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memo – inHaematology SPECIAL ISSUE

Congress Report EHA 2020

A GLOBAL CONGRESS DIGEST ON B-CELL MALIGNANCIES AND RARE DISEASES IN HAEMATOLOGY

Report from the Virtual Edition of the 25th European Hematology Association (EHA)
Annual Congress 11th–21st June 2020

IMPRESSUM/PUBLISHER

Media owner and publisher: Springer-Verlag GmbH, Professional Media, Prinz-Eugen-Straße 8–10, 1040 Vienna, Austria, **Tel.:** +43(0)1/330 24 15-0, **Fax:** +43(0)1/330 24 26, **Internet:** www.springernature.com, www.SpringerMedizin.at. **Copyright:** © 2020 Springer-Verlag GmbH Austria. Springer Medizin is a Part of Springer Nature.

Managing Directors: Joachim Krieger, Juliane Ritt, Dr. Alois Sillaber. **Medical Writer:** Judith Moser, MD. **Corporate Publishing:** Elise Haidenthaler.

Editorial Support: Anna Fenzl, PhD. **Layout:** Katharina Bruckner. **Published in:** Vienna. **Produced in:** Fulda. **Printer:** Druckerei Rindt GmbH & Co KG, Fulda, Germany; The editors of "memo, magazine of european medical oncology" assume no responsibility for this supplement.

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Supported by Apellis Pharmaceuticals and BeiGene Ltd.
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Preface

Dear Colleagues,

Due to the circumstances brought about by the COVID-19 pandemic, the 25th European Hematology Association (EHA) Annual Congress had to take place as a virtual edition, although this raised new possibilities such as a 10-day program. Like its predecessors conducted onsite, the EHA25 Virtual Congress offered original unpublished scientific hematology data, hematological innovations, and evidence-based knowledge of primary clinical relevance. This memo in Haematology publication summarizes content presented on the topics of B cell malignancies, paroxysmal nocturnal hemoglobinuria, and cold agglutinin disease.

Within the field of non-Hodgkin lymphoma, Bruton's tyrosine kinase (BTK) inhibitors have emerged as important players in the management of patients with Waldenström's macroglobulinemia and mantle cell lymphoma but were also shown to be active in diffuse large B cell lymphoma, follicular lymphoma, and marginal

zone lymphoma. Next-generation agents with optimized features are under development. In patients with mantle cell lymphoma, promising results obtained with novel agents challenge the role of chemotherapy, particularly in the front-line setting. Both single-agent and combined regimens containing various classes of targeted agents might open up new dimensions and are being extensively evaluated in clinical trials.

BTK inhibition has also transformed the treatment of chronic lymphocytic leukemia and continues to be investigated alone and together with other agents. The advent of modern treatment options has given rise to an increasing demand for time-limited therapy in these patients. Fixed-duration approaches, possibly guided by the assessment of minimal residual disease, represent a feasible road ahead.

Although rare, paroxysmal nocturnal hemoglobinuria is a potentially life-threatening condition that calls for effective management. The range of available agents targeting the complement system is currently being expanded. Novel agents, by addressing various factors that enhance residual anemia, contribute to more complete disease control. Likewise,



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cold agglutinin disease shows a low prevalence but considerably affects patient prognosis and quality of life. As in paroxysmal nocturnal hemoglobinuria, inhibition of certain components of the complement system can lead to rapid and durable clinical improvements. Global registry data will elucidate clinical characteristics as well as the use of treatments, patient outcomes and the natural history of this disease.

Constantine Tam, MB, BS (Hons), MD, FRACP, FRCPA
Peter MacCallum Cancer Centre,
Royal Melbourne Hospital,
and University of Melbourne
Melbourne, Australia

Waldenström's macroglobulinemia: BTK inhibition and other treatments

Within the group of non-Hodgkin lymphoma, Waldenström's macroglobulinemia (WM), an indolent B-cell lymphoplasmacytic lymphoma, accounts for approximately 2 % of cases [1]. This disease is deemed incurable and typically involves infiltration of tissues such as bone marrow, lymph nodes and/or spleen with clonal lymphoplasmacytic cells, as well as serum monoclonal paraprotein production. The B-cell receptor signaling pathway is constitutively activated in WM [2, 3]. In more than 90 % of patients, *MYD88* mutations can be found.

As Bruton's tyrosine kinase (BTK) represents an integral component of the

B-cell receptor signaling pathway, BTK inhibition has emerged as a new treatment standard. BTK inhibitors that are currently in use or are being clinically evaluated include the first-generation agent ibrutinib that has been licensed for the treatment of WM in the USA and the EU, and second-generation agents with improved efficacy and tolerability.

ASPEN: zanubrutinib vs. ibrutinib

The selective, irreversible second-generation BTK inhibitor zanubrutinib has been designed to maximize BTK occupancy and to minimize off-target inhibi-

tion of other kinases [4]. Zanubrutinib is as potent against BTK as ibrutinib, but its increased selectivity allows for an optimized adverse event (AE) profile [4, 5]. Its efficacy and safety in WM are being assessed in the ongoing open-label, multicenter, randomized phase III ASPEN study. At EHA 2020, Dimopoulos et al. reported the results for Cohort 1, which included patients with *MYD88*-mutated WM who met at least one criterion for treatment initiation and had not received prior BTK inhibition [6]. They were treated with either zanubrutinib 160 mg twice daily (BID; n = 102) or ibrutinib 420 mg daily (n = 99). Both pretreated and treatment-naïve patients

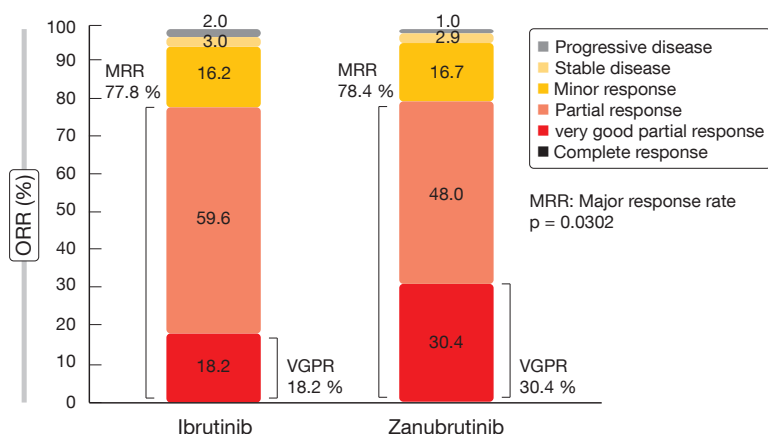


Figure 1: ASPEN trial: Response rates observed with ibrutinib vs. zanubrutinib according to the investigators

participated; enrollment of the latter was only permitted if they were considered unsuitable for standard chemotherapy. Out of 201 individuals, 164 had relapsed or refractory disease.

Superiority of zanubrutinib *versus* ibrutinib with respect to the rate of complete responses (CRs) plus very good partial responses (VGPRs) in the relapsed/refractory group according to independent review was defined as the primary endpoint. Although this analysis only revealed a trend in favor of zanubrutinib (28.4 % vs. 19.2 %; $p = 0.0921$), superior efficacy of the second-generation agent with respect to CR plus VGPR was demonstrated according to investigator assessment (secondary endpoint; 30.4 % vs. 18.2 %; $p = 0.0302$; **Figure 1**). Major responses emerged in approximately 78 % in both arms. Also, with regard to IgM levels, zanubrutinib induced a significantly deeper reduction over time ($p = 0.037$). Both arms showed excellent event-free rates at 12 months for progression-free survival (PFS; 89.7 % vs. 87.2 %) and overall survival (OS; 97.0 % vs. 93.9 %).

Lower incidence of adverse events

Zanubrutinib demonstrated clinically meaningful advantages in terms of safety and tolerability. AEs leading to death or treatment interruption and discontinuation emerged less frequently in the experimental arm. The risk of atrial fibrillation or flutter was significantly reduced (2.0 % vs. 15.3 %), as were the rates for diarrhea (20.8 % vs. 31.6 %), major hemorrhage (5.9 % vs.

9.2 %), and hypertension (10.9 % vs. 17.3 %). While the incidence of atrial fibrillation/flutter increased constantly over time in ibrutinib-treated patients, it remained stable at a low level in the zanubrutinib-treated group. A similar trajectory became evident for hypertension. Infections did not occur more frequently in the experimental arm (66.3 % vs. 67.3 %) despite higher rates of neutropenia (29.7 % vs. 13.3 %). Quality-of-life analyses demonstrated improvement for both drugs over time, although the zanubrutinib-treated patients who achieved VGPR showed a more favorable course that probably reflects improved safety and tolerability.

The results for Cohort 1 of the ASPEN study have already been presented at the 2020 ASCO Virtual Meeting [7] and were included in the ASCO highlight session on hematologic malignancies. In her discussion of the findings, Nancy Bartlett,

MD, Washington University, St. Louis, USA, pointed out that longer follow-up might be necessary for obtaining deeper responses. Given the higher tolerability of the new-generation BTK inhibitor, Dr. Bartlett noted that in her opinion, zanubrutinib will be the therapy of choice once it has received approval for the treatment of patients with WM.

Assessment in WM patients with MYD88 wildtype

In Cohort 2 of the ASPEN study, zanubrutinib 160 mg BID was assessed in treatment-naïve and pretreated WM patients who had *MYD88* wildtype [8] based on the observation that response rates and survival are worse with ibrutinib in the absence of *MYD88* mutations [9–11]. Twenty-eight patients were enrolled 26 of whom had *MYD88* wildtype, while the mutation status was unknown in two. Relapsed or refractory disease was present in 23 individuals. After a median follow-up of 17.9 months, 17 (60.7 %) were still on study treatment.

Single-agent zanubrutinib resulted in a major response rate of 50.0 %, including VGPR in 26.9 %. Patients with relapsed/refractory disease had a higher major response rate than the treatment-naïve group (52.4 % and 40.0 %, respectively). The median time to first major response was 2.9 months. One patient obtained IgM CR. Median PFS and OS had not been reached yet; event-free rates at 12 months were 72.4 % and 96.2 %, respectively. Zanubrutinib was well tolerated, with disease progression representing the primary reason for

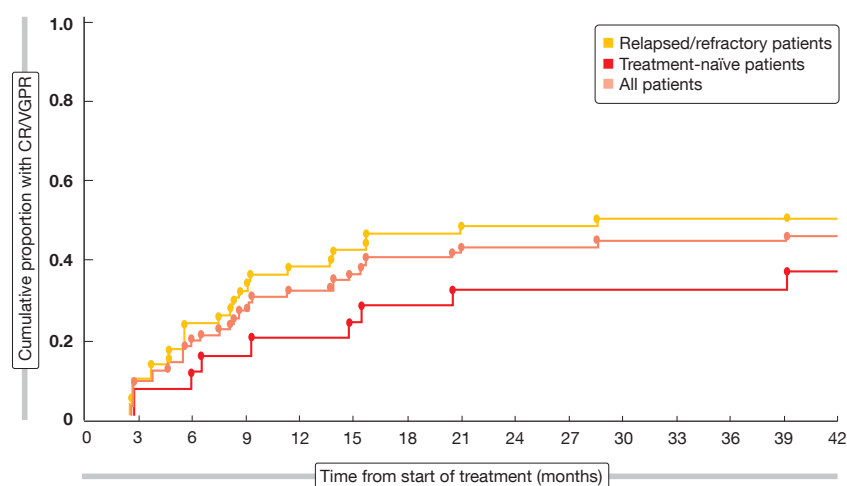


Figure 2: Increases in the rates of patients with CR and VGPR over time with zanubrutinib

treatment discontinuation. The AE profile was consistent with that observed in Cohort 1. No fatal AEs were reported. At 3.6 %, the rate of all-grade atrial fibrillation/flutter was low.

Three-year update of phase I/II results

Opat et al. reported the three-year update of the first-in-human, multicenter, phase I/II AU-003 study that was designed to evaluate the safety, pharmacokinetics and anti-tumor activity of single-agent zanubrutinib in patients with B-cell malignancies [12]. Seventy-seven patients with WM were treated in this trial. Among these, 24 had been treatment-naïve prior to study inclusion, while 53 had relapsed/refractory disease.

After a follow-up of 35.3 months, deep responses were observed in both treatment-naïve and relapsed/refractory settings and in all molecular subtypes including *MYD88* wildtype. The overall response rate (ORR) was 96 % in the total evaluable group ($n = 73$), with an excellent CR/VGPR rate of 46 %. Kaplan-Meier estimates of the cumulative proportion of patients with CR/VGPR showed that the rate increased over time (**Figure 2**). At 36 months, 80.3 % and 83.4 % of patients were progression-free and alive, respectively. Median hemoglobin and IgM levels showed fast improvement after the initiation of treatment and remained stable over time.

Long-term treatment with zanubrutinib was generally well tolerated. AEs led to treatment discontinuation in 13.0 %. Among AEs of interest, infections occurred most frequently, fol-

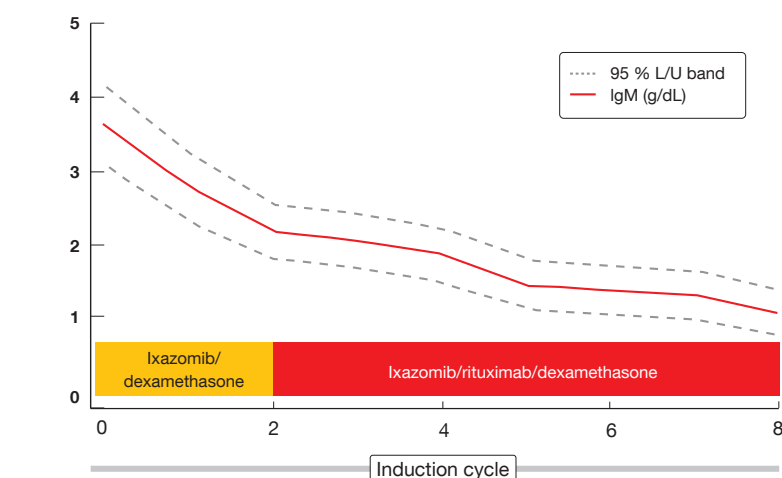


Figure 3: IgM response with ixazomib/rituximab/dexamethasone: decrease in IgM levels even prior to the initiation of rituximab treatment

lowed by bruising and minor bleeding. Grade ≥ 3 infections were most common in the first year of treatment and decreased thereafter, while the percentage of patients affected by hypertension increased over time. The rate of grade ≥ 3 atrial fibrillation/flutter was 1.3 %.

Ixazomib plus rituximab and dexamethasone

The combined regimen of the proteasome inhibitor ixazomib, the anti-CD20 antibody rituximab and dexamethasone (IRd) showed favorable clinical activity in the relapsed/refractory setting according to the recent analysis of the prospective, international, phase I/II HOVON124/ECWM-R2 study [13]. Phase I of this trial identified ixazomib 4 mg on days 1, 8 and 15 every 28 days as the recommended phase II dose. Rituximab 1,400 mg was administered on day 1 of cycles 3 to 8, and dexamethasone

20 mg on days 1, 8, 15 and 22 of each cycle. The induction therapy consisted of 8 cycles. Responders who achieved at least stable disease went on to receive maintenance with rituximab 1,400 mg every 3 months for 2 years. ORR after induction based on the IgM levels was defined as the primary outcome. Forty-five patients completed all eight cycles, and 41 continued on to maintenance.

IRd was shown to be a feasible and active regimen with high ease of administration. The primary endpoint was met, with an ORR of 71 %; 51 % of patients achieved at least partial remissions. With regard to best response obtained during the induction phase, the ORR was 85 %. Significant IgM and hemoglobin responses already occurred before the start of rituximab treatment. The IgM levels decreased between baseline and cycle 2 ($p < 0.0001$; **Figure 3**), while the hemoglobin levels simultaneously increased ($p = 0.0004$).

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IgM flares were not observed. Median PFS, OS and duration of response had not been reached at the time of the analysis. At 24 months, 56 % of patients were progression-free and 88 % were alive.

Although neuropathy worsened or emerged in 16 patients, it was mostly grade 1 or 2 and reversible in 10 individuals. Patient-reported outcomes according to the EORTC QLQ-CIPN20 questionnaire demonstrated that the neuropathy-associated symptom burden did not increase during treatment. The majority of AEs were grades 1 and 2; no grade-4 AEs occurred. Global health status improved significantly during induction according to the EORTC HR-QoL QLQ-C30 questionnaire ($p = 0.03$ in cycle 8 vs. baseline).

Bendamustine and rituximab

International consensus guidelines recommend the combination of bendamustine and rituximab for the treatment of WM in both frontline and relapsed settings [14]. However, the optimal dose and schedule of this regimen has not been well established yet. An international, multicenter, retrospective cohort analysis assessed clinical outcomes in untreated or relapsed consecutive WM patients who received bendamustine with or without rituximab [15]. Overall, 217 individuals were included in the analysis; among these, 122 had been treated in the frontline setting.

The outcomes obtained in this unselected group were excellent, with more favorable results in hitherto untreated

patients. These tolerated higher total doses of bendamustine than relapsed patients and achieved comparatively deeper responses with higher combined rates of CR and VGPR (47.5 % vs. 20 %; $p < 0.001$). PFS was significantly longer in the frontline setting ($p < 0.05$) and also varied according to the depth of response, with 2-year PFS rates of 98.2 % vs. 84.3 % for patients achieving CR/VGPR vs. PR ($p < 0.001$). Performance status and total bendamustine dose affected both depth of response and PFS. A total bendamustine dose of $\geq 800 \text{ mg/m}^2$ was shown to be critical for obtaining a depth of response sufficient to achieve durable remissions. Surrogate markers of toxicity including truncation of treatment were less frequent in the frontline setting. ■

Optimizing timing, efficacy and tolerability in chronic lymphocytic leukemia

Acalabrutinib vs. ibrutinib

In both treatment-naïve and relapsed/refractory patients with chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL), inhibition of Bruton's tyrosine kinase (BTK) represents a treatment standard as it has improved clinical outcomes [1]. Compared to the first-generation agent ibrutinib, the second-generation, highly selective BTK inhibitor acalabrutinib shows minimal off-target kinase inhibition [2], thus potentially offering an optimized safety profile. Acalabrutinib has been approved for the treatment of CLL in various countries including the USA, Australia, and India.

Given the lack of head-to-head trials, Davids et al. conducted matching-adjusted indirect comparisons of acalabrutinib and ibrutinib either as monotherapies or in combination with the anti-CD20 antibody obinutuzumab in patients with treatment-naïve CLL [3]. Indeed, the analysis suggested lower rates of clinically important AEs with the second-generation BTK inhibitor. At the same time, acalabrutinib with and without obinutuzumab showed a trend to-

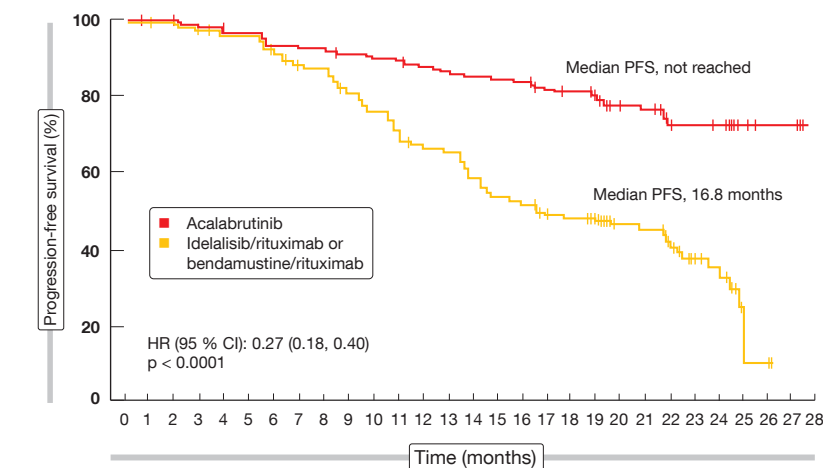


Figure 1: ASCEND: progression-free survival for acalabrutinib vs. idelalisib/rituximab or bendamustine/rituximab in the relapsed/refractory setting

wards improved PFS and OS compared to ibrutinib with and without obinutuzumab. Acalabrutinib monotherapy significantly reduced the mortality risk *versus* ibrutinib plus obinutuzumab by 84 % ($p < 0.001$). As the authors noted, this warrants further investigations. The ongoing, randomized, head-to-head ELE-VATE-CLL R/R study comparing ibrutinib with acalabrutinib will provide answers in a prospective manner.

ASCEND: final results in r/r CLL

The randomized, phase III ASCEND study compared acalabrutinib ($n = 155$) with investigator's choice of idelalisib/rituximab ($n = 119$) or bendamustine/rituximab ($n = 36$) in patients with relapsed/refractory CLL (r/r CLL). After a median follow-up of 16.1 months, the pre-planned interim analysis already demonstrated significant superiority of acalabrutinib

versus the comparator regimens with regard to PFS [4]. At the EHA 2020 Congress, Ghia et al. reported the final results of ASCEND after 22 months [5].

The findings confirmed the results of the interim analysis, supporting the favorable efficacy and safety of acalabrutinib. PFS was significantly prolonged, with a 73 % reduction in the risk of progression or death (not reached vs. 16.8 months; HR, 0.27; $p < 0.0001$; **Figure 1**). At 18 months, PFS rates were 82 % vs. 48 % for acalabrutinib and the comparator regimens, respectively. Significant PFS benefits were also observed in patients with high-risk genetics including 17p deletion and *TP53* mutations (HR, 0.11) and unmutated *IGHV* (HR, 0.28). The ORRs did not differ significantly across the arms, although the duration of response was significantly longer in the experimental arm (not reached vs. 18.0 months; HR, 0.19). Responses persisted in 85.4 % vs. 49.4 % at 18 months.

The incidences of grade ≥ 3 AEs, serious AEs, treatment-related AEs, drug discontinuations and dose modifications were lower with acalabrutinib than with idelalisib/rituximab, and similar to the respective rates observed for bendamustine/rituximab. Among events of clinical interest, any-grade hemorrhages were more common with acalabrutinib, but the incidence of major bleeding events was low and similar across arms. These data support the use of acalabrutinib in patients with r/r CLL, including those with high-risk features.

Long-term acalabrutinib therapy

In the untreated symptomatic setting, the mature results of the single-arm, phase II ACE-CL-001 trial provide the longest safety and efficacy follow-up to date for single-agent acalabrutinib [6]. After 53 months, the analysis showed durable remissions and long-term tolerability of this treatment in 99 patients. The ORR amounted to 97 %, with CR and PR rates of 7 % and 90 %, respectively. Median duration of response had not been reached yet. In each high-risk group (i.e., unmutated *IGHV*, 17p deletion, *TP53* mutation, complex karyotype), the ORR was 100 %. Reductions in lymph node disease occurred in all patients. Median event-free survival had not been reached yet at the time of the

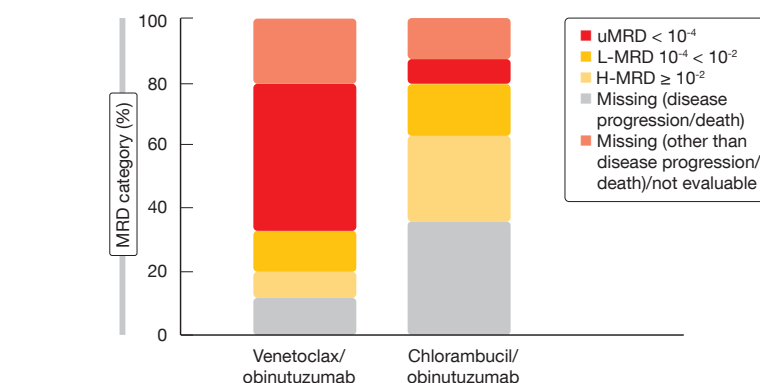


Figure 2: MRD results with venetoclax/obinutuzumab vs. chlorambucil/obinutuzumab at 18 months in a population of untreated patients with comorbidities included in the CLL14 study

analysis; at 48 months, 90 % of patients were event-free.

AEs were mild, with only 6 % of patients discontinuing treatment due to toxicity. At data cut-off, 86 % were still on therapy. Diarrhea, headache and upper respiratory infections emerged as the most common AEs. No patient discontinued acalabrutinib due to bleeding events, hypertension, or atrial fibrillation. The incidence of side effects generally decreased over time. According to the authors' conclusion, these long-term data support the positive phase III results obtained with acalabrutinib in treatment-naïve patients with CLL.

CLL14: fixed-duration venetoclax/obinutuzumab

With the advent of new targeted agents, there is increasing desire for time-limited treatment options. The open-label, randomized, phase III CLL14 trial assessed a fixed-duration approach in previously untreated patients with CLL and coexisting medical conditions. They were randomized to either the orally available BCL-2 inhibitor venetoclax plus obinutuzumab for 6 cycles followed by venetoclax for another 6 cycles or chlorambucil plus obinutuzumab followed by chlorambucil for the same number of cycles. Eligibility criteria included Cumulative Illness Rating scale (CIRS) scores > 6 (indicating clinically relevant burden of coexisting conditions) and/or creatinine clearance < 70 mL/min. In each arm, 216 patients were treated. A considerable fraction showed an unfavorable molecular setup including unmutated *IGHV* status (approximately 60 % in both arms) and deleted and/or mutated *TP53* (14 % each). For

PFS, which was defined as the primary endpoint, the primary analysis yielded a significant 65 % risk reduction with the venetoclax-based regimen (HR, 0.35; $p < 0.001$) [7].

Al-Sawaf et al. reported updated results of the CLL14 study at the EHA Congress [8]. More than 2 years after treatment cessation, after a follow-up of 39.6 months, the reduction in the risk of progression and death in the experimental arm had risen to 69 % (not reached vs. 35.6 months; HR, 0.31; $p < 0.0001$). At 3 years, 81.9 % vs. 49.5 % of patients were progression-free. Venetoclax/obinutuzumab was superior to chlorambucil/obinutuzumab in the subgroup of patients with *TP53* aberrations, although *TP53* still remained a prognostic factor. Patients with both mutated and unmutated *IGHV* status definitely derived greater benefit from the venetoclax-based regimen than from the chlorambucil combination. Time to next treatment was considerably longer in the experimental arm, with 3-year rates of 84.5 % vs. 72.1 % (HR, 0.51), which implies long-term disease control. Correspondingly, approximately half of venetoclax-treated patients maintained undetectable minimal residual disease (uMRD) 18 months after treatment cessation (47.2 %), while this was only the case in 7.4 % in the chlorambucil arm (**Figure 2**).

With regard to safety, the analysis showed that AEs subsided after cessation of therapy. However, the post-treatment rate of second primary malignancies was higher in the experimental arm (6.4 % vs. 1.9 %). This difference was mainly driven by solid organ tumors, with no clear pattern of neoplasms occurring more often in venetoclax-treated patients. Further follow-up is warranted here as the clinical signifi-

cance of this observation is currently unknown. The investigators noted that the updated results of the CLL14 study confirm the indication of venetoclax/obinutuzumab in patients with previously untreated CLL.

CAPTIVATE: MRD outcomes with ibrutinib/venetoclax

The multicenter, single-arm, phase II CAPTIVATE study evaluated the combination of ibrutinib and venetoclax to assess the depth of the MRD response in the first-line treatment of CLL/SLL. Two cohorts (MRD and Fixed Duration) have been implemented in this trial. The MRD Cohort received an ibrutinib lead-in followed by 12 cycles of ibrutinib plus venetoclax prior to restaging and MRD-guided randomization. Here, patients with confirmed uMRD were randomized to either ibrutinib or placebo, while those without confirmed uMRD received either ibrutinib alone or ibrutinib plus venetoclax. At the EHA Congress, Siddiqi et al. presented the pre-randomization results for the MRD Cohort ($n = 164$) [9]. Considerable proportions of patients had poor-risk features such as 17p deletion, complex karyotype and unmutated *IGHV*. Ninety percent completed all 12 cycles of ibrutinib/venetoclax.

Three cycles of ibrutinib lead-in already induced tumor debulking and reduced the risk of tumor lysis syndrome (TLS). Among patients with high baseline TLS risk, 90 % shifted to medium or low risk. Ibrutinib plus venetoclax gave rise to high rates of uMRD in both peripheral blood and bone marrow (75 % and 72 %, respectively). This was achieved irrespective of baseline disease risk characteristics such as the presence of 17p deletion or *TP53* mutation. The proportion of patients with uMRD in the blood increased over time. ORR resulted in 97 % of patients, with CR or CR with incomplete bone marrow recovery (CRi) in 51 %. The group obtaining CR achieved uMRD in the blood and marrow in 85 % and 80 %, respectively.

AEs with ibrutinib/venetoclax were mostly grade 1/2 events. Among grade 3/4 events, neutropenia (35 %), hypertension (7 %), thrombocytopenia (5 %) and diarrhea (5 %) prevailed. No patient developed clinical TLS. The rates of grade 3 atrial fibrillation, major hemorrhage, infections, febrile neutropenia,

and laboratory TLS were low. Only 5 % discontinued treatment due to AEs. At present, the post-randomization follow-up is ongoing, and PFS data will be reported at future meetings.

GIVE: response-adapted treatment for up to 15 cycles

In patients with CLL and high-risk genetic aberrations such as 17p deletion or *TP53* mutation, clinical outcomes are still inferior, even with novel agents [10, 11]. Therefore, the multicenter, open-label phase II CLL2-GIVE trial is investigating the triple combination regimen of obinutuzumab, ibrutinib and venetoclax (GIVE) as first-line therapy in 41 patients with 17p deletion and/or *TP53* mutation [12]. Patients received obinutuzumab for six 28-day cycles during the induction phase. Venetoclax was started on day 22 of cycle 1 and continued for up to 12 cycles throughout the induction and consolidation periods. The ibrutinib treatment covered the longest period, with 12 cycles of induction and consolidation followed by maintenance until cycle 36. However, if uMRD ($< 10^{-4}$) was observed after both cycles 9 and 12 and CR/CRi was confirmed, the treatment was discontinued at cycle 15. Almost 90 % of patients belonged to the very high CLL-IPI risk group. The TLS risk was increased in 95 %.

In cycles 9 and 12, 87.8 % of patients had uMRD in the peripheral blood. At cycle 15, uMRD was present in the blood and bone marrow in 80.4 % and 68.3 %, respectively. The CR rate at cycle 15 was defined as the primary endpoint;

here, 58.5 % of patients showed CR or CRi. PR was achieved in 34.2 %. Among patients with CR/CRi, 95.8 % had uMRD in the blood, with no MRD-positive case. The bone marrow analysis demonstrated uMRD in 87.5 % and MRD-positivity in 4.2 %. In comparison, the percentages of patients with uMRD were considerably lower in the group that only achieved PR.

Overall, the safety profile was acceptable. Grade ≥ 3 neutropenia occurred in 43.9 %, and grade ≥ 3 infections and infestations were observed in 19.5 %. One patient developed grade 4 cerebral aspergillosis. In their summary, the investigators emphasized that the obinutuzumab/ibrutinib/venetoclax triple combination is a promising first-line regimen for patients with high-risk CLL. The response rates are encouraging, although some high-grade infections have raised concerns.

Zanubrutinib, obinutuzumab & venetoclax

Another trial using a time-limited, MRD-driven chemotherapy-free triple regimen investigated the use of obinutuzumab, venetoclax and the second-generation BTK inhibitor zanubrutinib in the first-line setting [13]. Given its improved off-target tyrosine kinase inhibition profile [14, 15] and 100 % BTK occupancy in lymphoid tissue [16], zanubrutinib appears to be a favorable combination partner of anti-CD20 therapy and venetoclax. In the study, this regimen was discontinued if the pre-specified uMRD endpoint was achieved after a minimum of 8 cycles and a maxi-

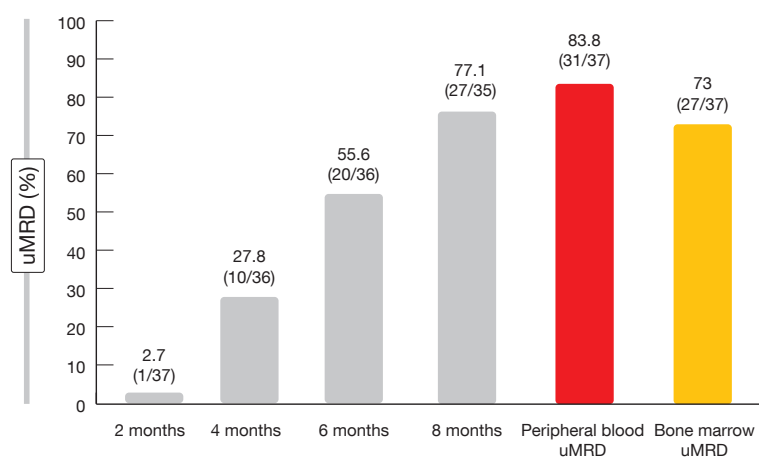


Figure 3: Rapid emergence of undetectable MRD with the triple combination of zanubrutinib, obinutuzumab and venetoclax

mum of 24 cycles. The treatment was discontinued if uMRD was obtained twice in the peripheral blood and once in the bone marrow. Among 39 patients included in the analysis, 72 % had high or very high risk according to CLL-IPI scoring. Unmutated *IGHV* status and *TP53* aberrations were present in 72 % and 15 %, respectively.

A 2-month zanubrutinib/obinutuzumab lead-in preceded the initiation of venetoclax and indeed prevented the occurrence of laboratory or clinical TLS. The uMRD rates increased rapidly over time (**Figure 3**). After a median follow-up of 11 months, a total of 83.8 % and 73 % of patients had achieved uMRD in blood and bone marrow, respectively. Sixty-two percent met the uMRD endpoint and stopped therapy at a median of 8 months. At treatment discontinuation, CR/CRi had been obtained in 57 %, and PR was present in 43 %.

The regimen proved well tolerable, with a low rate of grade 3/4 neutropenia of 15.4 %. Atrial fibrillation occurred in one patient who had a history of paroxysmal atrial fibrillation. The value of MRD-directed treatment duration will be evaluated with continued post-discontinuation follow-up.

Kinetics of response in r/r CLL

Based on the previously published phase II CLARITY trial that investigated ibrutinib plus venetoclax in patients with r/r CLL [17], Rawstron et al. investigated the impact of early MRD clearance on long-term outcomes [18]. Fifty patients after at least one previous therapy were included in the combination part of the study that started after a 2-month ibrutinib lead-in. The duration of the combined administration of ibrutinib and venetoclax was defined by sequential MRD assessments, with treatment being discontinued at certain timepoints once MRD eradication had been achieved. Twelve months was the minimum amount of time on combination treatment. Eventually, the trial was amended to allow for a third year of treatment after the administration of venetoclax had initially been limited to 24 months.

The CR rate improved steadily over time, from 40 % at month 8 to 62 % at month 26. ORRs were 100 % and 90 % at months 8 and 26, respectively. MRD

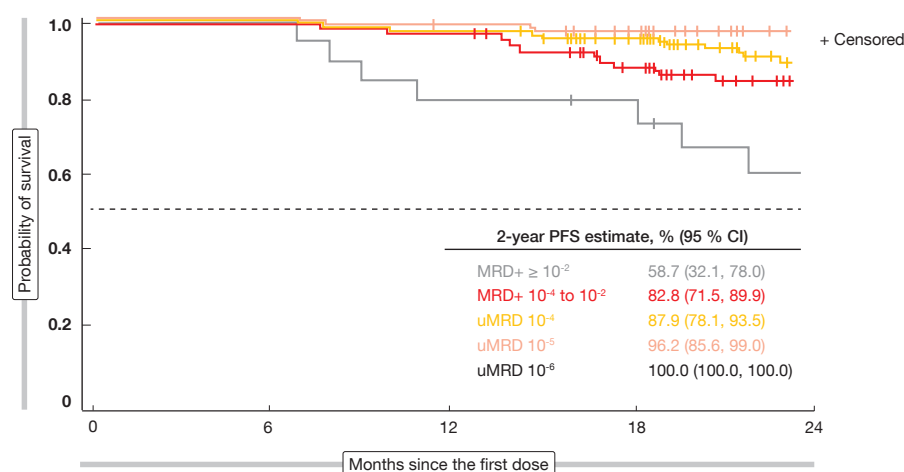


Figure 4: Progression-free survival in patients with relapsed/refractory CLL who were treated with single-agent venetoclax according to their MRD status

eradication (< 0.01 % CLL cells) in the bone marrow after 12 months of combination therapy was defined as the primary endpoint. This was 40 % in all patients. Around month 24, the depth of response appeared to reach its peak and did not change substantially thereafter. The MRD levels in the peripheral blood at 8 months correlated with the marrow MRD response at 14 months.

The initial rate of disease depletion was shown to be highly predictive of longer-term response. Half of patients ($n = 25$) achieved > 2 log depletion in the first 2 months. In this group, the CR rates with MRD < 0.01 % at 14 and 26 months were markedly higher than in patients with < 2 log depletion. Overall, 23 patients stopped treatment because of achieving sustained MRD < 0.01 % in both blood and bone marrow. One year after treatment discontinuation, MRD levels remained undetectable or low in the majority of patients. Fifteen individuals continued to have MRD < 0.01 % in the blood, while 6 had 0.01 % to 1 % and only 2 showed levels > 1 %. These data demonstrated that patients with rapid disease clearance can experience prolonged remission and treatment-free periods. Those who did not achieve rapid depletion and had persistent MRD after 12 months of ibrutinib and venetoclax still showed stable or slowly decreasing disease levels.

Long-term results with venetoclax monotherapy

Single-agent venetoclax has demonstrated deep and durable responses in

patients with r/r CLL, including those with 17p deletion [19, 20]. The phase IIIb VENICE-I trial is the largest multicenter study to evaluate the efficacy of venetoclax monotherapy in relapsed and refractory disease to date. Kater et al. reported efficacy and safety results at 48 weeks at the EHA Congress [21]. A total of 258 patients with and without 17p deletion or *TP53* mutation were included in this trial. Previous B-cell receptor pathway inhibition (BCRi) was permitted.

VENICE-I met its primary endpoint. At week 48, the CR/CRi rate in the BCRi-naïve population ($n = 191$) was 35 %, with an ORR of 85 %. For the total group, these were 33 % and 80 %, respectively. Two-year PFS rates amounted to 79.4 % in the BCRi-naïve population (total group, 77.0 %). Patients who achieved a CR showed a higher 2-year PFS rate than those who obtained PR (95.0 % and 80.9 %, respectively). Moreover, PFS results were more favorable after only one prior treatment line (82.6 % at 2 years) than after ≥ 3 lines (68.9 %). Exploratory PFS was assessed for patients with prior ibrutinib failure; here, patients who had discontinued this treatment due to toxicity showed a considerably higher 2-year PFS rate than those who had experienced progression on ibrutinib therapy (76.2 % and 48.7 %, respectively).

The rates and depth of MRD responses increased over time. uMRD $< 10^{-4}$ plus $< 10^{-5}$ was present in 25 % in the total population at week 24. Another 24 weeks later, 33 % had at least 10^{-4} , with 5 % even showing $< 10^{-6}$. Although the study was not powered to assess changes in MRD, the analyses indicated

that deeper responses correlate with, and might be predictive of, longer PFS. In patients who achieved uMRD 10^{-6} , the 2-year PFS rate was 100 %, while it was only 58.7 % in the group with MRD

$\geq 10^{-2}$ (**Figure 4**). The study revealed no new safety signals. In 14.3 %, discontinuation was due to AEs. No clinical cases of TLS occurred. As the authors noted, VENICE-I confirms that venetoclax

monotherapy can achieve deep and durable responses and has a tolerable and manageable safety profile in patients with r/r CLL. ■

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Changing paradigms in the management of mantle cell lymphoma

Mantle cell lymphoma (MCL) is a rare, heterogenous and generally aggressive subtype of B-cell non-Hodgkin lymphoma that remains incurable in the majority of cases. Median survival in non-trial patients has been estimated at 3 to 5 years [1]. First-line therapy usually consists of chemoimmunotherapy, while both immunochemotherapy and targeted agents are recommended in relapsed disease [2]. However, trials increasingly challenge the role of chemotherapy against the novel agents, especially in the front-line setting.

OAsis: venetoclax, ibrutinib and obinutuzumab

Venetoclax combined with ibrutinib and obinutuzumab was assessed in the

phase I/II, non-randomized OAsis trial that included patients with newly diagnosed and relapsed/refractory MCL. Le Gouill et al. reported the results for 15 untreated patients enrolled in Cohort C [3]. The treatment schedule was ibrutinib 560 mg once daily until progression, obinutuzumab 1 g administered on days 1, 8 and 15 of cycle 1 and on day 1 thereafter (from cycle 8, it was given every 2 cycles), and venetoclax 400 mg daily after dose ramp-up in cycle 2. Treatment duration for both obinutuzumab and venetoclax was limited to 2 years. A considerable proportion of patients in this small cohort had high-risk cytogenetics such as *TP53* mutation or 17p deletion.

The triple combination was generally well tolerated, with most AEs from cycle

1 to 6 being grades 1 and 2. Complete remissions emerged early; after 2 cycles, 53 % of patients achieved CR or unconfirmed CR according to the Cheson 99 criteria. At cycle 6, this was 80 %, and the ORR was 93 %. All patients evaluable for MRD (n = 12) obtained MRD negativity in the peripheral blood at cycle 3 and remained MRD-negative in both blood and bone marrow at the end of cycle 6. After a follow-up of 14 months, 14 patients remained in CR and on treatment. The 1-year PFS rate was 93.3 %, and all patients were alive at 2 years.

Although only a small cohort was assessed, the high complete response rate reported compares favorably even to standard immunochemotherapy induction and provides further evidence of the high potency of venetoclax/ibruti-

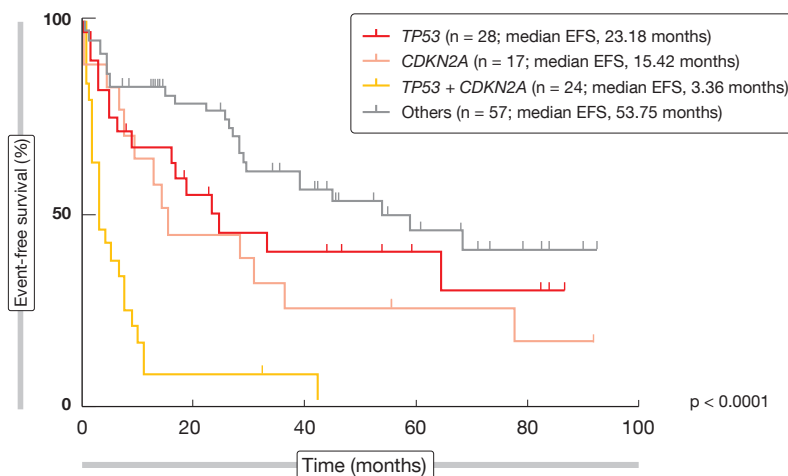


Figure: Shortest event-free survival in patients showing both *TP53* aberrations and deletion of *CDKN2A*

nib-based combinations in MCL. The MRD negativity rates, which compare favorably to those observed in the relapsed setting, suggest that the treatment may be most beneficial when given upfront. According to the authors' conclusion, the ibrutinib/obinutuzumab/venetoclax triple therapy is a highly attractive option for untreated MCL patients regardless of age and deserves to be investigated in a larger trial. The OAsis II study assessing venetoclax, ibrutinib plus an anti-CD20 antibody compared to ibrutinib plus an anti-CD20 antibody in the frontline setting will start in late 2020.

Genetic aberrations as markers of chemoresistance

MCL typically involves a large number of recurrent molecular aberrations. Given the lack of reliable markers of chemoresistance at the time of diagnosis, Malarikova et al. evaluated the prognostic impact of 7 recurrent gene aberrations (*TP53*, *CDKN2A*, *ATM*, *BCL2*, *MYC*, *RB1* and *CDK4*) in a real-world cohort of 126 newly diagnosed consecutive MCL patients with bone marrow involvement $\geq 5\%$ [4].

The investigators found that the total number of gene aberrations correlated with shorter survival and is therefore a strong predictor of outcome. Here, the largest difference was seen between any two aberrations and any isolated aberration. *CDKN2A* deletion was observed exclusively in the context of other aberrations, which suggests that it represents a later event. Concurrent deletion and/or mutation of *TP53* and deletion

of *CDKN2A* represented the most significant predictor of short event-free survival (**Figure**) and OS. The investigators noted that concurrent aberration of *TP53* and *CDKN2A* is a new, simple and relevant index of chemoresistance in MCL. These patients should be offered innovative anti-lymphoma therapy and upfront consolidation with allogeneic stem cell transplantation.

Real-world evidence for ibrutinib

In the relapsed setting, the role of novel agents, especially BTK inhibitors, is increasingly being established [1]. Real-world data from a national audit database in the United Kingdom for patients receiving second-line ibrutinib show that this agent is both effective and well tolerated in frail patients unsuitable for most standard frontline immunochemotherapy regimens [5]. All patients re-

ceiving second-line ibrutinib were retrospectively divided into three cohorts using first-line therapy as a surrogate marker for overall fitness.

In the group treated with less intensive regimens (i.e., rituximab plus chlorambucil) prior to ibrutinib, second-line ibrutinib gave rise to a median PFS of 9.8 months compared to the median PFS with frontline therapy of only 4.0 months. The median OS from the start of ibrutinib was 10.7 months. Seventy-one percent of these patients responded, and almost 10 % obtained CR. Ibrutinib was generally well tolerated in the cohort of frail patients, and disease progression constituted the most common reason for treatment discontinuation. The more durable responses observed with second-line ibrutinib suggest that this patient group may benefit from frontline BTK inhibitor therapy, and further exploration in clinical trials is warranted.

Zanubrutinib in the second and later lines

The specific, potent next-generation BTK inhibitor zanubrutinib has shown complete and sustained 24-hour BTK occupancy in both blood and lymph node biopsies and elicits durable responses in patients with non-Hodgkin lymphoma including MCL [6, 7]. A phase II study showed an ORR of 84 % in zanubrutinib-treated patients with relapsed/refractory MCL, with 78 % obtaining complete remissions [7]. At EHA 2020, Zhou et al. presented pooled clinical outcomes in patients with relapsed/refractory MCL who received zanubru-

TABLE

Clinical outcomes at 6 and 12 months with zanubrutinib in patients with relapsed/refractory MCL in the second line (Arm A) and later lines (Arm B)

	Arm A	Arm B	Total
Response rates			
At 6 months, %	92.3	83.6	86.9
At 12 months, %	81.8	74.7	77.4
Progression-free survival			
At 6 months, %	89.0	76.2	80.9
At 12 months, %	82.5	66.4	72.3
Overall survival			
At 6 months, %	96.2	92.1	93.6
At 12 months, %	87.5	83.6	85.0

tinib in phase I (NCT02343120) and phase II (NCT03206970) trials [8]. Forty-one and 71 patients were treated in the second-line (Arm A) and later-line (Arm B) settings, respectively. Imbalances in baseline characteristics between groups with different prior lines of therapy were adjusted using inverse propensity score weighting.

Complete responses occurred significantly more often in Arm A than in Arm B (74.6 % vs. 61.1 %). The adjusted odds of achieving CR when treated with zanubrutinib in the second line were 3.4 times as high as in later lines. Likewise, Arm A fared better with respect to duration of response as well as PFS and OS rates at 6 and 12 months (**Table**). In

general, patients in Arm A also showed an improved safety profile of zanubrutinib, particularly regarding AEs of special interest such as diarrhea, major hemorrhage, and atrial fibrillation/flutter. The rates of discontinuation due to AEs were low in both arms. ■

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Targeted approaches in various B-cell malignancies

Zanubrutinib plus rituximab

BTK inhibitors are active in many B-cell malignancies such as mantle cell lymphoma, CLL and Waldenström's macroglobulinemia, but also in diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and marginal zone lymphoma (MZL). Zanubrutinib is currently being assessed in pivotal phase II and III studies in all of these indications. An ongoing, single-arm, multicenter, phase II study is evaluating zanubrutinib plus rituximab in patients with relapsed/refractory non-germinal center B-cell-like (non-GCB) DLBCL (n = 20), FL (n = 16) and MZL (n = 5). While zanubrutinib is administered at a dose of 160 mg twice daily until progression, patients are receiving rituximab 375 mg/m² on days 1, 8, 15 and 22 of cycle 1 and subsequently on day 1 of cycles 4, 6, 8, and 10.

The preliminary results reported by Zhang et al. at the EHA 2020 Congress indicated anti-tumor activity of the combination in all three entities [1]. After a median follow-up of 10.3 months, 34.1 % of patients were still on treatment at data cut-off. Overall response rates were 35.0 %, 56.3 % and 60.0 % for non-GCB

DLBCL, FL, and MZL, respectively (**Table**). In each group, at least one patient achieved complete response. At 12 months, the percentages of event-free patients were 17.4 %, 66.0 % and 75.0 %, respectively. The safety profile observed in this study matched previous results for zanubrutinib. Infections occurred in 34.1 % (grade ≥ 3 events, 9.8 %) and hemorrhage in 26.8 % (no grade ≥ 3 events). As the authors noted, these findings encourage further investigation of the combination of zanubrutinib and anti-CD20 antibodies in FL and MZL and prompted the development of mechanism-based combinations as well as biomarker-driven individualized treatment in patients with non-GCB DLBCL.

Non-GCB DLBCL: biomarker-related outcomes

The non-GCB subtype of DLBCL is associated with poor clinical outcomes [2]. Yang et al. presented data on the activity of zanubrutinib in 121 patients with relapsed/refractory non-GCB DLBCL treated with the BTK inhibitor as monotherapy (n = 79) or in combination with anti-CD20 antibodies (n = 42) in four

clinical studies conducted in the phase I and II settings [3]. Also, results of biomarker identification, which has become the focus of DLBCL research, were reported.

Zanubrutinib alone or combined with an anti-CD20 antibody showed activity in the overall non-GCB DLBCL population. The unadjusted ORR was similar across the four trials, with an average of 30 %. Median PFS ranged from 2.8 to 4.9 months, and median OS ranged from 8.4 to 11.8 months. According to the retrospective biomarker analysis, certain subsets of patients derived greater benefit from the treatment. In the group of 56 patients for whom HTG gene expression profiles were established, *PAX5* expression was higher in monotherapy responders than in non-responders. Likewise, *PIM1*, *BCL2*, and *FOXP1* expression was higher in combination therapy responders than in non-responders. In the group with NGS panel data, those with *CD79B* mutations (n = 25) showed significantly higher ORR than patients without these mutations (n = 52) according to the pooled analysis (60 % vs. 26.9 %; p = 0.005).

TABLE

Outcomes obtained with zanubrutinib and rituximab in patients with relapsed/refractory non-germinal center B-cell-like diffuse large B-cell lymphoma (non-GCB DLBCL), follicular lymphoma (FL), and marginal zone lymphoma (MZL)

	Non-GCB DLBCL (n = 20)	FL (n = 16)	MZL (n = 5)
Best overall response rate, n (%)			
Complete response	1 (5.0)	3 (18.8)	1 (20.0)
Partial response	6 (30.0)	6 (37.5)	2 (40.0)
Stable disease	4 (20.0)	5 (31.3)	2 (40.0)
Progressive disease	6 (30.0)	0 (0.0)	0 (0.0)
Discontinued prior to the first tumor assessment	3 (15.0)	2 (12.5)	0 (0.0)
Overall response rate, n (%)	7 (35.0)	9 (56.3)	3 (60.0)
Duration of response, months	8.79	Not estimable	Not estimable
Progression-free survival, months	3.38	Not estimable	Not estimable
12-month event free rate, %	17.4	66.0	75.0

Durable responses in marginal zone lymphoma

Compared with chemotherapy-based approaches, BTK inhibitors have shown improved efficacy and tolerability in MZL [4]. Clinical evidence in this field was generated by the first-in-human, open-label, multicenter, phase I/II AU-003 trial assessing the efficacy and safety of single-agent zanubrutinib [5]. AU-003 included a total of 384 patients with B-cell malignancies 20 of whom had relapsed/refractory MZL.

After a median follow-up of 27.1 months, zanubrutinib elicited durable responses in the MZL subgroup. Here, the ORR was 80 %, with 15 % and 65 % of patients obtaining CR and PR, respectively. At 18 months, 66.2 % were still responding to treatment. PFS and OS rates at 24 months amounted to 59.4 % and 83.2 %, respectively. Median PFS had not been reached yet.

Responses emerged in all MZL subtypes; for the extranodal, nodal and splenic types, ORRs were 77.8 %, 100 % and 66.7 %. The zanubrutinib therapy demonstrated a favorable safety profile. One patient discontinued treatment due to an AE. Among AEs of interest, infections occurred most commonly, whereas no patient experienced atrial fibrillation or flutter.

Safety of acalabrutinib in a range of entities

Furman et al. provided an overall summary of the safety profile of acalabrutinib

when used as monotherapy in various mature B-cell malignancies [6]. The authors analyzed pooled data from nine clinical studies investigating acalabrutinib in patients with CLL/SLL, prolymphocytic leukemia, Richter transformation, mantle cell lymphoma, Waldenström's macroglobulinemia, activated B-cell-like subtype of DLBCL, FL, and multiple myeloma. In these studies, acalabrutinib was administered orally once or twice daily until progression, at total daily doses of 100 mg to 400 mg. Most patients received acalabrutinib 100 mg twice daily. Among the 1,040 included patients, 366 (35 %) were treatment-naïve, while 674 (65 %) had relapsed or refractory disease.

At the time of the analysis, the median follow-up was 26.4 months, and 65 % of patients remained on acalabrutinib treatment at data cut-off. In those who had discontinued treatment, progression was the most common reason. The median relative dose intensity was 98.7 %. Among AEs, headache and diarrhea occurred most frequently and were predominantly grade 1 and 2. Grade ≥ 3 AEs mainly included neutropenia (11.2 %), anemia (7.8 %), and pneumonia (5.1 %). AEs led to dose modifications, dose delays and treatment discontinuation in 4 %, 38 % and 9 %, respectively. Most events of clinical interest such as atrial fibrillation and hypertension were low-grade and infrequent. Twelve percent of patients developed second primary malignancies, primarily non-melanoma skin cancer. Overall, these results support the

long-term safety of acalabrutinib in various B-cell malignancies including relapsed/refractory mantle cell lymphoma and CLL.

Polatuzumab/obinutuzumab/venetoclax

Induction treatment with the antibody-drug conjugate polatuzumab in combination with obinutuzumab and venetoclax was tested in the setting of relapsed/refractory FL. At the EHA Congress, Yuen et al. reported a pre-planned interim analysis of this phase Ib/II trial [7]. Complete response at the end of induction (EOI) was defined as the primary efficacy endpoint. The dose escalation and dose expansion populations comprised 33 and 38 individuals, respectively. At the time of the interim analysis, 15 patients had completed induction and constituted the efficacy-evaluable population.

Polatuzumab plus obinutuzumab and venetoclax showed promising activity. Eighty-seven percent of patients responded at EOI, and 60 % of these were complete responders. The triple combination proved tolerable, with the safety profile being consistent with the known profiles of the individual drugs. Infections, diarrhea, nausea, neutropenia and fatigue occurred most commonly. AEs were manageable with supportive care. Treatment discontinuations due to AEs occurred in 14 %, dose delays/interruptions in 54 % and dose reductions in 32 %. Meanwhile, enrollment has been completed for the phase II expansion

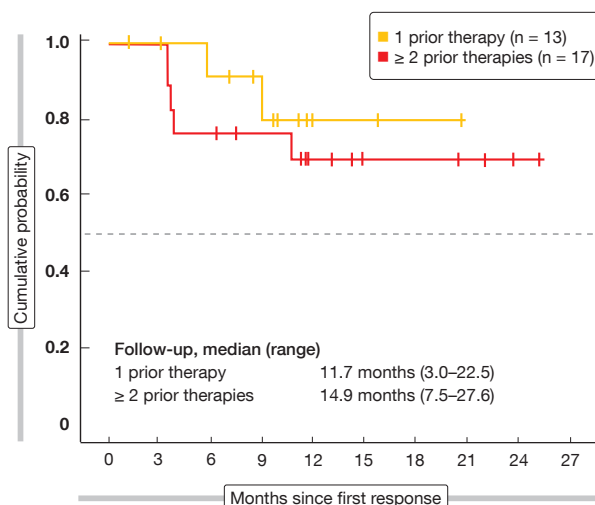


Figure: Duration of response with the PI3K δ inhibitor ME-401 according to the line of treatment

(n = 40), and the results will be presented at a future meeting.

Findings with the PI3K δ inhibitor ME-401

Pagel et al. sought to determine the efficacy and safety of the novel oral PI3K δ inhibitor ME-401 in patients with relapsed/refractory FL and other B-cell malignancies [8]. ME-401 has been developed to fulfill the criteria of optimal

pharmaceutical properties, such as long half-life and high potency. An intermittent schedule has been evaluated as a strategy to mitigate delayed immune-related toxicities associated with the continuous daily delivery of oral PI3K inhibitors; here, daily dosing in cycles 1 and 2 is followed by daily dosing for 1 week and treatment interruption for 3 weeks in later cycles. ME-401 was tested using the intermittent schedule in a phase Ib, single-arm, dose-escalation/

dose-expansion study. Overall, 57 patients were recruited. Two treatment groups received either ME-401 60 mg daily as monotherapy or 60 mg daily in combination with 4 doses of rituximab 375 mg/m² weekly followed by 4 doses on day 1 of cycles 3 to 6.

ME-401 gave rise to high ORR in patients with FL (83 %) and CLL/SLL (89 %). CRs were achieved in 22 % and 11 %, respectively. In the FL setting, median duration of response had not been reached after a follow-up of 13.2 months. Durable responses were achieved here irrespective of prior lines of therapy (**Figure**), treatment group (15.4 vs. 12.8 months with ME-401 monotherapy and ME-401 plus rituximab, respectively), and tumor bulk (12.5 vs. 13.3 months for ≥ 5 cm and < 5 cm, respectively).

Grade ≥ 3 AEs of special interest occurred infrequently and were restricted to the first two cycles. Treatment was discontinued due to AEs in 7 %. The evaluation of ME-401 on the intermittent schedule as a single-agent as well as in combination regimens is ongoing. TIDAL, a global phase II trial assessing ME-401 monotherapy on the intermittent schedule in pretreated FL patients, is currently enrolling. ■

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Paroxysmal nocturnal hemoglobinuria: improving outcomes with novel strategies

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, potentially life-threatening clonal hematopoietic stem cell disorder characterized by hemolytic anemia, bone marrow failure, thrombosis, and peripheral blood cytopenia. The

disease results from an acquired loss-of-function mutation of the *PIGA* gene involved in the synthesis of the glycosylphosphatidylinositol-anchored complement inhibitors CD55 and CD59 [1–4]. The absence of these proteins

leads to uncontrolled activation of the terminal complement pathway and complement-mediated lysis of erythrocytes. PNH is associated with a high burden of disease and impaired health-related quality of life [4].

Treatment options for hemolytic PNH remained limited until the monoclonal antibody eculizumab became available. Eculizumab is administered intravenously; this agent targets the component 5 (C5) of the complement cascade, thereby preventing intravascular hemolysis [5, 6]. However, only one third of PNH patients was shown to achieve complete normalization of hemoglobin levels with eculizumab treatment [7]. Many continue to experience some degree of anemia, in some cases requiring regular red blood cell transfusions. Factors contributing to residual anemia include underlying bone marrow dysfunction, residual intravascular hemolysis, and the emergence of C3-mediated extravascular hemolysis, which is not improved by C5 inhibitors such as eculizumab [8]. Therefore, novel anti-complement treatment approaches focus on some of these mechanisms. Strategies that are being investigated in the setting of proximal complement inhibition include agents directed against C3 as well as factors D and B that are involved in the formation of the alternative pathway C3 convertase.

PEGASUS: pegcetacoplan induces hemoglobin increase

The investigational compound pegcetacoplan is a subcutaneously administered C3 inhibitor that has the potential to control both intra- and extravascular hemolysis in PNH [9]. Pegcetacoplan monotherapy was assessed in the randomized, open-label, controlled, phase III PEGASUS trial that included PNH patients who had been on eculizumab

treatment for ≥ 6 months but still showed hemoglobin levels < 10.5 g/dL [10]. During the 4-week run-in period, all patients received pegcetacoplan 1,080 mg twice weekly in addition to the eculizumab standard dose. Subsequently, they were randomized to either pegcetacoplan 1,080 mg twice weekly ($n = 41$) or their current dose regimen of eculizumab ($n = 39$). The primary endpoint of the study was the change in hemoglobin from baseline level to week 16. At that time, the control patients crossed over and the entire population continued single-agent pegcetacoplan therapy for a 32-week open-label period.

The experimental treatment resulted in a highly significant improvement in hemoglobin levels compared to the standard of care, with an adjusted treatment difference of 3.84 g/dL ($p < 0.0001$). Baseline hemoglobin had been 8.7 g/dL in both groups; while this increased by 2.37 g/dL with pegcetacoplan, it further decreased by 1.47 g/dL in the eculizumab-treated group. This effect was observed irrespective of transfusion history (< 4 vs. ≥ 4 transfusion events). The Kaplan-Meier estimate shows that the increase was achieved during the run-in period and maintained in the pegcetacoplan arm, whereas it was lost again in the control patients whose hemoglobin levels returned to the baseline values within 4 weeks after randomization (Figure 1).

Benefits regarding secondary outcomes

With respect to the key secondary endpoint of transfusion avoidance, the anal-

ysis yielded an adjusted risk difference of 62.5 % favoring pegcetacoplan (85.4 % vs. 15.4 %). This benefit was particularly pronounced in patients who had a history of high transfusion requirements (85.7 % vs. 4.3 %), but also emerged in those with low numbers of transfusions (85.0 % vs. 31.3 %). Reticulocyte counts decreased with pegcetacoplan treatment by $136 \times 10^9/L$ but increased with eculizumab by $28 \times 10^9/L$, resulting in a significant difference of $164 \times 10^9/L$. According to the sensitivity analysis without censoring for transfusion, normal ranges were restored for lactate dehydrogenase (LDH) levels, reticulocyte counts and bilirubin levels with pegcetacoplan, while eculizumab hardly affected these outcomes. Normalization regarding hemoglobin levels was achieved in 34 % vs. 0 %; for LDH levels, this was 70.7 % vs. 15.4 %, and for reticulocytes, 78 % vs. 2.6 %. Patients in the experimental arm also had less fatigue as assessed by the FACIT-Fatigue score throughout the study. Here, 73.2 % showed improvement of ≥ 3 points from baseline, whereas none did with eculizumab.

Adverse events were mainly mild or moderate. Among AEs of interest, injection site reactions occurred most frequently (36.6 % vs. 2.6 % with pegcetacoplan and eculizumab, respectively), although the majority of events were mild and restricted to the initial treatment period. Discontinuations due to breakthrough hemolysis were seen in 3 patients in the experimental arm; 2 of these had lower than expected serum concentrations of pegcetacoplan prior to the events, and neither patient increased dosing to 1,080 mg every 3 days prior to treatment discontinuation. Overall, the PEGASUS results highlighted the ability of pegcetacoplan to control both intravascular and extravascular hemolysis in patients with PNH, leading to a potential new treatment option.

Age-related activity of eculizumab

Lee et al. presented an analysis evaluating the clinical outcomes obtained with eculizumab in patients aged ≥ 65 years included in the International PNH Registry [11]. This registry is an ongoing, prospective, international study on the natural history of PNH and the long-term efficacy and safety of eculizumab.

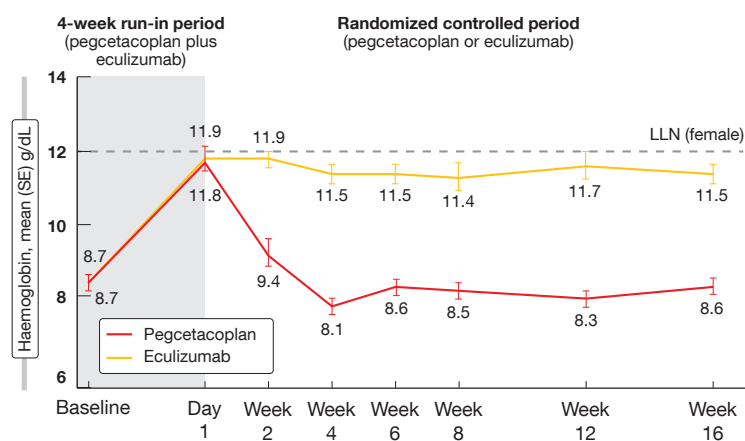


Figure 1: PEGASUS: hemoglobin increase is maintained with pegcetacoplan therapy but lost with eculizumab after randomization

Adult patients (aged 18-64 years, $n = 1,537$) were compared with advanced-age patients ($n = 270$) enrolled in the registry.

The results suggested age-independent efficacy of eculizumab in terms of reduction of intravascular hemolysis, obtaining transfusion independence, and prevention of thrombotic events and major adverse vascular events. Both patients in the adult and advanced-age cohorts achieved substantial reductions in the LDH ratio from more than 5 times the upper limit of normal (ULN) at baseline to normal or near normal range at last follow-up. Transfusion independence was achieved by approximately one third in both groups (35.9 % vs. 31.2 %). Also, changes in the proportions of patients with physician-reported PNH-related symptoms (e.g. abdominal pain, dysphagia, dyspnea) were comparable. However, younger patients showed significantly higher increases in hemoglobin levels from baseline to last follow-up (1.4 g/dL vs. 0.4 g/dL; $p < 0.0001$). Major vascular events occurred significantly more frequently in the advanced-age cohort, although both cohorts experienced similar changes from baseline to last follow-up regarding this outcome.

Infections occurred at low and comparable rates across cohorts. A larger proportion of patients in the advanced-age group died, although these deaths were generally unrelated to treatment with eculizumab. The authors concluded that eculizumab is effective and well tolerated as treatment of PNH in patients of advanced age in a real-world setting.

Danicopan: effect on transfusion requirements

The orally available factor D inhibitor danicopan blocks C3 convertase formation, thus potentially controlling both intra- and extravascular hemolysis. A phase II dose-finding, proof-of-concept trial tested the addition of danicopan to the current eculizumab regimen in PNH patients with an inadequate response to eculizumab who were transfusion-dependent. Eleven of 12 patients who completed treatment achieved clinically meaningful improvements in hemoglobin levels, transfusion needs, and other parameters [12].

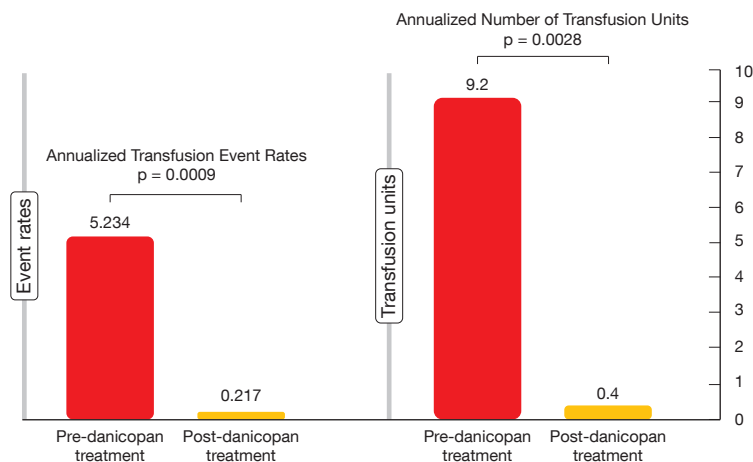


Figure 2: Impact of danicopan treatment on annualized transfusion requirements

A post-hoc analysis of this study presented at EHA 2020 evaluated the impact of the addition of danicopan on transfusion requirements [13]. In the course of 24 weeks, the hemoglobin level increased from 7.9 g/dL to 10.3 g/dL, and the transfusion frequency showed a highly statistically significant 95.8 % reduction ($p = 0.0009$; **Figure 2**). This also applied to the number of transfused red cell units ($p = 0.0028$). As the authors noted, the added benefit is likely due to the prevention of C3-mediated extravascular hemolysis. Danicopan was generally well tolerated. Almost all treatment-emergent AEs were mild or moderate except for one case of breakthrough hemolysis and a case of severe pneumonia in a patient who had a history of neutropenia.

Long-acting formulation of ravulizumab

Ravulizumab, a C5 inhibitor designed for intravenous application, is an emerging standard of care for patients with PNH in countries where it has been approved. The long duration of action of this agent enables a decreased infusion frequency with dosing intervals of 8 weeks. Ravulizumab 100 mg/mL has demonstrated efficacy and safety in two large phase III trials [14, 15]. An open-label, phase II study assessed multiple ascending doses of ravulizumab in complement-inhibitor-naïve patients with PNH based on the observation that the 100 mg/mL formulation decreases the dose infusion time by 78-102 minutes compared with the 10 mg/mL formulation. Twenty-five patients were divided

into 4 cohorts that received ravulizumab maintenance doses of 1,000 mg/4 weeks, 1,600 mg/6 weeks, 2,400 mg/8 weeks, or 5,400 mg/12 weeks. After the initial treatment period, cohorts 1-3 began weight-based dosing regimens during the extension period, which is ongoing. All cohorts started on ravulizumab 10 mg/mL and switched to 100 mg/mL during the extension period.

The interim analysis showed similar efficacy, safety, pharmacokinetics, and immunogenicity of ravulizumab 100 mg/mL compared to the 10 mg/mL formulation [16]. LDH levels did not change significantly after the switch in all cohorts. Treatment-emergent AEs were consistent with the established safety profile of ravulizumab 10 mg/mL. No toxicities necessitated treatment discontinuation or interruption. Also, serum trough concentrations did not differ in a meaningful manner after the switch, and neither formulation gave rise to anti-drug-antibody responses. Compared with the 10 mg/mL formulation, the infusion times were reduced by 78-102 minutes. The investigators concluded that ravulizumab 100 mg/mL provides a reduction in infusion time of 60 % to 77 % while maintaining efficacy, thus reducing the treatment burden for patients, their caregivers, and healthcare providers.

Novel C5 inhibitor pozelimab

An ongoing, open-label, single-arm, phase II study is assessing the C5 inhibitor pozelimab in patients with active PNH who are treatment-naïve to complement inhibitor therapy or have not recently received complement inhibition [17]. Poze-

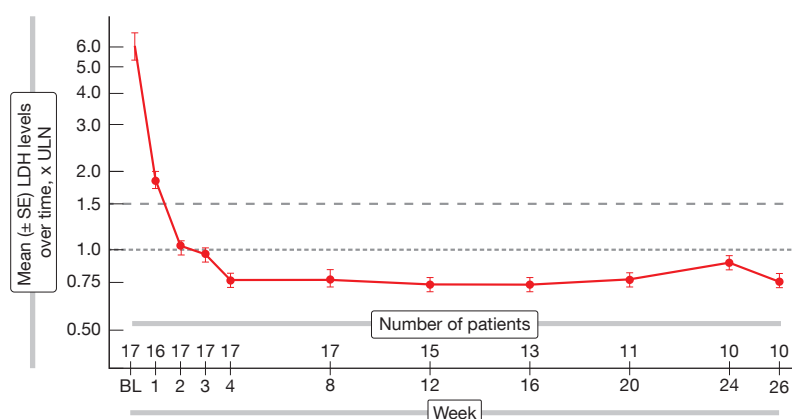


Figure 3: Rapid and sustained reduction of the LDH levels with pozelimab

limab is administered subcutaneously once weekly for 26 weeks. An interim analysis including 17 patients demonstrated that pozelimab led to rapid and durable LDH responses (**Figure 3**). All patients achieved reductions to below the

clinically significant threshold of $\leq 1.5 \times \text{ULN}$ that were sustained until study day 183. At week 2, 16 individuals achieved control of intravascular hemolysis ($\text{LDH}, \leq 1.5 \times \text{ULN}$), and at week 4, normalization of LDH levels ($\leq 1.0 \times \text{ULN}$)

was observed in all but one patient. Importantly, one patient who is a carrier of a C5 variant known to be resistant to blockade by eculizumab/ravulizumab showed rapid and sustained normalization of LDH. Hemoglobin levels increased over 26 weeks, which was mirrored by improvement of the FACIT-Fatigue score. Pozelimab was well tolerated. No serious AEs, AEs leading to treatment discontinuation, or breakthrough hemolysis events occurred. Headache and nausea were reported as the most common AEs.

According to the investigators, these interim data support the continued development of pozelimab for the treatment of patients with PNH and potentially other complement-mediated diseases. The findings indicated that a subcutaneous regimen might provide an alternative to currently available intravenous regimens. ■

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Cold agglutinin disease: on the road to new insights and potential treatment options

Cold agglutinin disease (CAD) is a rare type of autoimmune hemolytic anemia (AIHA) elicited by cold-sensitive antibodies including cold agglutinins. Ninety percent of cold agglutinins be-

long to the IgM kappa category and bind to red blood cell surface antigens at temperatures of $\leq 37^\circ\text{C}$, thus inducing hemolysis [1-3]. CAD accounts for approximately 25 % of AIHA cases, with an

incidence and prevalence of 1 case per million persons per year and 16 cases per million persons, respectively [4, 5].

The primary type of this disease is a chronic condition usually associated

with low-grade lymphoproliferation and is typically found in older adults (median age of onset, 67 years) [4, 5]. Secondary CAD is termed cold agglutinin syndrome (CAS) and arises based on underlying conditions such as malignancies or acute infections [5, 6]. An associated disorder is mixed warm and cold antibody AIHA [5].

Patients affected by CAD show a high burden of disease. IgM-antigen complexes activate complement-dependent extravascular and (to a lesser degree) intravascular hemolysis, which leads to anemia and debilitating fatigue [7, 8]. The risk of thromboembolism is increased, and the 5-year mortality is higher than in matched controls [9, 10]. Approved treatments for CAD are still lacking. Current approaches such as B-cell-directed therapies and chemotherapies elicit only poor response rates and can give rise to substantial toxicity [6, 11].

The CADENCE Registry

Given the rarity of CAD, there is a paucity of prospective longitudinal data describing patient and clinical characteristics as well as outcomes. This gap will be filled by the observational, non-interventional, multicenter, prospective, longitudinal CADENCE Registry that was launched in December 2019 [12]. Data from more than 700 adults ≥ 18 years of age with CAD, CAS, or mixed warm and cold antibody AIHA are being collected at 121 sites in 11 countries across the globe including the US, France, UK, Germany, Austria, Japan and Australia. The recruitment period will end in late 2021, and patients will be followed until late 2024.

Objectives of this registry are to better understand patient and clinical characteristics, patterns and use of CAD treatments, long-term clinical outcomes, patient health-related quality of life, and healthcare resource utilization (**Table**). Also, the natural history of CAD including complications and comorbidities will be explored. Interim analyses will be conducted after the enrollment of 100, 250, and 500 patients.

Quality of life data from the Cardinal study

The first-in-class humanized monoclonal anti-C1s antibody sutimlimab is be-

ing investigated for the treatment of patients with CAD. By inhibiting the serine protease C1s of the C1 complex, sutimlimab blocks complement-mediated tissue damage and prevents the long-term activation of autoimmune B cells, as well as the production of autoantibodies [13]. The open-label, single-arm, multicenter, phase III Cardinal study evaluated the efficacy and safety of sutimlimab in CAD patients with baseline hemoglobin levels ≤ 10 g/dL and active hemolysis (i.e., total bilirubin $>$ normal) who had received at least one blood transfusion within 6 months of enrollment. Part A of the trial assessed the efficacy and safety of sutimlimab 6.5 g (body weight < 75 kg) or 7.5 g (≥ 75 kg) intravenously on days 0 and 7 followed by the same doses every 2 weeks for a total of 26 weeks. Part B is an ongoing, long-term extension study.

Health-related quality-of-life outcomes were secondary, exploratory endpoints of the trial. Röth et al. reported the results for this outcome at the EHA Congress 2020 [14]. Measurements included the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale, the 12-Item Short Form Health Survey (SF-12), the EuroQoL (EQ)-5D Index and visual analog scale scores, the Patient Global Impression of Change (PGIC) scale, and the Patient Global Impression

of (Fatigue) Severity (PGIS) scale. The patients ($n = 24$) had a mean age of 71 years and were mainly female (62.5 %). Over the previous 6 months, they had received a mean of 3.2 transfusions. Within the last 5 years, the majority had been treated with at least one targeted CAD therapy. One third had a history of at least one thromboembolic event.

Rapid and durable improvements

Treatment with sutimlimab was shown to give rise to rapid, clinically meaningful improvements in all patient-reported outcome measures evaluated. Almost 90 % of patients achieved clinically meaningful improvement (≥ 3 -point increase) of the FACIT-F score. This change occurred already within a week from the initiation of treatment and was associated with an inhibition of the classical complement pathway as measured by the Wieslab-CP assay and assessment of the C4 levels. Likewise, improvement in the SF-12 scores correlated with near-complete inhibition of the complement pathway and normalization of C4. These observations suggest that in addition to anemia, pathway activation with subsequent hemolysis is a key driver of fatigue and poor quality of life in patients with CAD.

TABLE

Select parameters and data collection schedule for the CADENCE Registry that is prospectively evaluating CAD characteristics and outcomes

Data	Enrollment visit	Follow-up visits	Final study visits
Demographic data	✓		
Diagnosis date	✓		
CAD subtype	✓		
CAD symptoms	✓	✓	
Thromboembolic events	✓	✓	
Other CAD complications (e.g., acute hemolytic crisis, acral gangrene)	✓	✓	
Comorbidities	✓	✓	
Infection testing (e.g., Epstein-Barr virus, cytomegalovirus)	✓	✓	
Transfusions	✓	✓	
CAD treatments	✓	✓	
Vaccines	✓	✓	
Health resource utilization		✓	
Death		✓	✓
Reasons for premature registry discontinuation			✓

Clinically meaningful increases in both the SF-12 physical and mental component scores were observed at week 5 and proved durable. The EQ-5D index and EQ-5D VAS scores increased by 0.074 and 16.8, respectively, until week 26. Improvements were observed for each of the EQ-5D domains; moderate, severe or extreme problems with regard to mobility, self-care, usual activities, pain/discomfort and anxiety/depression decreased in the course of the study. With respect to PGIC, 93.8 % of patients observed global improvement until week 26 (**Figure**). Seventy-five percent noted that their condition had improved much or very much.

Fatigue was mild or moderate in 88.2 % of patients according to PGIS at week 26, with the remaining 11.8 % indicating no change. At baseline, a total

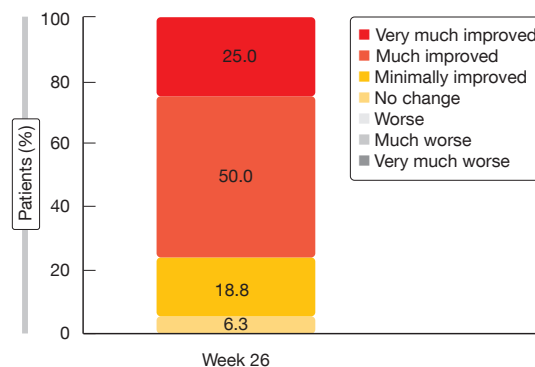


Figure: Patient Global Impression of Change (PGIC): patient-reported results at the end of the 26-week sutimlimab treatment period

of 83.3 % of patients had reported fatigue that had been severe in a third of cases. No patient experienced worsening of their general condition or severe fatigue at the end of treatment. Overall,

these outcomes further support the efficacy of targeting the classical complement pathway in the management of patients with CAD. ■

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Patient and disease characteristics in a small CAD cohort

A retrospective analysis hints at the wide range of cold agglutinin disease (CAD) clinical behavior. Koudouna et al. investigated the characteristics of 8 patients with CAD at the time of diagnosis [1]. Median age was 62 years, and 5 patients were women. Hematologic malignancies constituted 50 % of underlying medical conditions; in 37 %, hepatitis B/C was the associated disease, and in 13 %, autoimmune disorders. The median hemoglobin level at presentation was 8.9 g/dL. Slightly elevated serum CRP and ferritin levels represented common findings. All patients had cold-sensitive antibodies, with one also showing cryoglobu-

lins. Cold agglutinins titers were disproportionate to the degree of hemolysis in 4 patients with underlying lymphoproliferative disorders. Low serum monoclonal IgM prevailed in 4 cases even in the presence of hypogammaglobulinemia. Fatigue dominated among symptoms, followed by hepatomegaly and jaundice, skin complications, and splenomegaly. The patient who had cryoglobulinemia showed skin necrosis due to vascular occlusion.

All patients initially received corticosteroids. Complete or partial responses were observed in 3 patients with primary CAD treated with corticosteroids, splenectomy

and mycophenolate mofetil. Additional approaches included plasma exchange and anti-CD20 therapy. In 5 cases, additional treatment for the underlying disease was administered. During a median follow-up of 42.5 months, 2 patients died from infection and sepsis, while another 2 completely recovered and the remaining patients experienced relapses and remissions.

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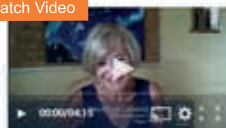
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