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# Editorial Board:

# Preface

**Dear Colleagues,**

The 11th International Workshop on Waldenström's Macroglobulinemia (iwWM), held in Madrid, Spain, and virtually from 27th–30th October 2022, featured 20 sessions with more than 100 presentations.

Until now, primary treatment options for WM included combination strategies with anti-CD20 monoclonal antibodies, chemotherapy, proteasome inhibitors and covalent BTK inhibitors. However, intolerance and acquired resistance – either due to the acquired BTK-C481 mutation or other so far unknown mechanism – are challenging. Following the Workshop's mission to further improve the understanding, diagnosis, treatment, and prevention of disorders affecting the blood, bone marrow, and the immunologic system, by promoting targeted research, clinical care methods, education, training, and advocacy for Waldenström's macroglobulinemia, this memo inHaematology issue looks closely at new covalent, as well as non-covalent BTK inhibitors, BCL2- and CXCR4-antagonists.

Moreover, important genomic approaches, identifying new robust biomarkers and genomically driven algorithms for the treatment of WM are outlined. For instance, the ASPEN biomarker trial demonstrated deeper responses in patients with $CXCR4^{MUT}$ or $TP53^{MUT}$ among patients treated with zanubrutinib compared to ibrutinib.

A range of relevant and potentially practice-changing findings in treatment-naïve, pretreated as well as ibrutinib and/or acalabrutinib intolerant WM patients are described. Data on new covalent BTKi inhibitors tirabrutinib and orelabrutinib are shown. In the relapse/refractory setting, a novel non-covalent, orally administered, potent, irreversible, and highly selective BTKi demonstrated promising efficacy and a manageable safety profile with the potential to become a major therapy option for this patient population.

Long-term follow-up data on ibrutinib or zanubrutinib in treatment-naïve WM patients and on zanubrutinib also in relapsed/refractory WM patients, as well as the treatment efficacy of BTKi versus chemoimmunotherapy, are discussed. Finally, data on the use of venetoclax (anti-BCL2) either alone in pretreated

WM patients or in combination with ibrutinib in treatment naive WM are discussed, highlighting their challenges in WM therapy.

Once again, this year's iwWM workshop highlighted the importance of multidisciplinarity and collaborations, while presenting a range of relevant and potentially practice-changing findings for accelerating the approval of most effective treatments and ultimately finding a cure for Waldenström's macroglobulinemia.

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# New insights into BTKi treatment of Waldenström's macroglobulinemia

## New insights into BTKi treatment of Waldenström's macroglobulinemia

Waldenström's macroglobulinemia (WM) is a low-grade non-Hodgkin B-cell lymphoplasmacytic lymphoma, characterized by the accumulation of clonal lymphoplasmacytic cells secreting monoclonal IgM protein in the bone marrow and other organs [1]. WM is a lymphoma accounting for only 1–2 % of all hematologic tumors, with an annual incidence of three to four cases per million people in the USA and Europe, classifying it as a rare disease [2]. Activating mutations in *MYD88* and *CXCR4* are

common in WM and are found in about 90 % and 40 % of patients, respectively [3, 4]. By promoting the proliferation and survival of malignant B-cells, bruton tyrosine kinase (BTK) is a crucial player in the physiopathology of WM [5, 6] and BTK inhibition has been studied as a potential therapeutic approach. Given the efficacy of BTK inhibitors (BTKi), this therapy has rapidly become a new standard-of-care for WM patients [2, 7].

However, research is moving quite fast with the clinical development of new covalent as well as non-covalent BTK inhibitors, BCL2- and CXCR4-antagonists [8, 9].

## Effects of BTKi on bone marrow immune microenvironment

BTK, an essential element of the B-cell receptor signaling cascade, plays a crucial role in pathways that regulate tumor microenvironment interactions [6]. Moreover, the bone marrow tumor microenvironment is implicated in WM disease progression and treatment resistance [10]. Thus, Christian et al. investigated immune microenvironmental changes in the bone marrow of BTKi-treated WM patients and assessed their correlation with the molecular profile of patients [11].
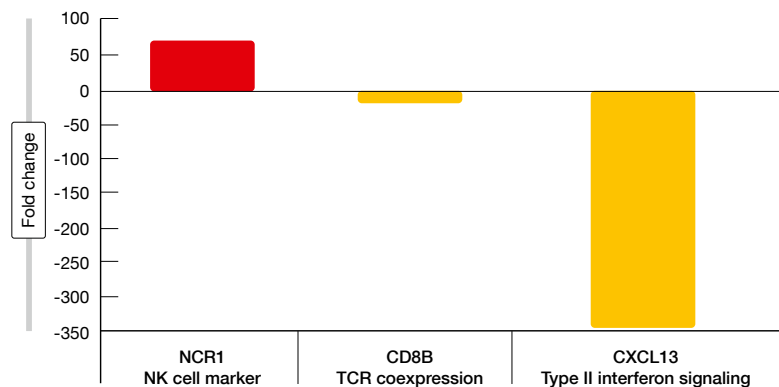
**Figure 1:** Fold change in gene expression between pre- and post-BTKi treatment for *MYD88^{L265P}* positive patients ($p < 0.03$).

The Oncomine™ Immune Response Research assay was used to measure the expression of targeted genes. Overall, 400 genes involved in the tumor microenvironment were interrogated with an Ion S5™ sequencing system. In total, 15 patients underwent FFPE trephine bone marrow biopsies before and twelve months after BTKi treatment. Patients' *MYD88* mutational status was correlated with gene expression changes and the Affymetrix™ Transcriptome Analysis Console software was used to perform differential analysis between the two time points.

Of the 30 samples plus one control, 14 passed quality control. Nine were positive for the *MYD88^{L265P}* whereas five were negative. A minor response to treatment or better was achieved in all patients at twelve months. In *MYD88^{L265P}* positive samples, differences were seen between pre ($n = 5$) and post ($n = 4$) treatment in type II interferon signaling, checkpoint and T-cell receptor pathways. *NCR1*, an NK-cell marker was significantly upregulated and *CD8B* as well as *CXCL13* were significantly downregulated twelve months post BTKi treatment (**Figure 1**). BTKi treatment types in *MYD88^{L265P}* positive patients included acalabrutinib (four patients), zanubrutinib (one patient) and ibrutinib (one patient). Of note, *CXCL13* downregulation was predominantly observed in patients who received acalabrutinib. Analysis of *MYD88^{L265P}* negative samples revealed a different gene expression pattern compared to *MYD88^{L265P}* positive samples with a downregulation of *B3GAT1*, *IL6* and *TLR7*.

Downregulation of *NCR1* gene expression has been shown in patients with B-cell chronic lymphocytic leukemia (B-CLL) but being preserved in patients with small lymphocytic lymphoma [12]. Although ibrutinib was associated with decreased NK-cell cytotoxicity in patients with mantle cell lymphoma (MCL) [13], this report shows for the first time that *NCR1*, encoding for a cytotoxicity-activating receptor on NK cells, is upregulated upon BKTi treatment in *MYD88^{L265P}* positive WM patients. The downregulation of *CXCL13* after BTKi treatment observed in this study is consistent with that previously described by Vos et al. in WM patients who received ibrutinib [14].

After twelve months of BTKi treatment, this pilot study showed changes in gene expression patterns in the WM immune environment. However, to confirm these findings, a larger cohort with matched samples pre and post BTKi treatment is warranted.

## BiRD study: real-world data of ibrutinib

Ibrutinib, a first-generation BTKi, has been approved in 2015 as monotherapy or in combination with rituximab for the treatment of adults with WM [15].

The ongoing observational Belgian ibrutinib Real World Data (BirD) study is currently evaluating the effectiveness and safety of ibrutinib in adults with CLL, MCL or WM in routine clinical practice [16]. Progression-free survival (PFS) and overall response rate (ORR) are the primary endpoints; overall survival (OS), time-to-next-treatment (TTNT) and safety are the secondary endpoints. Adverse events (AEs) considered to be related to ibrutinib are collected retrospectively, whereas treatment-emergent AEs (TEAEs) are collected prospectively.

At the time of this third interim analysis, 42 WM patients were included, 39 being analyzed for effectiveness and 41 for safety. Most patients (64.1 %) were male, the median age at initiation of ibrutinib was 67 years (range, 49-89), the median time from diagnosis to ibrutinib initiation was 8.6 years (range, 0.1-20.5), and all evaluable patients ($n = 29$) carried the *MYD88* mutation. IgM-related pathology (63.4 %) was the most common reason for initiating ibrutinib therapy and. most patients received ibrutinib monotherapy (97.6 %). Combination therapy, monotherapy or both had been previously administered in 33.3 %, 15.4 % and 51.3 % of patients, respectively, with more than half of patients (53.8 %) having received at least three lines of prior therapy.

After a median follow-up of 26.9 months, the median PFS reached 50.6 months, while the best ORR attained 87.2 %. The median time to first response was 2.9 months. The median duration of response (mDoR), median OS, and median TTNT were not estimable. While the median duration of ibrutinib treatment was 22.8 months (range, 2.6-55.7), a total of 15 patients (36.6 %) required dose modifications.

No new safety signals were observed; AEs occurred in 79.2 % of the patients in the retrospective group and 94.1 % of them in the prospective group, whereas serious AEs were reported in 20.8 % and 41.2 %, respectively. In both groups, the AEs of interest (AESIs) included major bleeding, infection, hypertension, atrial fibrillation, arthralgia/myalgia, diarrhea, and rash (**Table 1**). Among the 41 patients analyzed for safety, 14 (34.1 %) discontinued treatment, five of which were due to disease progression.

This third interim analysis of the BiRD study confirmed the effectiveness and safety of ibrutinib for the treatment of patients with WM in a real word setting. The safety profile of ibrutinib was consistent with that previously described.

## Histological transformation after ibrutinib therapy

In WM, histological transformation (HT) to diffuse large B-cell lymphoma (DLBCL) is rare but can occur during the course of the disease or upon treat-

TABLE 1

**Safety results in patients with WM**

| | Retrospective group N = 24 | Prospective group N = 17 |
|---|---|---|
| | % patients | % patients |
| **AEs** | **79.2 %** | **94.1 %** |
| **AE of interest:** | | |
| -Infection | 58.3 % | 47.1 % |
| -Diarrhea | 20.8 % | 11.8 % |
| -Arthralgia/myalgia | 20.8 % | 5.9 % |
| -Hypertension | 12.5 % | 11.8 % |
| -Rash | 12.5 % | 5.9 % |
| -Major bleeding | 0 % | 11.8 % |
| -Atrial fibrillation | 0 % | 5.9 % |
| **Serious AEs** | **20.8 %** | **41.2 %** |
| **AEs leading to dose reduction** | **20.8 %** | **5.9 %** |
| **AEs leading to treatment interruption** | **12.5 %** | **35.3 %** |
| **AEs leading to withdrawal** | **8.3 %** | **35.3 %** |

ment and is associated with a poor prognosis [17]. To date, the development of HT has been studied in WM patients treated with chemoimmunotherapy [18-20] but data on its association with newer targeted therapies such as ibrutinib are scarce. From an international multicenter database of 279 patients with transformed WM, 17 patients treated with ibrutinib before developing HT were identified. Their clinical data were reviewed, and a retrospective analysis performed which was presented at this year's iwWM meeting [21].

At the time of WM diagnosis, patients had a median age of 63 years (range, 36-86); $MYD88^{L265P}$ and $CXCR4$ mutations were found in 93 % and 57 % of patients respectively. Ibrutinib was administered as primary therapy in two patients only; among the other 15 previously treated patients, the most frequent prior therapies were rituximab (93 %), bendamustine (67 %), proteasome inhibitors (60 %) and rituximab-dexamethasone cyclophosphamide (33 %). At the time of HT, a median of four lines of treatment for WM (range, 1-9), including ibrutinib, had already been administered to patients.

From the diagnosis of WM, HT occurred after a median time of 4.2 years (range, 1–17). Of the ten patients on active treatment with ibrutinib at the time HT, five showed a partial response (PR),

two had a very good partial response (VGPR), one had a progressive disease (PD) and one was in complete remission (CR). More than half of the patients (59 %) had extranodal involvement, and five patients presented with central nervous system involvement (3 were detected at the time of HT diagnosis, two of which were on ibrutinib treatment, and two were detected at relapse). Elevated serum LDH levels were observed in 62 % of patients, and 82 % of patients harbored a non-GC phenotype according to the Hans' algorithm.

Fifteen patients received HT therapy, including R-CHOP in seven patients (47 %), RICE in three patients (20 %), RD-HAP in two patients (13 %) and high-dose methotrexate in one patient; a CR was observed in seven patients (50 %), a PR in three (21 %) and a PD in four (29 %). Over time, most patients (86 %) had a disease progression, and the median PFS reached 5.5 months. At the time of last follow-up, 53 % of patients had died with most deaths attributed to disease progression (78 %) or infections (11 %).

Overall, these data show that HT can develop in WM patients even under ibrutinib therapy and that the clinicopathological features appear similar to those previously described in studies on transformed WM. Further studies are needed to better characterize HT in treat-

ment-naïve and in previously treated WM patients as well as to compare HT development after chemoimmunotherapy and novel targeted agents, respectively

## Predictors for ibrutinib response: multi-omic genomics

Mutations in the $MYD88$ and $CXCR4$ genes impact the response to ibrutinib, notably by impacting the time to major response, depth of response and PFS in WM patients [22]. Testing for $CXCR4$ mutation is challenging – with false negative results in up to two-third of WM patients by next generation sequencing [23]. Moreover, $CXCR4$ mutations do not fully predict the response activity to BTKi. However, achieving a major response (>PR) at Month 6 is a validated predictor of long-term PFS with ibrutinib [24]. Using a multi-omics approach, easily translatable to the clinical setting, Richardson et al. sought to identify one or more biomarkers predicting response to ibrutinib [25].

Whole exome and methylome sequencing, RNA-Seq and ATAC-Seq were performed in treatment-naïve, symptomatic patients with $MYD88$-mutated WM receiving ibrutinib as primary therapy in a prospective clinical trial [26, 27]. At six months, patients with a major response had a longer PFS (median not reached) than patients with a non-major response (64.5 months; p = 0.10). Whole exome sequencing showed that the $CXCR4$ mutation was the only mutation significantly associated with a major response at six months (p = 0.002). Interestingly, while the $CXCR4$ mutation was associated with nonresponders, 23 % of the $CXCR4$-mutated patients were major responders at 6 months. RNA-Seq analysis identified 13 differentially expressed genes between major and non-major responders, including three top hits in major responders (wild-type and mutated $CXCR4$) namely $WNK2$ (p = 0.00005), $DUSP22$ (p = 0.0008) and $GPER1$ (p = 0.0008). ElasticNet regression analysis using RNA-Seq and ATAC-Seq subjected to 500 bootstraps revealed many regulators of ERK1/2 signaling such as $WNK2$, $DUSP22$, $GPER1$, $TNIK$, and $PRDM15$ among the best hits (**Figure 2**). A strong association was identi-
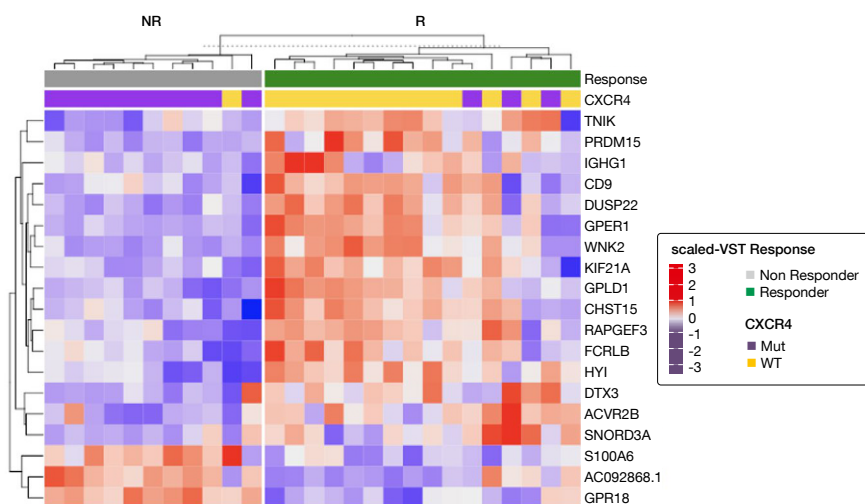
**Figure 2:** A heatmap showing the scaled variance stabilizing transformation gene levels selected by ElasticNet for baseline expressed genes in *MYD88* mutated WM patients who received ibrutinib monotherapy and who attained a major response (green) or no major response (gray) at six months.

fied between attainment of a major response at six months and the expression of *WNK2* (p = 0.0043) as well as *DUSP22*, *GPER1*, *TNIK* and *PRDM15* (all p < 0.0001). For these biomarkers, long-term PFS correlated with achieving a major response at six months. Of note, *WNK2* expression was validated by immunohistochemistry in bone marrow biopsy samples, too.

By use of a multi-omics approach, robust biomarkers predicting major response to ibrutinib at six months were identified in *MYD88*-mutated WM patients, including ERK1/2 signaling regulators that further correlated with long-term PFS.

## Real-world experience with zanubrutinib

Zanubrutinib is a second generation BTKi that has been designed to maximize BTK occupancy and minimize off-target effects [28]. It was recently approved for the treatment of adult WM patients in USA, Canada, and Europe [3, 9, 29]. In a randomized phase III trial comparing the use of zanubrutinib with ibrutinib in WM patients, 28 % of patients who received zanubrutinib achieved a VGPR and the major response rate reached 77 % [30].

The objective of this single-arm expanded access study (NCT04052854) was to provide real-word data on zanubrutinib in treatment-naïve WM patients who were not eligible for chemo-immunotherapy or patients with relapsed/refractory WM [31]. Zanubrutinib was administered at a dose of 320 mg once daily or 160 mg twice daily. Co-primary endpoints included the number of patients enrolled and treated, and the number of enrolling sites, while secondary endpoints included TEAEs, ORR, VGPR or better, PFS and OS. According to the 6th International Work-

shop on WM [32], response to the treatment was assessed by an investigator at least every sixth month.

From December 2019 to June 2021, 50 WM patients – including 17 treatment-naïve and 33 relapsed/refractory ones – were enrolled in ten US academic and community medical centers. Baseline characteristics included a median age of 72 years, intermediaterisk disease in 54 % of patients and highrisk disease in 40 % of them. Patients with relapsed/refractory disease had a median of two prior therapies. Overall, median treatment exposure was 9.2 months (range, 1.4-20.0).

The safety profile of zanubrutinib was consistent with previous reports. At least one TEAE and one TEAE of special interest was reported in 76 % and 72 % of patients, respectively. Grade ≥3 TEAEs of special interest included hypertension (8 %), infection (8 %), and atrial fibrillation or flutter, neutropenia and second primary malignancy (2 % each).

Among the 41 patients analyzed for efficacy, the ORR was 85.4 % (95 % CI, 70.8-94.4), with a major response rate of 73.2 % (95 % CI, 57.1-85.8). A best overall response of VGPR was achieved in 39.0 % of patients (n = 16; 95 % CI, 24.2-55.5). Of the four patients who had PD, three presented IgM values that met the criteria for partial response before the first response assessment at six months. Because of the short follow-up, PFS and OS were immature and the median was not met.

Real-world experience with zanubrutinib administered as a monotherapy at 320 mg daily in patients with treatment-naïve or relapsed/refractory WM was consistent with the established zanubrutinib profile in WM and other B-cell malignancies. ■

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# Management of WM patients previously exposed to BTK-inhibitors

## Zanubrutinib in ibrutinib- or acalabrutinib-intolerant patients

Many patients with WM require continuous treatment with BTK inhibitors, but difficult-to-manage AEs often lead to treatment discontinuation [1]. Zanubrutinib is a potent and selective next-generation BTKi designed to minimize off-target kinase binding and associated side effects [2, 3]. Randomized phase III studies have shown that, in patients with chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/ SLL) or WM, zanubrutinib has a more favorable safety profile than ibrutinib, particularly regarding cardiovascular toxicities [4, 5].

The BGB-3111-215 study (NCT04116437) is evaluating the tolerability and efficacy of zanubrutinib in patients with WM, CLL/SLL, MCL or marginal zone lymphoma (MZL), who did not tolerate prior BTKi-treatment (responded to BTKis but had adverse events). Ibrutinib- (Cohort 1) or acalabrutinib-intolerant patients (Cohort 2) are enrolled in this study. El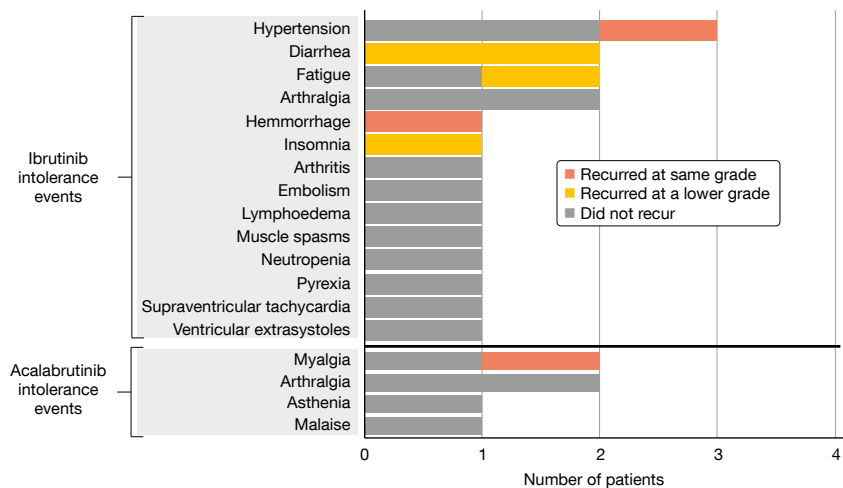igible patients in both cohorts receive zanubrutinib (160 mg twice daily [BID] or 320 mg once a day [QD]) and are treated until disease progression or toxicity. Early results from the BGB-3111-215 study have already shown, that zanubrutinib was well tolerated in patients with B-cell malignancies who are intolerant to ibrutinib or acalabrutinib [3].

At iwWM 2022, Shadman et al. presented new data on patients with WM from this trial [6]. Eleven patients with WM were enrolled in the study, nine of them being intolerant to ibrutinib (Cohort 1), and two being intolerant to acalabrutinib (Cohort 2). Median age was 71 years and patients had received a median of two prior therapies (range, 1-12). The median duration of treatment was eleven months with ibrutinib and three months with acalabrutinib. At a



**Figure 1:** Recurrence and severity change of intolerance AEs in patients with WM under zanubrutinib-treatment.

median follow-up and median duration of treatment of 14,9 months (range, 6.5-20.5), 68 % of AEs that previously occurred from ibrutinib treatment and 83 % of AEs that resulted from acalabrutinib treatment did not recur with zanubrutinib. Events that recurred mostly occurred at lower grade in case of diarrhea, fatigue, and insomnia (**Figure 1**). In 45 % of patients, there was no recurrence of any prior BTKi-related intolerance AE on zanubrutinib. Cardiovascular AEs were less common in patients receiving zanubrutinib compared to ibrutinib. In terms of efficacy, data must be interpreted with caution since active disease was not a requirement for study enrollment. Nevertheless, WM patients treated with zanubrutinib either maintained (n = 1; 9.1 %) or improved (n = 10; 90.9 %) their disease status compared to baseline. However, one patient discontinued zanubrutinib because of myalgia, which recurred with the same severity as with prior acalabrutinib or ibrutinib therapy.

Consistent with a more selective BTK inhibition, zanubrutinib showed few side effects associated with off-target kinase activity in patients with WM, who were intolerant to ibrutinib and/or acalabrutinib. The authors concluded, that zanubrutinib represents a viable treatment option for patients with WM intolerant to other BTK inhibitors.

## Venetoclax as single agent in previously treated WM

B-cell lymphoma 2 (BLC2) is an essential regulator of apoptosis in both normal and malignant cells. It is overexpressed in WM cells, with similar levels of BCL2 expression regardless of *CXCR4* mutation (*CXCR4^mut*) [7]. Venetoclax is an oral BCL2 antagonist approved for the treatment of CLL and acute myeloid leukemia [8]. In a prospective phase I study, four patients with WM received venetoclax as a single agent, with all attaining a major response (MR) [9].

In a recently published phase II study (NCT02677324), patients with relapsed or refractory WM received venetoclax orally once daily at increasing doses: 200 mg for one week, 400 mg for another week, and 800 mg for up to two years [10, 11]. After each dose increase, the occurrence of tumor lysis syndrome was assessed, as previously described in

CLL patients receiving venetoclax. In this study, a total of 32 WM patients were allocated to treatment, with 53 % of them presenting with *CXCR4^mut*. The median age of WM diagnosis was 58 years and the age of ibrutinib initiation was 66 years. The overall response rate (ORR) was 84 %, with a lower ORR in patients with previous BTKi exposure (no prior BTKi: 93 %, prior BTKi: 75 %). Although the ORR was similar in *CXCR4^wt* and *CXCR4^mut* WM patients the VGPR was lower in *CXCR4^mut* WM patients (29 % vs 12%, respectively). The median time to minor response was 1.9 months (95 % CI, 1.1-2.1), and the time to major response (TTMR) was 5.1 months (95 % CI, 4.7-8.2). Similarly, the time to minor and major responses were significantly longer in patients with prior BTKi exposure. Neither the ORR nor the time to response (TTR) were affected by a *CXCR4^mut*. The median follow-up time was 30 months and the 12-month and 24-month PFS rates were 83% and 80%, respectively. Disease progression occurred in six patients within the first 24 months and in 13 patients after completion of venetoclax therapy, including ten between 24 and 36 months as well as three after 36 months. There were no statistically significant differences in PFS related to a prior BTKi exposure or *CXCR4* mutational status.

Neutropenia was frequently observed and was effectively managed with G-CSF. One patient experienced a laboratory tumor lysis syndrome that was managed as an inpatient and responded to one dose of rasburicase and intravenous fluids. Seven patients (22 %) had venetoclax dose reduction, without affecting the ORR or PFS.

This study demonstrated that a venetoclax monotherapy resulted in a deep and durable response without unexpected AEs in patients with previously treated WM, including those previously treated with BTKis. An analysis of genomic material from the study is expected to be published next year.

## BRUIN study: pirtobrutinib in pretreated WM

Until now, primary treatment options for WM include combination strategies with anti-CD20 monoclonal antibodies, chemotherapy, or proteasome inhibitors [12]. Additionally, covalent BTK in-

hibitors have emerged as standard therapy, but intolerance and acquired resistance, due to the BTK-C481 mutation in WM, are challenging [13, 14].

Pirtobrutinib is a highly potent, selective, non-covalent (reversible) BTKi [15]. Compared to ibrutinib, pirtobrutinib has demonstrated similar *in vivo* efficacy in wild-type BTK and superior efficacy in BTK-C481S in xenograft models [16]. Moreover, it was shown to be well tolerated with promising efficacy in poor-prognosis B-cell malignancy patients following prior therapy, including prior covalent BTK inhibitors [15]. The currently ongoing phase I/II BRUIN study (NCT03740529) evaluating pirtobrutinib consisted of a dose-escalation and expansion cohort (25 - 300 mg pirtobrutinib QD), and a cohort at the recommended phase II dose (RP2D) of 200 mg pirtobrutinib QD [15]. In addition to patients presenting with CLL/SLL, MCL, and other B-cell malignancies, 26 patients with WM were enrolled in this study. Co-primary endpoints were safety and tolerability, determination of the maximum tolerated dose and RP2D, pharmacokinetics, as well as efficacy of pirtobrutinib.

At iwWM 2022, M.L. Palomba presented the outcomes of the WM patient cohort [17]. The median number of prior therapies was three. Overall, 92 % of patients had a prior anti-CD20 antibody therapy, 89 % a prior chemotherapy, 69 % a covalent BTK inhibitor therapy, 4 % a PI3K inhibitor therapy and 69 % a prior BTKi therapy that was discontinued due to disease progression or toxicity. Efficacy assessment (n = 19) showed an ORR of 68 % (95 % CI, 44-87; 47% with a PR, 21 % with a minor response [MR]). In the BTK naïve patients (n = 6), 67 % (95 % CI, 22-96; PR, 67 %, MR, none) and in the prior BTKi treated patients (n = 13), 69 % (95 % CI, 39-91; PR, 39 %, MR, 31 %) achieved an ORR, respectively. If prior BTKi was discontinued due to disease progression, the ORR reached 63 % (95 % CI, 25-92; PR, 50 %, MR, 13 %); if prior BTKi was discontinued due to toxicity, the ORR reached 80 % (95 % CI, 28-100; PR, 20 %, MR, 60 %). Measurable tumor burden was reduced – 42 % of patients had a maximum percent change in IgM from baseline > 50%. At the time of data cutoff (September 27, 2020), ten of the 13 responding patients were still on treat-
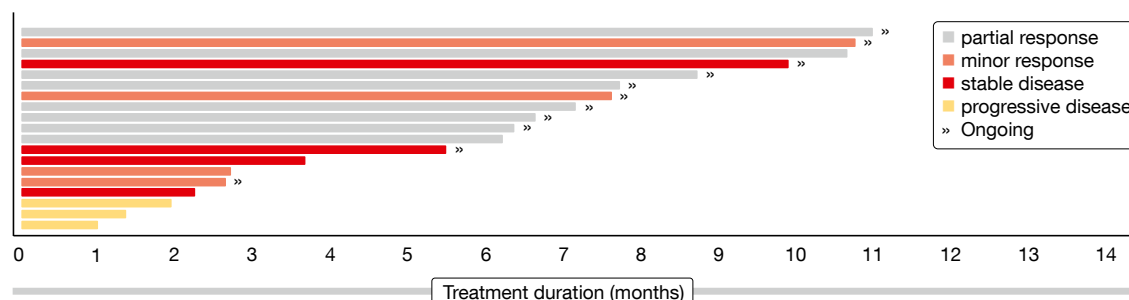
**Figure 2:** Swimmer plot on treatment duration of WM patients responding to pirtobrutinib.

ment **(Figure 2)**. With a median follow-up of 5.6 months, pirtobrutinib demonstrated a PFS of 71.7 % at seven months and 61.4 % at nine months.

The safety profile of pirtobrutinib was particularly notable in WM patients, as the only treatment-related adverse events (TEAEs) of grade 3 or higher was neutropenia (n = 2, 8 %). No TEAEs led to discontinuation of treatment.

The authors concluded that pirtobrutinib is highly active and well-tolerated drug in patients with previously treated WM, including those who have failed under prior covalent BTKi treatment.

## Novel treatment approaches to WM

### Ibrutinib plus venetoclax in treatment-naive WM

Both BTK inhibitors and BCL2 antagonists have been shown individually to be safe and effective treatments in WM [18]. The combination of the BTK inhibitor ibrutinib and the BCL2 antagonist venetoclax is safe and highly effective in CLL/MCL [19, 20]. In addition, preclinical work demonstrated a synergistic effect of ibrutinib and venetoclax in WM cell lines [21]. Based on these findings, a prospective single-arm, multicenter phase II study (NCT04273139) was designed to evaluate the combination of ibrutinib and venetoclax in therapy-naïve patients with WM. Results of this study were first presented at this year's iwWM meeting by Jorge Castillo [22].

According to the study design, patients received 420 mg ibrutinib orally (PO) QD in Cycle 1. In Cycle 2, venetoclax was added to ibrutinib with a weekly dosage ramp-up, starting at 100 mg in the first week, 200 mg in the

second week, and 400 mg in the following two weeks. Ibrutinib (420 mg, PO, QD) and venetoclax (400 mg, PO, QD) were further administered in Cycles 3 to 24, with dose reductions allowed for toxicity. Tumor lysis syndrome was assessed after each stage of dose escalation. Patients were to discontinue study treatment only in the event of disease progression or unacceptable toxicity. In total, participants will be on the research study for up to two years on combined venetoclax and ibrutinib and four years of follow-up.

A total of 45 patients with WM were enrolled in the study, with a median age at treatment initiation of 67 years (range, 39-81). Participants were predominantly male (67 %) and 38 % (n = 17) of patients had a *CXCR4* mutation (*CXCR4^{mut}*). The study population presented a higher percentage of acquired von Willebrand disease in *CXCR4^{mut}* (41 %) than in *CXCR4^{wt}* (7 %), and lower ß2-microglobulin levels in *CXCR4^{mut}* (2.8 mg/L) than in *CXCR4^{wt}* (4.2 mg/L). Both median TTR and time to major re-

sponse (TTMR) were 1.9 months, with a marginally significant difference (log-rank p = 0.048) in TTMR between *CXCR4^{mut}* (2.8 months) and *CXCR4^{wt}* (1.9 months) **(Figure 3)**. The ORR reached 100 % (7 % MR, 53 % PR, 40 % VGPR) and the major response rate (MRR) was 93 % in the total population. However, the MRR was lower in patients with *CXCR4^{mut}* versus *CXCR4^{wt}* (88 % vs. 96 %). After a median follow-up of eleven months, the 12-month PFS rate was 92 % and the 12-month OS rate 95 %.

The safety profile showed predominantly grade 2 AEs. The most frequent grade ≥ 3 AE was neutropenia (n = 13). Moreover, three patients had grade ≥ 3 ventricular arrhythmia (grade 4, n = 1; grade 5, n = 2). Consequently, both therapies were discontinued, but patient follow-up will continue until the end of the five planned years.

In summary, the combination of ibrutinib and venetoclax resulted in a fast and deep response in previously untreated WM, with an even stronger response in patients with *CXCR4^{mut}*. The
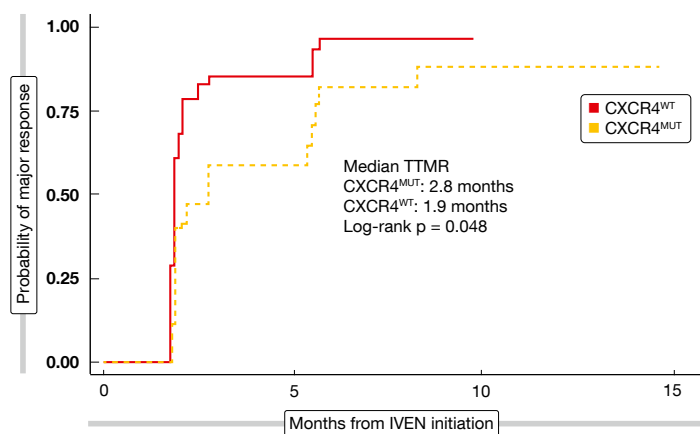


**Figure 3:** Time to major response in WM patients treated with ibrutinib plus venetoclax, assessed separately for patients with *CXCR4^{wt}* or *CXCR4^{mut}*.

high rate of ventricular arrhythmia prompted stopping study therapy, but follow-up off-therapy continues.

## Rituximab/acalabrutinib in WM with anti-MAG neuropathy

Monoclonal gammopathies encompass a spectrum of clonal plasma cell diseases that include monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), and Waldenström macroglobulinemia (WM). A known complication of monoclonal gammopathies is the peripheral neuropathy, which is challenging in terms of diagnosis and treatment [23]. Anti-myelin-associated glycoprotein (anti-MAG) antibodies are found in 40-50 % of patients with IgM monoclonal gammopathy [24]. Up to 50 % of patients with progressive neuropathy develop a significant disability within 10 to 15 years of diagnosis, severely impacting quality of life [25]. Current options for treatment of anti-MAG neuropathy include single agent rituximab or chemoimmunotherapy, but both result in poor and delayed responses and/or toxicity.

At iwWM 2022, S. Sarosiek presented the design of a phase II study (NCT05065554) evaluating the efficacy and safety of acalabrutinib plus rituximab for anti-MAG-mediated neuropathy in patients with WM or IgM mgUS [26]. It is expected that 33 patients will take part in this study, receiving rituximab (Days 1, 8, 15, 22) of Cycles 1 and 4 plus acalabrutinib (twice daily on Days 1-28) for 48 cycle or until disease progression or unacceptable toxicity. Participants will be followed for two years after completion of 48 cycles of treatment or until death. Main inclusion criteria include the presence of IgM monoclonal protein and anti-MAG antibodies, as well as sensory neuropathy with predominantly demyelinating features on nerve conduction tests (modified Rating Scale Score ≥ 1). Major exclusion criteria include serum IgM ≥ 4000 mg/dL, the fulfillment of other criteria for treatment besides neuropathy, no other known cause of peripheral neuropathy, a neuropathy for ≥ 5 years, or a prior exposure to other WM treatment except steroids, IVIg, or anti-CD20 antibodies > 90 days earlier.

Thus, the goal of this study is the assessment of the overall hematologic response rate (primary objective). The main secondary objective is to estimate the proportion of patients achieving improvement or stability on the I-RODS scale. Other secondary objectives are to evaluate various neuropathy rating systems/scales, including patient-directed rating systems and physician-directed rating systems.

## Tirabrutinib in treatment-naive and previously treated WM

Tirabrutinib is a second-generation oral covalent BTKi with kinase selectivity comparable to or higher than other BTKis [27]. In patients with WM, a phase II study (ONO-4059-05 study) of tirabrutinib monotherapy at a daily dose of 480 mg led to its approval in Japan [28]. Updated results of this study after a median follow-up of two years were presented at iwWM 2022 by Koji Izutsu [29, 30].

The multicenter, open-label, single-arm study included patients with treatment-naive (Cohort A) or with relapsed/refractory (Cohort B) WM. Eligible patients were treated with tirabrutinib (480 mg, PO, once daily) until disease progression or unacceptable toxicity. The primary endpoint was IRC-assessed MRR (best response ≥ PR), while secondary endpoints included ORR, TTMR, PFS, OS, and safety.

A total of 27 patients (Cohort A, n = 18; Cohort B, n = 9) with a median age of 71 years and a median serum immunoglobulin M level of 3600 mg/dL were enrolled. Most patients (n = 22) showed a $MYD88^{mut}/CXCR4^{wt}$ mutation status. At a median follow-up of two years, MRR was 94.4 % in treatment-naïve (Cohort A) and 88.9 % in the relapsed/refractory (Cohort B) WM patients, respectively. The median TTMR was 1.9 months/2.1 months in Cohorts A/B while the 2-year PFS reached 94.4 %/88.9 %, respectively. The 2-year OS rate was 100 % in both groups. The median PFS and median OS were not reached after a median follow-up of 23.8 months/25.4 months in Cohorts A/B, respectively.

The most common AEs of any grade in the total study population were rash (44.4 %), neutropenia (30 %) and nasopharyngitis (26 %). Eight bleeding events of grade 1 or 2 were reported (Cohort A, n = 5; Cohort B, n = 3). Atrial fibrillation occurred in two patients, one in each cohort, with one case being considered to be treatment related. All patients who showed either a complete response (n = 1) or a very good partial response (n = 8) were $MYD88^{mut}/CXCR4^{wt}$, but the impact of the mutational status remains unclear due to the small sample size.

In summary, this study demonstrated that tirabrutinib monotherapy is highly effective in both untreated and relapsed/refractory WM and has a manageable safety profile.

## Orelabrutinib in relapsed/ refractory WM patients

Orelabrutinib is a novel orally administered, potent, irreversible, and highly selective BTK-inhibitor. A nearly complete (99 %) BTK occupancy achieved with 150 mg orelabrutinib persisted for 24 hours, supporting once-daily dosing [31]. In December 2020, orelabrutinib received its first approval in China for the treatment of patients with mantle cell lymphoma or CLL/SLL, who have received at least one treatment in the past. Clinical development of orelabrutinib for various indications is underway in the USA and China [32].

At iwWM 2022 meeting, X. Cao presented the multicenter ICP-CL-00105 study (NCT04440059) of orelabrutinib in patients with relapsed or refractory WM who had at least one prior line of treatment [31, 33]. In this single-arm phase II study, orelabrutinib was administered orally at a daily dose of 150 mg until disease progression or unacceptable toxicity. The primary endpoint was the MRR, as assessed by the Independent Review Committee (IRC) according to IWWM-6 and NCCN guidelines; secondary endpoints included the MRR as assessed by investigator, ORR, duration of major response (DoMR), PFS, OS, and safety.

Among 66 relapsed or refractory WM patients assessed for eligibility, 47 eligible patients were evaluated for efficacy. The median age was 63 years, 83 % (n = 39) were $MYD88^{mut}/CXCR4^{wt}$ and had a median of one prior line of therapy.

A decline in serum IgM levels (median: -80.4 %) from baseline as well as a durable improvement in hemoglobin levels in 87.2 % of patients (median maximal improvement at 33 g/L) were reported. The MRR attained 80.9 %, the ORR 89.4 % (21.3 % VGPR, 59.6 % PR, 8.5 % MR) and the DCR 97.9 %, respec-
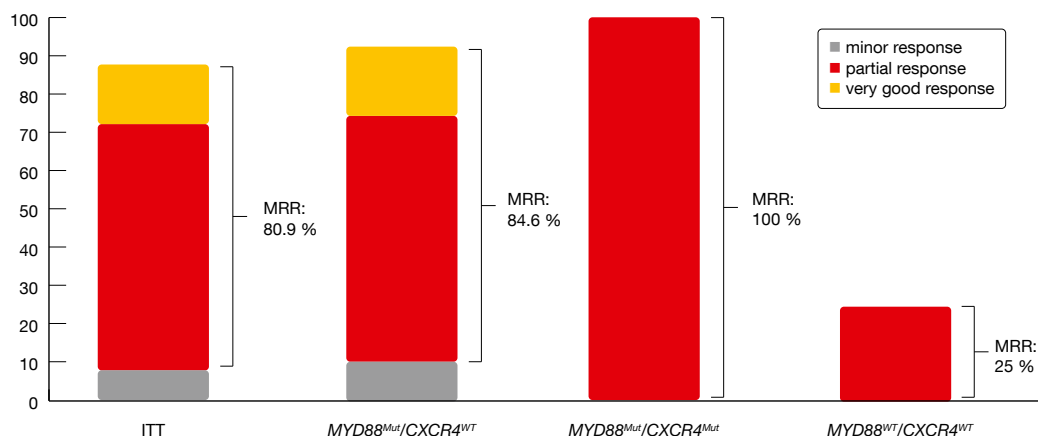
**Figure 4:** Response rates in different MYD88/CXCR4 genotype subgroups.

tively. The MRR was consistent in pre-specified subgroups, but the presence of MYD88 mutation was associated with a high major response: 84.6 % in $MYD88^{mut}/CXCR4^{wt}$, 100 % in $MYD88^{mut}/CXCR4^{mut}$ and 25.0 % in $MYD88^{wt}/CXCR4^{wt}$ **(Figure 4)**. At 12-months, a DoR of 88.8 %, a PFS rate of 85.1 %, an OS rate of 93.6 %, and a DoMR rate of 86.8 % were achieved.

Grade 3 treatment-related adverse events (TRAEs) occurred in 23.4 % of patients, one of them resulting in death because of a hepatitis B reactivation. The most common grade 3 or higher TEAEs were neutropenia (8.5 %), thrombocytopenia (6.4 %) and leukocytopenia (6.4 %).

Orelabrutinib has demonstrated a good efficacy and a manageable safety profile in patients with relapsed or refractory WM and has potential to become the preferred therapy for this patient population. ■

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# BTK inhibition in Waldenström's macroglobulinemia: trial updates and biomarker analysis

## BTK inhibition in Waldenström's macroglobulinemia: trial updates and biomarker analysis

The open-label, multicenter, randomized phase III ASPEN trial was set up to assess the efficacy and safety of the potent, selective, irreversible next-generation BTK inhibitor zanubrutinib in Waldenström's macroglobulinemia (WM). Cohort 1 of the study included patients with *MYD88*-mutated disease (n = 201); here, zanubrutinib was compared to ibrutinib after 1:1 randomization. In Cohort 2, 28 patients with *MYD88* wildtype received zanubrutinib in a non-randomized manner. Both treatment-naïve and pretreated patients participated, although no prior BTK inhibition (BTKi) was allowed. Untreated patients were eligible when considered unsuitable for standard chemoimmunotherapy.

With respect to the primary endpoint, which was complete response (CR) plus very good partial response (VGPR) for zanubrutinib vs. ibrutinib, no significant difference resulted at the time of the primary analysis [1], although the findings indicated clinically meaningful efficacy

and improved tolerability of the newer BTK inhibitor.

### 43-month follow-up of ASPEN

This impression was corroborated by the long-term follow-up reported at iwWM 2022 [2]. In Cohort 1, the CR + VGPR rate was numerically higher at all time points with zanubrutinib vs. ibrutinib. At 44.4 months, this was 36.3 % vs. 25.3 %, with shorter median time to CR + VGPR (6.7 vs. 16.6 months). Zanubrutinib elicited a higher event-free rate for the duration of CR + VGPR at 24 months (90.6 % vs. 79.3 %). Median PFS and OS had not yet been reached, with hazard ratios favoring zanubrutinib (PFS, 0.63; OS, 0.75). At 42 months, 87.5 % vs. 85.2 % of patients were alive, and 78.3 % vs. 69.7 % were progression-free. After almost four years, 66 % vs. 52 % remained on treatment.

Assessments of patients with *MYD88*$^{MUT}$ by *CXCR4* status demonstrated that patients with *CXCR4* mutation derived benefits from zanubrutinib compared to ibrutinib regarding VGPR or better (21.2 % vs. 10.0 %), major response (78.8 % vs. 65.0 %), time to major response (3.4 vs. 6.6 months), and PFS (HR, 0.50). Seventy-three percent of these patients treated with zanubrutinib

enjoyed freedom from progression at 42 months, while only 49.0 % in the ibrutinib arm did.

In Cohort 2, responses to zanubrutinib treatment continued to deepen over time. At 42.9 months of follow-up, one patient had achieved complete response, and the rate of major responses had risen to 65 %. Event-free rates of PFS and OS at 42 months were 53.8 % and 83.9 %, respectively.

Likewise, the safety advantages of zanubrutinib remained consistent over time, with less off-target activity *versus* ibrutinib. Zanubrutinib-treated patients showed lower cumulative incidences of atrial fibrillation, diarrhea, hypertension, muscle spasms, and pneumonia, and had fewer AEs leading to death, treatment discontinuation, or dose reductions. Among AEs of special interest observed in Cohort 1, neutropenia was more common with zanubrutinib (any grade, 34.7 % vs. 20.4 %), although infection rates were similar across the arms (any grade, 79.2 % vs. 79.6 %), with grade 3/4 events occurring less frequently in the experimental arm (21.8 % vs. 27.6 %). Interestingly, in Cohort 1, hemorrhage, neutropenia, diarrhea and infection prevalence decreased over time in patients treated with zanubrutinib **(Fig-**
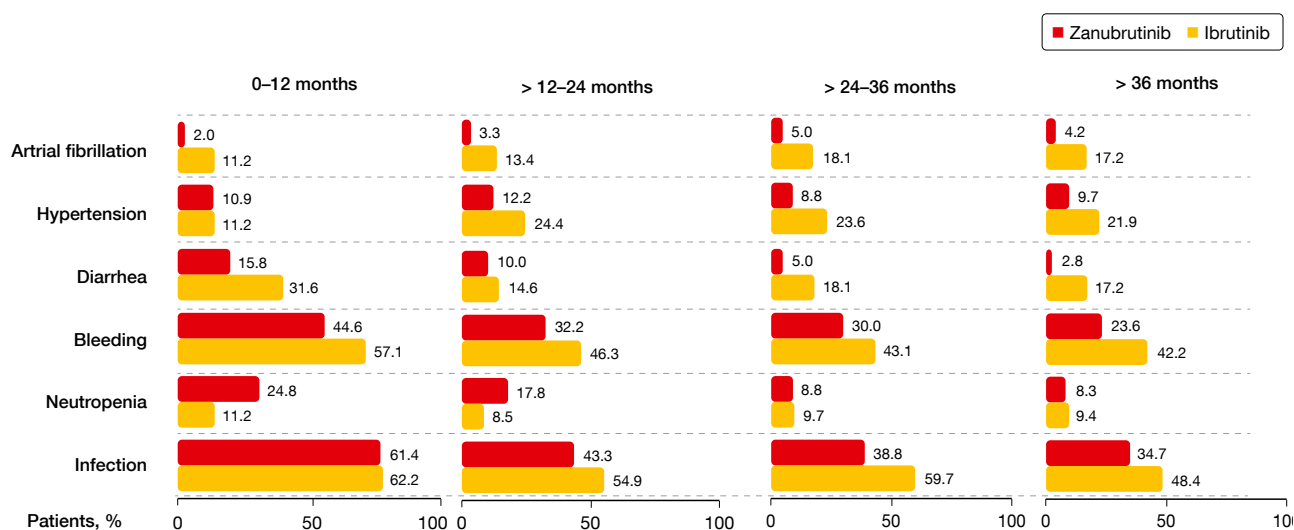


**Figure 1:** ASPEN trial – prevalence analysis for adverse events of interest (Cohort 1).

**ure 1).** Exposure-adjusted incidence rates of atrial fibrillation/flutter and hypertension were lower with zanubrutinib *versus* ibrutinib (7.9 % vs. 23.5 % and 14.9 % vs. 25.5 %, respectively).

The authors noted that over time, zanubrutinib showed a consistent trend of deeper, earlier, more durable responses and different safety advantages with less off-target activity compared with ibrutinib.

## BTKi treatment in WM patients with low frequency genetic alterations

With the advent of high-throughput technologies, it is now known that *MYD88* L265P and *CXCR4* nonsense (NS) and frameshift mutations (FS) are the most common recurrent variations observed in WM patients, with detection rates of 90 % and 40 %, followed by *ARID1A* with 17 %, respectively [3]. The mutation status of *MYD88* and *CXCR4* impacts the efficacy of BTKi in patients with WM. Overall response rates (ORR) are highest in $MYD88^{MUT}$ $CXCR4^{WT}$ patients, worse in $MYD88^{MUT}$ $CXCR4^{MUT}$ and lowest in $MYD88^{WT}$ $CXCR4^{WT}$ patients [3-6]. Thus, the biomarker study, presented at iwWM 2022, evaluated low-frequency genetic alterations and their association with efficacy of ibrutinib and zanubrutinib treatment in patients with WM included in the ASPEN phase III trial [7].

Next-generation sequencing NGS results were evaluable in 190 patients with $MYD88^{MUT}$ (98 treated with zanubrutinib, and 92 treated with ibrutinib, respectively) and 20 patients with $MYD88^{WT}$. Besides high rates of CXCR4 mutations (25.7 %), TP53 (24.8 %), ARID1A (15.2 %) and TERT (9.1 %) were the most frequently mutated genes identified in the study. $TERT^{MUT}$ was detected in patients with $MYD88^{MUT,}$ only, and $ARID1A^{MUT}$ and $TP53^{MUT}$ were more commonly associated with $CXCR4^{MUT}$ and more often detected in patients with $MYD88^{MUT}$.

In patients with $MYD88^{MUT}$ WM, those with $CXCR4^{MUT}$, $TP53^{MUT}$, and $TERT^{MUT}$ trended toward lower VGPR+CR rate or MPR and longer median time to response than patients with the respective WT alleles (**Table**), whereas $ARID1A^{MUT}$ showed limited clinical impact. Moreover, a less favorable PFS was shown in patients with $MYD88^{MUT}$ WM and $CXCR4^{MUT}$ (HR,
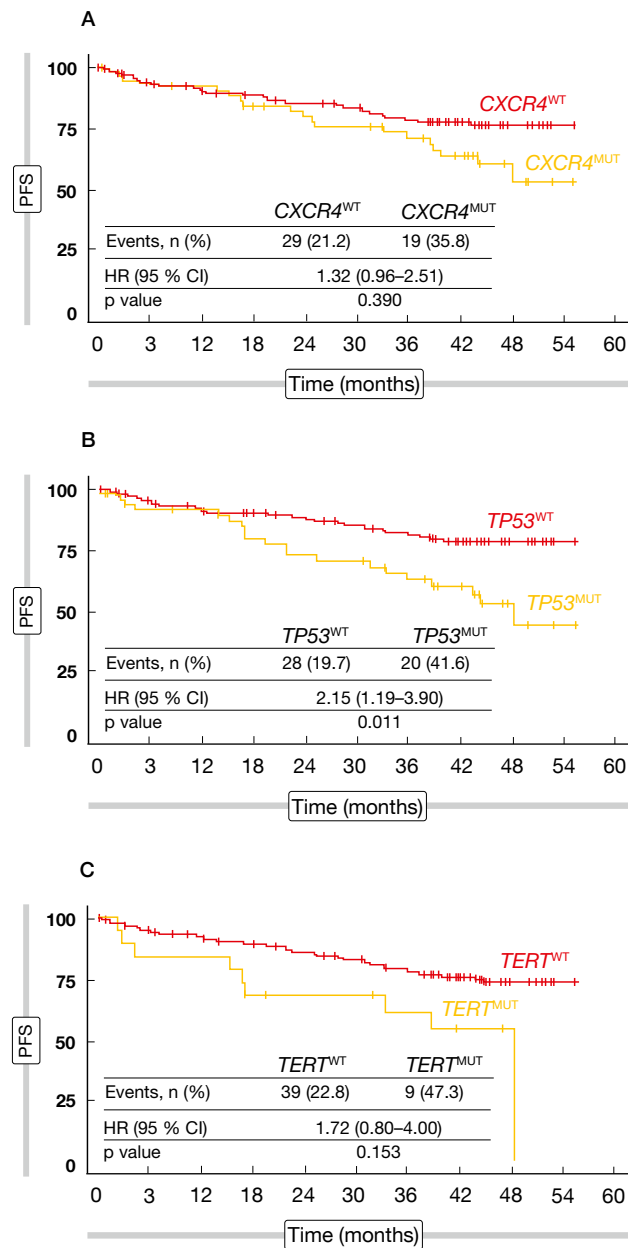
**Figure 2:** Progression-free survival (PFS) in patients with $MYD88^{MUT}$ WM by (A) *CXCR4*, (B) *TP53* and (C) *TERT* mutational status.

1.32; 95% CI, 0.96-2.51; *p* = 0.390), $TP53^{MUT}$ (HR, 2.15; 95% CI, 1.19-3.90; *p* = 0.011), or $TERT^{MUT}$ (HR, 1.79; 95% CI, 0.80-4.00; *p*=0.150), than patients with the respective WT allele (**Figure 2**).

Patients with $MYD88^{MUT}$ $CXCR4^{NS}$ WM treated with ibrutinib showed reduced VGPR (15.4 % vs. 30.6 %), MRR (53.8 % vs. 84.7 %) and PFS (43.5 % vs. 57.1 %, *p* = 0.017) than those with $CXCR4^{WT}$ whereas in the zanubrutinib arm only VGPR (14.3 % vs. 44.6%) was reduced and MRR (85.7 % vs. 83.1 %) and PFS (66.7 % vs. 81.3 %, *p* = 0.598) were

comparable. Although there were only a small number of patients in the $CXCR4^{FS}$ cohort treated with either zanubrutinib (n = 19) or ibrutinib (n = 7), zanubrutinib demonstrated a more favorable VGPR+CR rate compared to ibrutinib (26.3 % vs 0 %, *p* = 0.06).

Patients with $TP53^{MUT}$ had reduced VGPR (13.6 % vs. 30.0 %), MRR (63.6 % vs. 85.7 %) and PFS (57.9 % vs. 72.1 %, *p* = 0.027) than those with $CXCR4^{WT}$ in the ibrutinib arm. In the zanubrutinib arm no significant differences were reported [VGPR (34.6 % vs. 37.5 %), MRR

**TABLE**
**BTKi and low frequency genetic alterations**

| Response | $CXCR4^{WT}$ (n = 137) | $CXCR4^{MUT}$ (n = 53) | $TP53^{WT}$ (n = 142) | $TP53^{MUT}$ (n = 48) | $TERT^{WT}$ (n = 171) | $TERT^{MUT}$ (n = 19) |
|---|---|---|---|---|---|---|
| VGPR or better, n (%) | 51 (37.2)* | **9 (17.0)*** | 48 (33.8) | 12 (25.0) | 58 (33.9) | **2 (10.5)** |
| Major Response, n (%) | 115 (83.9) | **39 (73.6)** | 119 (83.8) | **35 (72.9)** | 143 (83.6) | **11 (57.9)** |
| Median time to VGPR or better (min-max), months | 8.4 (1.9–50.0) | 11.1 (2.8–46.0) | 9.3 (1.9–50.0) | 11.1 (3.0–46.9) | 9.3 (1.9–50.0) | 34.1 (22.2–46.0) |
| Median time to Major Response (min-max), months | 2.8 (0.9–49.8) | 4.6 (1.0–49.8) | 2.9 (0.9–49.8) | 2.9 (1.0–13.8) | 2.8 (0.9–49.8) | 5.6 (1.8–22.2) |

\* p-value < 0.05, based on a logistic regression model with *CXCR4* (WT, MUT), *TERT* (WT, MUT), *TP53* (WT, MUT); bold text indicates > 10% difference between MUT and WT.

(80.8 % vs. 81.9 %) and PFS (62.0 % vs. 84.6 %, *p* = 0.120)]. Of note, the VGPR rate for $TP53^{MUT}$ was significantly higher in the zanubrutinib arm than in the ibrutinib arm (34.6 % vs. 13.6 %, *p* < 0.05).

Patients with $TERT^{MUT}$ had reduced VGPR (11.1 % vs. 27.7 %) and MRR (44.4 % vs. 84.3 %) but comparable PFS (74.0 % vs. 68.4 %, *p* = 0.304) than those with $TERT^{WT}$ in the ibrutinib arm. In the zanubrutinib arm reduced VGPR (10.0 % vs. 39.8 %) and significantly re-duced PFS (37.5 % vs 83.4 %, *p* = 0.001) were reported, whereas MRR (70.0 vs 83.0) was comparable between $TERT^{MUT}$ and $TERT^{WT}$.

Overall, the authors concluded that in the ASPEN trial, $CXCR4^{MUT}$, $TP53^{MUT}$, and $TERT^{MUT}$ were correlated with inferior response to BTKi therapy. Consistent with more potent inhibition of BTK, zanubrutinib demonstrated deeper responses in patients with $CXCR4^{MUT}$ or $TP53^{MUT}$ WM. ∎

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# Emergent BTKi treatments in WM

Additionally to ibrutinib, to date the only once-daily BTK inhibitor approved in the USA and the European Union ei-ther as monotherapy or in combination with RTX for patients with WM [1], other BTKis, such as acalabrutinib and zanu-brutinib, are now emerging as potential therapeutic alternatives.

## Acalabrutinib in treatment-naïve or R/R patients

Acalabrutinib is an emergent, potent, and selective BTKi, which has received accelerated approval by the US FDA for the treatment of adult patients with re-lapsed or refractory (R/R) MCL and is in clinical development for CLL and DLBCL. Roger Owen presented the up-dated data of the phase II clinical trial (NCT02180724) evaluating acalabruti-nib activity and safety in the treatment of treatment naïve (TN) or R/R patients with WM after a five-year follow-up [2, 3].

Exclusion criteria included a prior BTKi therapy, a significant cardiovascu-lar disease, comorbidities (such as or-gan system dysfunction or uncontrolled active systemic infection) or requiring treatment with vitamin K, antagonists, or proton-pump inhibitors. Enrolled pa-tients were administered with acalabru-tinib (100 mg twice a day [BID] or 200 mg per day [QD] per os [PO]) for 28-day cycles until disease progression (PD) or unacceptable toxicity. The pri-mary endpoint was the ORR as assessed by investigator, while key secondary endpoints were duration of response (DoR), PFS, OS and safety.

Overall, 106 patients were enrolled across 27 sites in the USA and across Europe from September 2014 to De-cember 2015. The median follow-up time was 63.7 months at the time of data cut-off. Patients in the R/R disease cohort (n = 92) were slightly younger than in the TN cohort (n = 14) (median age, 69 vs 73 years). Patients in the R/R cohort had a median of two prior treat-ments, 45 % of them had at least three prior treatments, and most of them (87 %) had been exposed to anti-CD20 therapy. One third of the R/R cohort was refractory to the last therapy. Ac-cording to the modified 3rd iwWM crite-ria, the ORR in the R/R cohort reached 95 %, with a MRR of 82 % (VGPR, 41 %; PR, 38 %; MR, 13 %). In the TN cohort, the ORR was 93 % and the MRR 79 %, including a VGPR of 7 %. The treatment resulted in clinical benefits for patients, with a prompt decrease in IgM levels and Hgb improving at a rapid rate (**Fig-ure 1**). The median PFS for the whole cohort was 67.5 months, with an esti-mated 66-month PFS rate of 52 % in the R/R cohort and of 84 % in the TN cohort
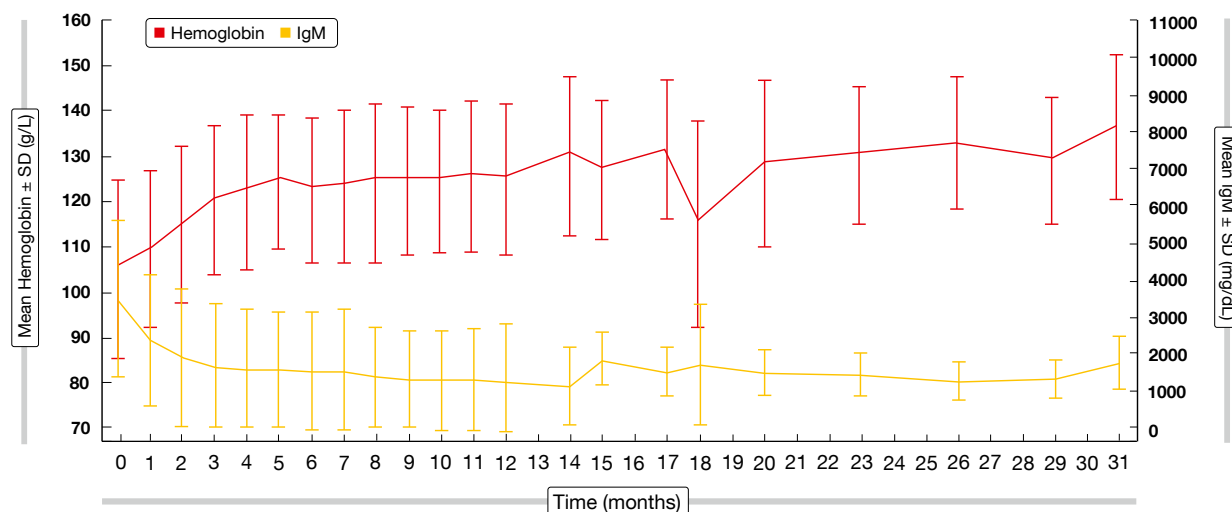
**Figure 1:** Mean hemoglobin and IgM levels of patients in the R/R disease cohort.

and an estimated 66-month OS rate of 71 % and 91 %, respectively. Multivariate analysis showed that having two prior lines of therapy had a significant negative impact on the PFS rate compared to two or less therapies (53.7 % vs 83.5 %; HR = 1.892; 95% CI, 1.007-3.557; p = 0.0441).

There were more AEs in the TN cohort than in the R/R cohort (29 % vs 16 %). Disease progression was reported in 7 % in the TN cohort and 22 % in the R/R cohort. The most common grade 3-4 AEs were infections (33% in the R/R cohort and 14 % in the TN cohort) and cardiac events (7 % and 14 %, respectively). Grade 3-4 bleeding (7 %), atrial fibrillation (2 %) and hypertension (4 %) were observed in the R/R group only.

This phase II trial demonstrated the high efficiency of acalabrutinib in treating WM, with a confirmed long-term efficacy in the R/R setting. The toxicity profile was favorable, with a relatively low discontinuation rate and a good cardiovascular profile. Further clinical evaluation of acalabrutinib in randomized controlled trials are warranted.

## Long-term follow-up of zanubrutinib

Zanubrutinib, another potent next-generation BTKi, shows a similar efficacy and a higher selectivity compared to ibrutinib. Zanubrutinib has specifically been designed to maximize BTK occupancy. Its advantageous pharmacokinetic (PK) and pharmacodynamic prop-

erties allow a median of 24-hour occupancy of 100 % with BID dosing in peripheral blood mononuclear cell (PBMC) and lymph nodes [4]. Moreover, zanubrutinib showed a reduced off-target inhibition of other tyrosine kinases family members [5]. Besides, zanubrutinib can be administered along with strong/moderate cytochrome P3A (CYP3A) inhibitors at a reduced dose, as well as proton pump inhibitors, acid-reducing agents, and antithrombotic agents [6].

Zanubrutinib safety, PK, antitumor activity, and optimal dosing in B-cell malignancies including WM have been assessed in the phase 1/2 BGB-3111-AU-003 trial [7]. Safety and efficacy data of the 3.5-year follow-up analysis were presented at iwWM 2022 by Judith Trotman [8].

Initially, this international trial included patients with R/R disease, then broadened up to include TN patients in phase II of the study. Eligibility criteria included having a WHO-defined B cell malignancy, at least one prior therapy (in the R/R cohort), no available higher-priority treatment, an ECOG PS scoring of two or less, a minimal absolute neutrophil count of 1000/μL and a minimal platelet count of 100,000/μL. Other eligibility criteria enclosed having an adequate renal and hepatic function, as well as no significant cardiac disease. The dose escalation phase consisted of 40, 80 and 160 mg of zanubrutinib QD, followed by the dose expansion phase consisting of 320 mg QD or 160 mg BID.

Amongst the 78 WM patients recruited, 73 were evaluable for efficacy, 32 discontinued due to PD or toxicity and 46 rolled-over to long-term extension study. Patients' genotype slightly differed amongst R/R and TN patients ($MYD88^{MUT}$, 72 % vs 83 %). Most patients responded to the treatment (ORR = 96 %) and the major response rate reached 82 %. VGPR and CR were attained by 49 % and 2 % of the R/R patients, as well as 33 % and 4 % of the TN population. To note, there was a comparable response rate between the QD (n = 22, ORR = 91 %, VGPR + CR rate = 32 %) and BID (n = 47, ORR = 98 %, VGPR + CR rates = 49 %) doses. The median follow-up of R/R patients was 48.8 months compared to 39.6 months in the TN population. The 4-year PFS rate was higher in the TN population (71.2 % vs 64.7 %). Of note, the rate of patients without subsequent therapy plateaued over a median of three years, just below 100 %, in the TN population and over 80 % of the R/R patients have not moved on to the next line of treatment either (**Figure 2**).

All WM patients experienced TEAEs; 64 % of them had grade ≥ 3 TEAEs. Most common grade ≥ 3 AEs were infections (29.5 %), neutropenia (16.7 %), second primary malignancies (12.8 %) and anemia (11.5 %). In total, 17 % of the AEs led to a treatment discontinuation, with 3.8 % of them being related to zanubrutinib. A comparable safety was observed regardless of the dosage timing (QD or BID).
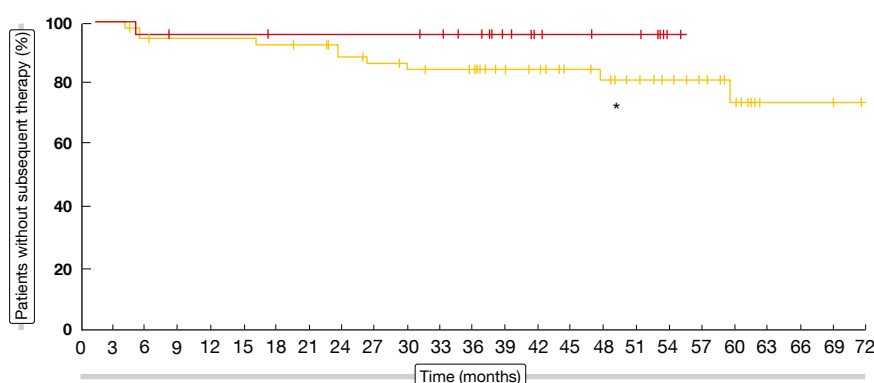
**Figure 2:** Time to next treatment in patients with TN or R/R WM. *, median follow-up

Long-term treatment with zanubrutinib was very well tolerated and resulted in durable responses. Deep responses were observed in both TN and R/R patients, as well as in all molecular subtypes including $MYD88^{WT}$. There was no apparent exposure safety and efficacy relationships between the QD and BID groups, which allowed for extrapolation despite the small number of patients treated QD. Both regimens have been approved for WM by US Food and Drug Administration (FDA), Health Canada, Australia, and European Medical Agency (EMA).

## Long-term data of zanubrutinib therapy in a Chinese R/R population

Zanubrutinib efficacy and safety have been evaluated in Chinese patients with R/R WM in the phase II BGB-3111-210 trial (NCT03332173) [9]. Shuhua Yi presented the long-term analysis of this multicenter trial after a median follow-up of 33 months at this year's iwWM meeting [10].

Patients included in this study were over 18-year old, had a confirmed WM pathology, met at least one treatment criteria according to the 7th iwWM panel consensus [11], had received at least one prior line of standard CIT regimen and documented failure to achieve MR of disease progression (PD). Patients received zanubrutinib monotherapy (160 mg, PO, BID) until PD or intolerable toxicity. The primary endpoint was MRR rate (CR + VGPR + PR) as assessed by an independent review committee according to the response criteria updated at the 6th iwWM [12]. PFS, ORR, duration of major response (DoMR) and safety were set as secondary endpoints.

A total of 44 patients were recruited, whose median age was 65 years and ECOG performance status was 0/1 for most of them (93.2 %). Three quarters had an intermediate or high-risk WM prognostic score, and they had received a median of two prior therapies. The rate of patients with $MYD88^{WT}$ was surprisingly high (15.9 %) in this cohort. Peripheral blood cytopenia at study enrollment were frequent (anemia 75 %, thrombocytopenia 20.5 % and neutropenia 25 %).

The MRR attained 69.8 % (VGPR, 32.6 %; PR, 37.2 %) and was close to the ORR of 76.7 % (MR or better). After a median follow-up of 33 months, the median PFS and DoMR rates were not reached. The 18- and 24-month PFS rates were 68.1 % and 60.5 %, respectively, while the 18- and 24-month DoMR rates both reached 75.1 %. The median time to major or overall response was 2.8 months each, and the median time to VGPR or CR was 4.2 months. The subgroup analysis confirmed the MRR benefit of zanubrutinib in all items analyzed – including $MYD88^{WT}$ and $CXCR4^{MUT}$ genotypes. However, the best MRR was obtained within the $MYD88^{MUT}/CXCR4^{WT}$ WM patients.

The rate of grade ≥ 3 TEAEs or serious TEAEs was 77.3 % and 56.8 %, respectively. Overall, 11.4 % of TEAEs led to a treatment discontinuation and 4.5 % of them led to death. No atrial fibrillation or flutter events were reported.

After a 33-month follow-up, administrating zanubrutinib to Chinese patients with R/R WM proved to be an effective treatment, as demonstrated by the high rate of deep, rapid, and durable response. The safety profile and tolerability of zanubrutinib was satisfactory and comparable to prior study results. ∎

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# Latest updates on BTKi-treatment in WM

### Long-term BTKi monotherapy

Ibrutinib monotherapy is approved for all lines of therapy in patients with WM, although its initial trial was focused on patients who relapsed, only (NCT01614821) [1]. Thus, clinical research on the use of ibrutinib monotherapy in the frontline setting of WM is warranted. At this year's iwWM congress, Jorge Castillo presented long term data (4 years) of ibrutinib monotherapy in treatment-naïve WM patients [2].

In this investigator-initiated, open-label, prospective phase II study, single-agent ibrutinib (420 mg once daily) was evaluated in treatment-naive patients with WM (NCT02604511) [3]. At the data cut-off date (March 16, 2021), 31 patients were allocated to treatment intervention and 19 patients completed the study. The median patients' age was 63 to 64 years and about half of them had a $CXCR4$ mutation ($CXCR4^{MUT}$, n = 14; $CXCR4^{WT}$, n = 16). Both groups presented with similar characteristics, although $CXCR4^{MUT}$ patients had significantly lower rates of adenopathies (14 % vs 50 %, p = 0.04) and lower β2-microglobulin levels (3.4 mg/L vs 4.2 mg/L, p = 0.07) than $CXCR4^{WT}$ patients.

Ibrutinib-treatment induced a 100 % response rate, including 87 % of patients with a major response. Between $CXCR4^{MUT}$ and $CXCR4^{WT}$ patients, there was a slight difference in major response (78 % vs 94 %; p = 0.09) and a numerically, though not significant, lower VGPR rate in patients with than without CXCR4 mutations (14% vs. 44%). Median time to ibrutinib response (TTR) was 0.9 months in $CXCR4^{WT}$ and a little longer in $CXCR4^{MUT}$ patients (1.7 months). Median time to major response (TTMR) was significantly shorter in $CXCR4^{WT}$ (1.8 vs 7.3 months, p = 0.01). The 4-year progression-free survival (PFS) rate was 76 % for the overall study population, 59 % in patients with a $CXCR4$ mutation and 92 % in patients without $CXCR4$ mutation (p = 0.06).

The most frequent grade ≥3 adverse events (AEs) included elevation of alanine aminotransferase (ALT), hypertension and neutropenia (in 3 patients each). Patients also experienced anemia, rash, urinary tract infection (in 2 patients each); one case of grade 4 cardiac arrest and one case of grade 4 thrombocytopenia were also reported. Of note, six patients experienced atrial fibrillation (grade 2). In all cases, therapy was further administered during the management of AEs.

Ibrutinib monotherapy, as frontline treatment in patients with WM was associated with rapid, deep, and durable responses without unexpected adverse events. While ibrutinib responses were affected by $CXCR4$ mutation, long-term disease control was attained regardless of $CXCR4$ mutational status.

### INNOVATE study: BTKi combined therapy

The INNOVATE trial (NCT02165397) was designed to evaluate the efficacy of the combination ibrutinib plus rituximab (RTX) for the treatment of patients with WM [4]; this combination was not yet approved at the time of trial initiation. Data from a primary analysis with a median follow-up of 26.5 months previously demonstrated significant higher PFS rates with this combination compared to placebo plus RTX [4]. Additionally, outcomes of recent real-world studies confirmed the clinical trial results [5, 6]. At iwWM 2022 meeting, Christian Buske presented the final analysis of the INNOVATE trial after a 63-month median follow-up [7].

INNOVATE is a large international, prospective, randomized phase III trial. Patients' eligibility criteria included confirmed WM, a measurable disease (serum IgM > 0.5 g/dL), and a sensitivity to RTX. Patients were randomized 1:1 and allocated to either experimental arm A (ibrutinib per os [PO], 420 mg, once daily until progressive disease
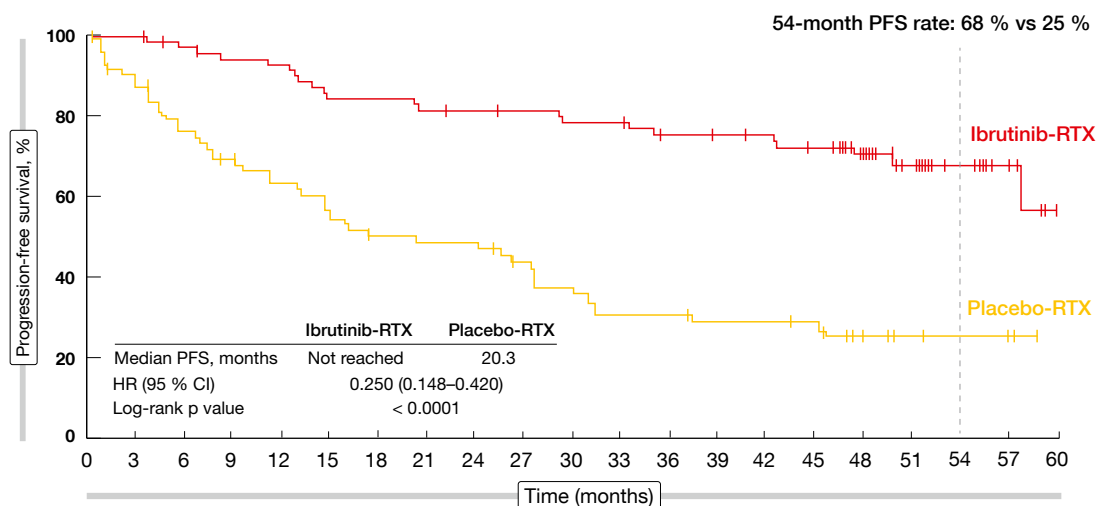


**Figure 1:** Progression-free survival rate after five years of ibrutinib plus RTX treatment in the intention to treat population of the INNOVATE study.

(PD) plus RTX intravenously [IV] 375 mg/m$^2$ on Day 1 of Weeks 1-4 and 17-20) or to arm B (placebo until PD plus RTX, same administration and dosage as in arm A). Patients in arm B were allowed to crossover to single-agent ibrutinib after progression. Patients were stratified according to International Prognostic Scoring System for WM (IPSSWM), number of prior regimens and ECOG performance status (PS). The primary endpoint was PFS, and secondary endpoints enclosed response rates as assessed by an independent central review committee (ICR), OS, Hbg improvement, time to next treatment (TTNT) and safety. At study closure, patients without PD were allowed to further receive ibrutinib in an extension program.

Median age was 70 years in arm A (n= 75) and 68 years in arm B (n= 75), and IPSSWM was intermediate or high for around 80 % of the patients. Although most patients had received one or two prior systemic therapies, there was a substantial proportion of treatment-naïve patients (45 %) in each arm. About 45 % of the patients were MYD88$^{MUT}$, one third of them were CXCR4$^{MUT}$ and 12 to 15 % presented with both mutations.

Whereas the median PFS was not reached with five years of treatment (NR vs 20.3 %; HR = 0.250; 95 % CI, 0.148-0.420; p < 0.0001), the 54-month PFS rate demonstrated a strong benefit of ibrutinib plus RTX over placebo plus RTX (68 % vs 25 %, **Figure 1**). Interestingly, the PFS-benefit of adding ibrutinib to RTX was observed regardless of patients' genotype and prior treatment status. The major response rate (MRR) was higher in arm A than in arm B (76 % vs 31 %). Although ibrutinib plus rituximab acted quite fast, remission deepened during the study, indicating that some patients were late responders. The higher response rates observed in arm A were independent of genotypes or prior treatment status. Ibrutinib plus RTX was faster than placebo plus RTX in improving and sustaining IgM and Hgb levels. The median OS was not reached in either treatment arm over the five-year follow-up period. There was a substantially higher number of patients with PD in arm B compared to arm A (45 % vs 9 %), as well as more patients receiving a subsequent treatment (63 %

vs 12 %, respectively). In total, 47 % of patients in arm B crossed over to single agent ibrutinib after PD.

The prevalence of AEs leading to dose reduction or to treatment discontinuation were quite low (11% in year 3 to 5 % in year 5). Most common treatment-emergent AEs (TEAEs) were arthralgia (13 %), hypertension (10 %) and diarrhea (3 %) in year 4 to 5, whereby the frequency decreased over time (15 %, 17 % and 11 %, respectively, in year 3 to 4).

After a 63-month follow-up, the combination of ibrutinib plus RTX showed its ongoing superiority over placebo plus RTX in patients with WM. Surprisingly, clinical outcomes were independent of patients' genotype. Over the long-term therapy of ibrutinib plus RTX, a stable and manageable safety profile with no new signals was observed in this patient population.

## Real world data on CIT and BTKi: the WhiMSICAL registry

WhiMSICAL is the first global registry collecting patient-derived data in WM. It aims for a continuously expanding patient-derived dataset, as well as generating hypotheses around WM presentations, treatment, and patient-reported outcomes (PROs) [8].

One of the many gaps in WM clinical research is a head-to-head comparison of BTKis with chemoimmunotherapy (CIT). A recent real-world study demonstrated the relative equivalence of the combination bendamustine plus rituximab (BR) and BTKi in terms of efficacy [9]. In this context, the WhiMSICAL registry was used to identify the treatment

efficacy (TTNT) of BTKi versus CIT in real-life conditions, as well as the treatment-related quality of life (QoL). The study presented at iwWM 2022 by Ibrahim Tohidi-Esfahani was initiated and driven by patients of the International Waldenström's Macroglobulinemia Foundation (IWMF) and affiliates, partnered with international clinicians. Patients were recruited globally through social media [10], completed their consent online (www.cart-wheel.org) and entered information retrospectively and prospectively about their symptoms, pathology, treatment (regimen and date), QoL (EORTC QLQ-C30 score), as well as on COVID-19 infection and vaccines.

After six years, the registry recruited 644 patients from 21 countries. Most patients originated from English speaking countries (USA, 53 %; Australia, 20 %; UK, 9 %). Regarding the first line of treatment, 370 patients were administered CIT (BR, n = 110; rituximab [R], n = 64; dexamethasone/rituximab/cyclophosphamide [DRC], n = 37), while 53 patients received BTKi containing regimens (BTKi monotherapy, n = 42). The BTKi group was significantly older than the CIT group (median age, 66 vs 62 years, p = 0.02) at first treatment and time to 1st treatment was significantly longer (411 vs 82 days, p = 0.009). The median follow-up for the front-line setting was 56 months. With a median follow-up of 38 months, the median TTNT was 87 months with BR; with a median follow-up of 56 months, the median TTNT was 33 months with rituximab; and with a median follow-up of 51 months, the median TTNT was 84 months with DRC and not reached in
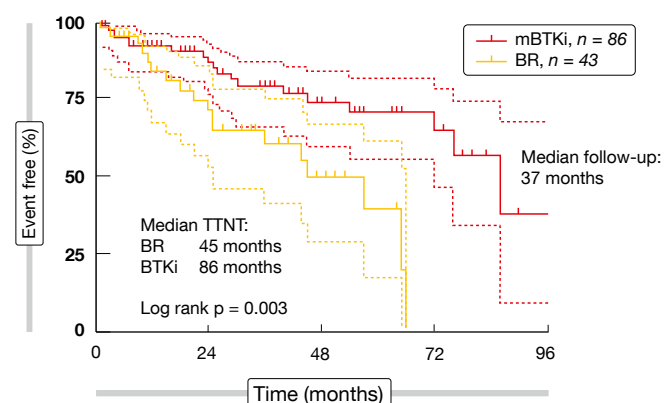


**Figure 2:** Time to next treatment (TTNT) of cohorts with bendamustine plus rituximab (BR) vs BTKi therapy in the relapsed/refractory setting.

the BTKi group, with only the rituximab vs BTKi difference being statistically significant.

In the relapsed/refractory setting, the most common administered treatments were BTKi monotherapy (n = 86) and BR (n = 43). Patients' characteristics were similar in terms of age, comorbidities, IgM and Hgb levels between both groups. In total, 40 % of BTKi patients received prior bendamustine treatment, while 9 % of BR patients received a prior BTKi therapy. The median follow-up was 37 months and median TTNT was twice as long in the BTKi group compared to the CIT group (86 months vs 45 months, p = 0.003) (**Figure 2**). Reported QoL across 1L and R/R setting was significantly higher (p < 0.01) in patients who were still receiving BTKi compared to those who had a BR therapy in the last twelve months.

Real-world data collected from the WhiMSICAL register on CIT versus BTKi treatment demonstrated the superiority of BTKi over BR in terms of TTNT in a relapsed/refractory setting and equivalent TTNT in the 1L. A better QoL was reported by patients treated with BTKi compared to BR. This registry keeps being implemented and will become more and more powerful, giving new insights into WM PROs, as well as facilitating treatment decisions for clinicians and patients. ∎

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## Expert interviews at iwWM 2022

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**Roger Owen** discusses whether the choice of BTK-inhibitor matters, what clinical data tell us about the long-term performance of acalabrutinib and talks about the different association of ibrutinib and zanubrutinib with efficacy in patients with Waldenström's Macroglobulinemia and low frequency genetic alterations while finally reflecting his highlights from the 11th International Workshop on WM especially the role of minimal residual disease as an independent predictor of patient outcomes.

**Jorge Castillo** highlights the most relevant findings regarding chemoimmunotherapy in patients with Waldenström's Macroglobulinemia presented at the 11th iwWM, discusses the management of WM patients who have been exposed to covalent BTK inhibitors, explains which clinical endpoint(s) should be reached in the treatment of patients with WM and shares his thoughts on promising novel treatment approaches.

For those who are not only interested in non-Hodgkin lymphoma but also in Hodgkin lymphoma please check out our congress report on a range of relevant and potentially practice-changing findings from the International Symposium on Hodgkin Lymphoma (ISHL12), too.

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**Steven P. Treon** explains where we are at present regarding curability of Waldenström's Macroglobulinemia, key questions in the management of patients with WM, genomic testing and genomically driven algorithms for the treatment of WM. Moreover, he discusses which treatments might be implemented in the future while finally summarizing his highlights from the 11th International Workshop on WM.

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### memo – inHaematology SPECIAL ISSUE
Congress Report ASH 2022

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

Report from the American Society of hematology (ASH) Annual Meeting, December 10–13, 2022

## Forthcoming Special Issue

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

# ASH 2022
# Annual Meeting
## 10 DECEMBER - 13 DECEMBER 2022