥ 1 CD20-based regimen. The primary endpoint is the overall response rate (ORR) as determined by independent review based on the Lugano 2014 classification. At EHA 2021, Opat et al. reported the results of the study after completed enrollment [3]. A total of 68 patients had received ≥ 1 dose of zanubrutinib. The efficacy population included 66 individuals.

MAGNOLIA met its primary endpoint. After a median follow-up of 15.7 months, the ORR was 68.2 %, thus exceeding the pre-specified null ORR of 30 % (p < 0.0001). Complete remissions emerged in 25.8 %. Responses were observed in all MZL subtypes and across patient and disease characteristics such as age, presence of bulky or extra-nodal disease, and type of pretreatment. Median progression-free survival and median duration of response had not been reached yet. At 15 months, 82.5 % of patients were alive and progression-free. The most common treatment-emergent adverse events (TEAEs) of interest included infections (all grades, 45.6 %), hemorrhage (36.8 %), and diarrhea (22.1 %). Among grade ≥ 3 events, infections (16.2 %) and neutropenia (10.3 %) prevailed. Atrial fibrillation or flutter occurred in two patients (2.9 %). No major hemorrhage was reported. TEAEs led to dose interruptions in 29.4 %, while dose reductions were not necessary in any of the patients. In four cases, treatment was discontinued due to TEAEs unrelated to zanubrutinib. Overall, zanubrutinib proved highly active and showed a favorable safety profile in patients with relapsed/refractory MZL.

REFERENCES

3 Opat S et al., Phase 2 study of zanubrutinib in patients with relapsed/refractory marginal zone lymphoma (MAGNOLIA study). EHA 2021, EP783

Novel bispecific antibodies in CD20-positive B-cell non-Hodgkin lymphomas

Glofitamab step-up dosing

The T-cell–engaging bispecific antibody glofitamab has been designed with a 2:1 configuration that enables bivalent binding to CD20 on B cells and monovalent binding to CD3 on T cells [1]. Compared to alternative bispecific formats, this offers greater avidity, potency and combinability with other anti-CD20 IgG antibodies. In the phase I setting, glofitamab step-up dosing after obinutuzumab pretreatment allowed for dose escalation of up to 30 mg to maximize efficacy while mitigating the cytokine release syndrome (CRS) risk [2]. At ICML 2021, Carlo-Stella et al. presented updated efficacy data for two cohorts (including the final, recommended phase II dose) from the ongoing phase I/II dose escalation and expansion study conducted in patients with relapsed/refractory non-Hodgkin lymphoma (NHL) [3].

In these cohorts, glofitamab was administered intravenously in step-up doses of 2.5 mg and 10 mg on days 1 and 8 of cycle 1, respectively, followed by two different target doses of 16 mg or 30 mg from day 1 of cycle 2. After cycle 1, which encompassed 14 days, glofitamab was given 3-weekly for up to twelve cycles. Obinutuzumab pretreatment was administered seven days prior to glofitamab therapy. Among 50 patients with CD20-expressing B-cell NHLs, 16 and 34, respectively, were assigned to the 2.5/10/16 mg and 2.5/10/30 mg schedules. Most patients were heavily pretreated; the median number of prior lines was 3, and 84.6 % were refractory to any prior therapy. All patients had received prior chemotherapy and anti-CD20 antibody therapy. Aggressive and indolent NHLs were present in 53.8 % and 46.2 %, respectively. Diffuse large B-cell lymphoma (DLBCL) was the most common aggressive entity. All patients with indolent NHL had follicular lymphoma (FL) grade 1-3a.

Durable CMRs

The update of the study revealed high response rates. Overall, 64.3 % and 79.2 % of patients with aggressive and indolent disease, respectively, responded. Those with aggressive NHLs receiving the 2.5/10/30 mg dose showed a trend, with a complete metabolic response (CMR) rate of 71.4 %. Four of five patients with mantle cell lymphoma (MCL) achieved CMR. The majority of patients experienced at least 50 % reductions in tumor burden, with anti-tumor activity evident across NHL subtypes.

The median duration of response for complete responders had not been reached after a median follow-up of 8.4 and 5.8 months for aggressive and indolent NHLs, respectively. In the group with aggressive lymphomas, 13 out of 16
CMRs were shown to be ongoing at the time of the analysis, and for indolent lymphomas, 16 of 17 CMRs were ongoing. Most patients in the entire population receiving the 2.5/10/30 mg schedule experienced significant durability of CMR even after treatment completion. Moreover, immunohistochemistry and immunofluorescence analysis of baseline tumor biopsies demonstrated that clinical responses were achieved across a range of CD20 expression levels and irrespective of the amount of tumor infiltration by CD8 T-cells.

Adverse events (AEs) mainly included CRS, neutropenia, and pyrexia. CRS events emerged in 67.3 % of patients, but they were confined to the first two cycles and were graded as 1 or 2 in the vast majority of cases (grade 1, 38.5 %; grade 2, 23.1 %). Glofitamab doses of 2.5 mg and 10 mg administered in cycle 1 gave rise to CRS events at 50.9 % and 40.3 %, respectively. In cycle 2, 12.4 % and 30.3 % of patients receiving 16 mg and 30 mg, respectively, developed CRS. Grade 3 CRS events were restricted to 3.8 % of patients treated with 30 mg in cycle 2. Overall, treatment-related grade 3/4 AEs occurred in 40.4 %. No grade 5 AEs were reported. Treatment discontinuation resulting from AEs was seen in 3.8 %. The authors noted in their conclusions that these glofitamab step-up dosing data showed impressive response rates, potentially translating into early and more durable responses for patients with aggressive and indolent relapsed/refractory NHL who have failed multiple lines of therapy.

**Epcoritamab: EPCORE™ NHL-1**

Similar to glofitamab, epcoritamab is a bispecific antibody that binds CD20 and CD3, which harnesses the patient’s immune system to induce T-cell–mediated killing of CD20-positive malignant B-cells [4]. However, epcoritamab is administered subcutaneously, thus ensuring more gradual increases and lower peaks in plasma cytokine levels compared to intravenous formulations, and this is regarded as a strategy to mitigate CRS. Other features include an ability for potent T-cell-mediated killing even at low levels of CD20 expression, as well as Fc domain mutations that prevent off-target T-cell cytotoxicity.

The dose-escalation part of the ongoing, first-in-human phase I/II EPCORE™ NHL-1 study has identified 48 mg as the recommended phase II dose in patients with relapsed/refractory CD20-positive B-NHL, previously treated with anti-CD20 antibodies [5]. No dose-limiting toxicities were observed, and the maximum tolerated dose was not reached. Patients are currently being treated in the expansion cohort. Hutchings et al. reported updated data for 68 patients after a median follow-up of 14.1 months at ICML 2021 [6]. The majority had DLBCL (n = 46), followed by FL and MCL. Most of them were heavily pretreated and refractory to their most recent line of therapy, as well as prior anti-CD20 combinations.

**Encouraging activity**

Despite these unfavorable prerequisites, epcoritamab demonstrated encouraging anti-tumor activity with deep responses across histologies. Among DLBCL patients who received 48–60 mg, the ORR was 91 %, with 55 % achieving complete remission (CR; Table). For patients with FL, this was 80 % and 60 %, respectively. Responses were obtained in all five DLBCL patients previously treated with CAR-T cell therapy. In the entire cohort, median time to response was 1.3–1.5 months across dose groups, and median duration of response had not been reached yet. All DLBCL patients who achieved CR with ≥12 mg doses have remained in remission; three of them went on to receive consolidation stem cell transplantation. Median progression-free survival was 9.1 month for those treated with ≥12 mg, while it had not been reached yet in the ≥48 mg dose group. Four of five FL patients who achieved CR with ≥0.76 mg doses remained in remission at a median follow-up of 11.1 months.

Epcoritamab was generally well tolerated. Most commonly, pyrexia (69 %) and CRS (59 %) occurred, followed by injection site reaction (47 %), fatigue (44 %), hypotension (31 %), diarrhea (26 %), dyspnea (25 %), anemia (23 %), and tachycardia (21 %). The safety profile was consistent across doses and histologies, and the majority of AEs were mild or moderate. Notably, no grade ≥3 CRS events were observed, and grade 1/2 events resolved with standard-of-care management. Almost all CRS events were restricted to cycle 1. The risk of CRS was mitigated by the subcutaneous administration, step-up dosing and corticosteroid prophylaxis during cycle 1. Neurotoxicity was rare, self-limiting and transient. No treatment-related deaths or discontinuations occurred.

The expansion part of the EPCORE™ NHL-1 study is ongoing. Furthermore, epcoritamab is currently being studied in the phase III EPCORE™ DLBCL-1 trial as monotherapy versus standard-of-care chemotherapy in patients with relapsed/refractory DLBCL, as well as in phase I/II trials across different B-cell NHL histologies, and in various combinations and settings.

**REFERENCES**

3 Carlo-Stella C et al., Glofitamab step-up dosing: updated efficacy data show high complete response rates in heavily pretreated relapsed/refractory non-Hodgkin lymphoma patients. ICML 2021, 015
4 Engelberts PJ et al., DuoBody-CD3xCD20 induces potent T-cell-mediated killing of malignant B cells in preclinical models and provides opportunities for subcutaneous dosing. EBioMedicine 2020; 52: 102625
5 Hutchings M et al., Subcutaneous epcoritamab induces complete responses with an encouraging safety profile across relapsed/refractory B-cell non-Hodgkin lymphoma subtypes, including patients with prior CAR-T therapy: updated dose escalation data. ASH 2020, 402

**TABLE**

Response rates for patients with relapsed/refractory DLBCL, FL, and MCL treated with epcoritamab

<table>
<thead>
<tr>
<th>Epcoritamab doses</th>
<th>DLBCL</th>
<th>FL</th>
<th>MCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-60 mg</td>
<td>15 (68)</td>
<td>10 (91)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>48-60 mg</td>
<td>15 (68)</td>
<td>10 (91)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>12-48 mg</td>
<td>15 (68)</td>
<td>10 (91)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>0.76-48 mg</td>
<td>15 (68)</td>
<td>10 (91)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Overall response rate, n (%)</td>
<td>15 (68)</td>
<td>10 (91)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Complete response</td>
<td>15 (68)</td>
<td>10 (91)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Partial response</td>
<td>15 (68)</td>
<td>10 (91)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Matthew Davids depicts the most interesting trial results in the field of CLL treatment at the EHA 2021 congress, gives an outlook on the most promising agents currently tested for use not only in elderly but also in young, fit CLL patients and talks about combinations that might be implemented as pillars of CLL treatment based on current trials.

Carol Moreno highlights the CLL study results from EHA and ICML, enlarges on fixed-duration regimens in CLL treatment, the importance of long-term follow-up findings obtained in important trials such as CLL14 and ELEVATE-TN as well as data from the ALPINE and ELEVATE-RR studies and shares her thoughts on the role of new agents such as zanubrutinib in the overall treatment landscape.

Anthony Mato talks about the study highlights presented at EHA and ICML, innovative treatment approaches currently tested for use in CLL that appear most promising and explains how the prognosis of CLL patients might change due to new therapies in the years to come and summarizes potential strategies to prevent and overcome resistance to targeted therapies.

Alvaro Alencar discusses which first-line treatment options might soon be established for newly diagnosed patients with mantle cell lymphoma who are not eligible for intensive therapy, what can be expected in terms of innovative approaches in the setting of R/R mantle cell lymphoma or marginal zone lymphoma and highlights the need for robust prognostic tools allowing stratification of treatment modalities.

Wojciech Jurczak gives an overview of the advantages of new BTK inhibitors, the results of the ALPINE trial comparing zanubrutinib with ibrutinib in patients with relapsed/refractory CLL/SLL and talks about which new developments can be expected in the field of innovative BTK inhibitors in the treatment of CLL and other indications.

Christian Buske relates to recent developments with respect to the role of BTK inhibitors and their potential future combination partners in the treatment of patients with Waldenström’s macroglobulinemia, the results of the iNNOVATE study and personalized treatment according to genotypes.

Forthcoming Special Issue
This special issue will be offering a synopsis from the ASH 2021 that will be held in December 2021. The report promises to make for stimulating reading, as the ASH Congress itself draws on the input from a number of partner organizations, representing a multidisciplinary approach to cancer treatment and care. Again, malignant and non-malignant hematologic diseases will be at the heart of this special issue.