BTK Inhibitors in the Frontline Management of Waldenström Macroglobulinemia

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KEYWORDS

• Waldenström macroglobulinemia • Untreated • Frontline therapy • BTK inhibitors • Ibrutinib • Acalabrutinib • Zanubrutinib • Tirabrutinib

KEY POINTS

- Bruton Kinase (BTK) inhibitors have demonstrated clinically meaningful efficacy in patients with previously untreated Waldenström macroglobulinemia.
- Compared with ibrutinib, zanubrutinib provided faster and deeper response in patients with CXCR4 mutations.
- Second-generation BTK inhibitors, acalabrutinib and zanubrutinib, have also shown activity in MYD88 Wild type (WT) patients.
- Safety profile of acalabrutinib and zanubrutinib is superior compared with ibrutinib, consistent with lesser off-target activity.

INTRODUCTION

The seminal discovery of the importance of BTK signaling through MYD88 in the pathogenesis of Waldenström macroglobulinemia (WM) ushered in a new era in the treatment of this rare non-Hodgkin lymphoma. Treon and others in 2012 described a recurring, activating somatic mutation in the MYD88 gene, L265P, present in more than 90% of patients with WM, demonstrating its importance in the proliferation and survival of the malignant clone.[1] In their article reporting this discovery, the authors noted, "It remains to be seen whether MYD88 L265P signaling can be targeted for the therapy of Waldenström's macroglobulinemia and non-IgM LPL." It did not take long.

A first-in-class BTK inhibitor (BTKi), ibrutinib, demonstrated remarkable efficacy in previously treated WM as reported by Treon colleagues in 63 patients in 2015,[2] which resulted in approval by the FDA that same year and by European Medicines Agency (EMA) in 2016. By then, whole genome sequencing had uncovered a second mutated

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gene, CXCR4, found in approximately 30% to 40% of patients with WM, the presence of which conferred a different phenotype. Moreover, patients harboring a CXCR4 mutation seemed to have an attenuated response to ibrutinib, with fewer, less robust, and more delayed responses. Treon and colleagues updated the data from their pivotal trial in 2021 and demonstrated the negative impact of CXCR4 mutations on ibrutinib efficacy.[3] The 5-year progression-free survival (PFS) for patients with MYD88 mutations both without and with CXCR4 mutations was 70% versus 38%, respectively. The efficacy of ibrutinib in the treatment of rituximab-refractory patients with WM was furthermore confirmed by arm C of the iNNOVATE study[4] (discussed below and elsewhere) and other subsequent study. Clinical trials utilizing ibrutinib in previously untreated patients with WM shortly followed.[5,6]

This review will address the role of ibrutinib as well as the next-generation inhibitors of BTK acalabrutinib, zanubrutinib, and tirabrutinib in the treatment of treatment-naïve (TN) patients with WM.

CURRENT EVIDENCE WITH BTK INHIBITORS AS INITIAL THERAPY FOR SYMPTOMATIC WALDENSTRÖM MACROGLOBULINEMIA

Ibrutinib

Data regarding ibrutinib therapy in the first line or TN patients with WM emanate primarily from 3 prospective studies, each of which differ in design but from which one can draw important and similar conclusions (**Table 1**).

In 2018, for the first time, data addressing the use of ibrutinib monotherapy in TN patients with WM were reported. Treon and colleagues published their single-center, prospective experience with first-line ibrutinib in 30 patients.[5] All patients met International Workshop for Waldenström Macroglobulinemia (IWWM) criteria for initiating therapy and the median age was 67 years (range: 43–83). All patients harbored the MYD88 L265P mutation. In addition, 14 patients (47%) had a concomitant CXCR4 mutation. The specific CXCR4 mutations were not initially reported. The primary endpoint was major response rate (MRR). Among the key secondary endpoints was the effect of

Table 1
Efficacy of BTK inhibitors in previously untreated patients with Waldenström macroglobulinemia

	N of Pts	Median Follow-Up (months)	ORR (%)	MRR (%)	CR + VGPR Rate (%)	PFS Rate (%)
Ibrutinib monotherapy						
Castillo, Leukemia 2022[6]	30	50.1	100	87	30	76% at 48 mo
Tam, Blood 2020[11,a]	18	19.4	89	67	17	94% at 18 mo
Ibrutinib + Rituximab						
Buske, JCO 2022[9]	34	50	91	76	27	70% at 48 mo
Acalabrutinib						
Owen, Lancet Haematol 2020[18]	14	63.7	93	78	7	84% at 66 mo
Zanubrutinib						
Trotman, Blood 2020[13]	24	23.5	100	87	33	91% at 24 mo
Tam, Blood 2020[11,a]	19	19.4	94	73	26	78% at 18 mo

[a] Updated at ASCO 2022.

CXCR4 mutational status on response. Responses were judged according to IWWM-6 criteria. All subjects received oral ibrutinib 420 mg daily until progression or tolerance dictated otherwise.

In the initial publication from 2018, with a median follow-up of 13.4 months, all patients (100%) responded to ibrutinib monotherapy, 83% attained a major response, whereas 17% demonstrated minor responses. Responses as judged by a reduction in Immunoglobulin M (IgM) levels and improvements in hemoglobin were brisk: the median times to a minor and major ($\geq$ partial response) response in IgM were 1 month and 1.9 months, respectively. CXCR4 mutations adversely affected both the depth of and time to response. Hemoglobin concentrations increased quickly, with marked improvements by cycle 2, regardless of CXCR4 mutational status (**Fig. 1**). No complete responses were noted.

The authors subsequently updated their findings with a longer median follow-up of 50 months.[6] Of the 14 patients with CXCR4 mutations, 13 had nonsense mutations, whereas 1 had a frameshift mutation. Nonsense CXCR4 mutations confer more BTKi resistance than do frameshift mutations.[7] With longer follow-up, no complete responses were reported but the very good partial response (VGPR) rate increased from 20% to 30% and the MRR had increased from 83% to 87%. The PFS rate at 4 years was 76%. Patients lacking CXCR4 mutations fared the best regarding time to response, depth of response, and PFS.

Tolerance of ibrutinib was excellent with 87% of subjects remaining on therapy at a median treatment duration of 13.4 months in the initial report. Dose reductions were uncommon (10%). At the end of the planned 4-year period of study, 66% remained on active treatment before transitioning to commercial ibrutinib. Side effects of interest included atrial fibrillation (increased from 10% in the 2018 report to 20% with longer follow-up) and hypertension (13%). Two patients progressed early on study, both of whom had CXCR4 mutations.

The phase III iNNOVATE study provided more information regarding the role of ibrutinib in TN patients with WM.[8] However, patients were treated with ibrutinib in combination with rituximab. At the time this study was conceived, single agent rituximab was the most common regimen chosen in the United States for the primary therapy for WM. This double-blind, randomized phase III study included TN patients and previously treated patients. In the latter group, those with known rituximab refractory disease received ibrutinib monotherapy (subgroup C); all other patients were randomized between rituximab and placebo or ibrutinib and rituximab (IR). One hundred fifty patients were included in the phase III portion of the study and randomized, 34 (45%) of whom were treatment naïve. Subjects randomized to ibrutinib plus rituximab received ibrutinib 420 mg orally daily and rituximab at 375 mg/m^2 for a total of 8 doses at weeks 1 to 4 and 17 to 20. Subsequently, more mature data with more than 4 years of follow-up were published; the MRR for the TN patients was 76% and the VGPR rate was 24%.[9] One of the 34 patients (3%) attained a complete remission (CR). Again, responses were rapid with the median times to any response and major response of 1 and 3 months, respectively. The 48-month PFS rate was 70%, in the previously untreated patients similar to the PFS rates in the relapsed patients (71% at 4 years). No new safety signals were seen, and the study confirmed previous experience with ibrutinib therapy for WM: 11% of patients discontinued due to an adverse event (AE), 19% developed any grade of atrial fibrillation, 25% any grade hypertension, and the risk of developing side effects appeared to diminish with prolonged ibrutinib administration.

The iNNOVATE trial yielded several provocative findings. From a safety and tolerability perspective, the addition of ibrutinib to rituximab decreased the incidence of

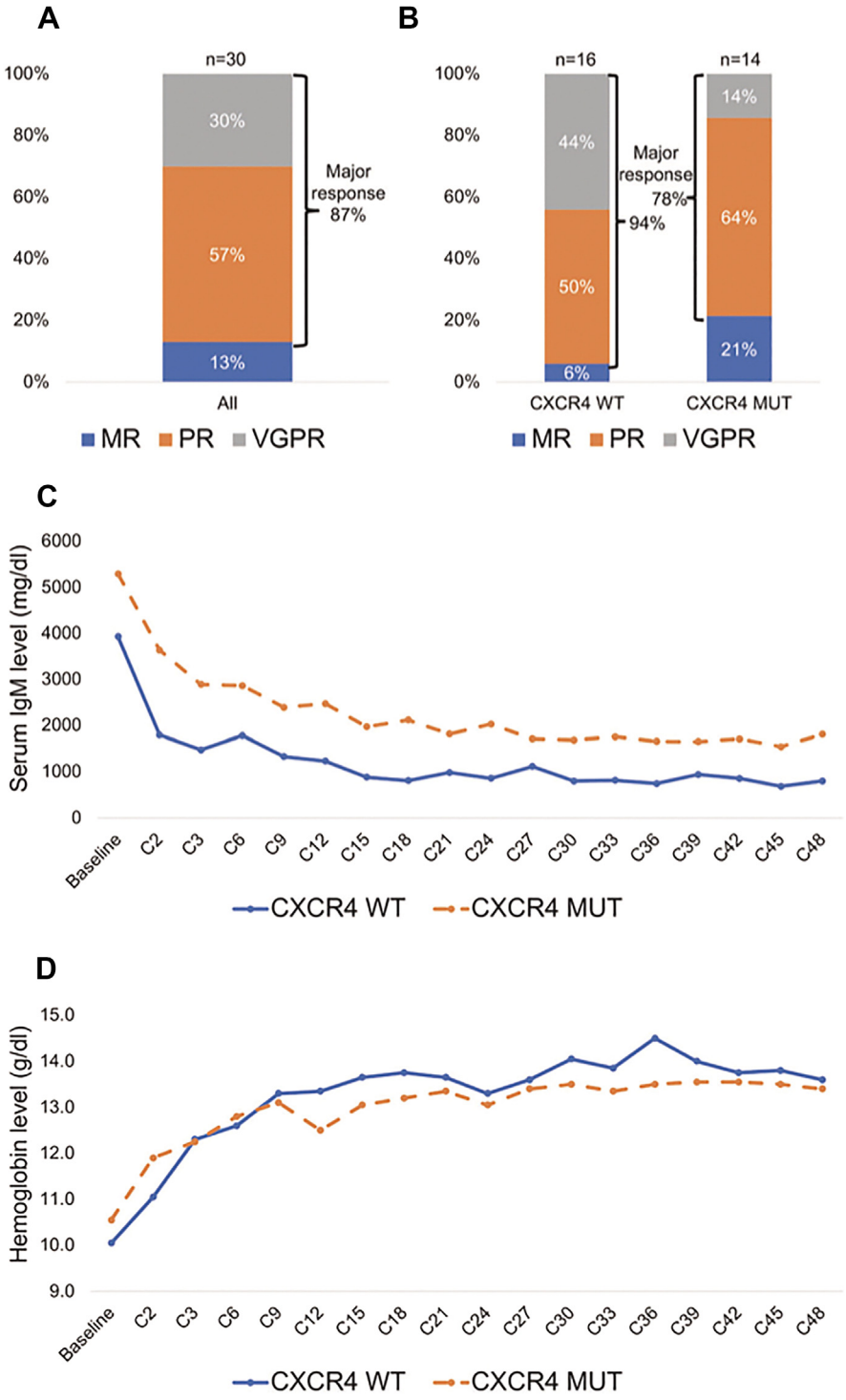

Fig. 1. Response to therapy. Categorical responses at the best response in 30 TN patients with WM treated with ibrutinib for the entire cohort (*A*), by CXCR4 mutational status (*B*), by serial IgM levels (*C*), and hemoglobin levels (*D*). MR, minor response; PR partial response; VGPR, very good partial response. (Reproduced with permission from the authors.)

both infusion-related reactions and IgM flare, both known risks of rituximab in WM, from 59% to 43% and from 47% to 8%, respectively. The PFS advantage of IR versus R plus placebo was seen regardless of genotype and lines of therapy (Fig. 2). However, the impressive response rate and PFS seen in the MYD88 WT population should be cautiously interpreted. In iNNOVATE, 16% of the patients randomized to ibrutinib and rituximab who were genotyped were categorized as MYD88 WT, which is at least 2-fold higher than reported in other studies. This discrepancy can be explained by the methodology used to assess MYD88 mutation status; the less-sensitive technique of NGS on unselected bone marrow or paraffin-embedded tissue is associated with higher rates of false-negative results.[10] This study has raised interesting questions in the treatment of WM. How much does the addition of rituximab to ibrutinib differ from ibrutinib alone? Is the finding of responses across CXCR4 mutational status practice changing? Should clinicians who do not have ready access to reliable CXCR4 testing be inclined to add rituximab to ibrutinib since we know that CXCR4-mutated patients carry inherent biologic resistance to ibrutinib? Nonetheless, the iNNOVATE trial clearly underlines the robust clinical activity and tolerance of ibrutinib and rituximab in patients not refractory to rituximab.

The third large trial to include ibrutinib in TN patients with WM is the ASPEN trial, which will be addressed in more detail later in this article. ASPEN is a phase III open-label study comparing ibrutinib to zanubrutinib, a next-generation BTKi, in both TN patients and previously treated patients with WM.[11] Of the 99 patients randomized to ibrutinib, only 18 (18.2%) were treatment naïve. All were MYD88 mutated and 20.2% carried CXCR4 mutations. Despite the small number of previously untreated patients, the study's findings, initially published in 2020 and more recently updated in 2022 (Dimopoulos and colleagues, in press), are very similar to those from Treon and colleagues and from iNNOVATE. Data were reported for all patients (not just treatment naïve) at a median follow-up of 44.4 months; the MRR was 80%, the PFS for all ibrutinib-treated patients was 70% (49% for the CXCR4-mutated patients), 20% discontinued due to AEs, and 27% required a dose reduction of ibrutinib. Adverse effects were also consistent with prior studies whereby 21% of subjects developed any grade atrial fibrillation and 25% any grade hypertension, of which 20% were grade 3 or greater.

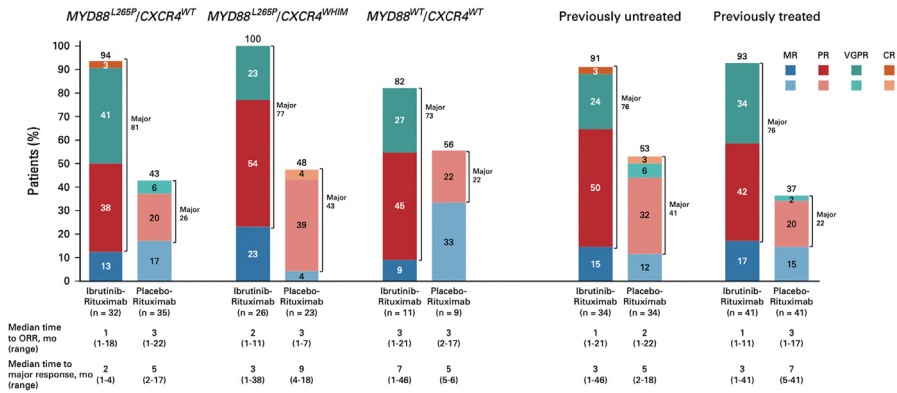

Fig. 2. iNNOVATE study. Overall and MRRs by treatment group, mutational status, and previously treated versus previously untreated patients. CR, complete response; MR, minor response; PR partial response; VGPR, very good partial response. (Reproduced and adapted by permission of the authors.)

What is clear from the limited numbers of patients treated initially with ibrutinib relative to the larger number treated beyond first line is that both the results in terms of efficacy and tolerability are remarkably similar. It is quite legitimate to extrapolate data utilizing ibrutinib beyond first line to TN patients.

More recently, so-called real-world data are emerging concerning the use of front-line ibrutinib in patients with WM. Abeykoon and colleagues from the Mayo Clinic retrospectively identified 13 TN patients treated with ibrutinib monotherapy with a relatively short median follow-up of 19 months.[12] Genotyping information was sporadic and response data were only available for 9 of 13 TN patients: all responded and the MRR was 78%. More recently, Abeykoon and colleagues reported at ASCO 2022 their retrospective experience in 347 TN patients with WM who received chemoimmunotherapy with bendamustine and rituximab (n = 208) or ibrutinib (n = 139) treated between 2011 and 2021. Again, with a median follow-up of 4.2 years, the 4-year PFS was 73% in both groups, although there was a higher VGPR rate in the bendamustine and rituximab group. This study, therefore, corroborates the findings of the smaller prospective studies detailed above.

Zanubrutinib

Zanubrutinib is a second-generation, potent, and more selective irreversible covalent BTKi designed to maximize BTK occupancy and minimize inhibition of off-target kinases, which may be responsible for adverse events typically observed with this class of drugs. The FDA has approved zanubrutinib for patients with relapsed refractory (R/R) mantle cell lymphoma (MCL), patients with marginal zone lymphoma (MZL) who have had at least one anti-CD20–based treatment, patients with WM and with chronic lymphocytic leukemia (CLL). Zanubrutinib has also received EMA approval for WM, MZL, and CLL.

Phase 1/2 study with zanubrutinib in B-cell malignancies

In the first-in-human, multicenter, phase 1/2 study of zanubrutinib in patients with B-cell malignancies (BGB-3111 AU-003),[13] no maximum tolerated dose was identified in part 1, and 160 mg twice daily or 320 mg daily were identified as the recommended phase 2 dose, the former being preferred based on more favorable pharmacodynamic profile with near complete BTK occupancy in lymph nodes. The part 2 of the study included 77 patients with WM, of whom 24 were TN and 53 relapsed/refractory. The primary efficacy endpoint was the rate of VGPR or CR. Of 73 patients evaluable for efficacy, the rate of VGPR or CR was 45% in TN and 51% in R/R patients. The proportion of patients achieving VGPR/CR increased with treatment duration, reaching 44% in TN cohort and 49% in R/R cohort at 24 months. Among 65 patients with available genotype, the VGPR/CR rate was 59%, 27% and 25%, respectively, in patients who were MYD88 (L265P)/CXCR4WT, MYD88 (L265P)/CXCR4WHIM and MYD88 WT.

The median PFS in patients with R/R disease was not reached after a median follow-up of 36.8 months. The estimated event-free rates at 18, 24, and 36 months were 84%, 76%, and 76%, respectively. The median PFS in TN patients was not reached after a median follow-up of 23 months. The estimated event-free rates at 18 and 24 months were both 92%. The estimated 3-year progression-free survival rate was 80.5%, and the overall survival rate was 85%. Adverse events of interest included contusion (32.5%, all grade 1), neutropenia (18%), major hemorrhage (3.9%), atrial fibrillation/flutter (5.2%), and grade 3 diarrhea (2.6%).

The ASPEN study

The randomized open-label multicenter phase III ASPEN trial was designed to compare the efficacy and safety of zanubrutinib with ibrutinib in MYD88 mutated patients with WM.[11] The study included either R/R patients with WM not previously treated with BTK inhibitors, or TN patients unsuitable to standard chemoimmunotherapy. Patients were stratified by CXCR4 status (CXCR4WHIM vs CXCR4WT vs missing) and number of prior lines of therapy (0 vs 1–3 vs > 3). The study included a larger cohort of 201 MYD88 mutated patients (Cohort 1, n = 201) randomized to receive zanubrutinib 160 mg BID or ibrutinib 420 mg once daily (QD), and a smaller cohort of 28 MYD88 WT patients who received zanubrutinib 160 mg *bis in die* (BID) (Cohort 2). Treatment was administered until progression, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. The study's primary endpoint was the CR or VGPR rate in cohort 1. Key secondary endpoints were MRR, PFS, DOR, OS and safety. The primary endpoint of the study was not met, since by IRC-assessment the CR + VGPR rate was not significantly higher in patients treated with zanubrutinib as compared with patients treated with ibrutinib (28.4% versus 17.2%, $P = .09$). Responses deepened over time and at 44.4 months the CR + VGPR rate reached 36.5% with zanubrutinib and 25.3% with ibrutinib in MYD88 mutated patients, and 30.7% in MYD88 WT patients.[14] In patients with CXCR4 mutation responses were deeper and faster with zanubrutinib than with ibrutinib (VGPR + CR rate 44.6% versus 21.2%, the median time to major response 3.4 months versus 6.6 months). In the single-arm Cohort 2 MYD88 WT patients, the MRR was 50%, including 27% VGPR.[15] At 18 months, PFS was similar in the 2 treatment arms (85% with zanubrutinib versus 84% with ibrutinib).

Zanubrutinib was associated with meaningful advantages in terms of safety and tolerability. In particular, a significantly lower rate of atrial fibrillation was observed in patients treated with zanubrutinib as compared with ibrutinib (3% versus 18%, $P = .0004$). On the other hand, zanubrutinib was associated with a significantly higher rate of neutropenia (32% versus 15%), which did not translate into a higher incidence of infections. With longer follow-up, zanubrutinib confirmed a favorable safety profile, with a significantly lower incidence of adverse events leading to treatment discontinuation or dose reduction. In particular, the cumulative incidence of atrial fibrillation (7.9% versus 23.5%) and hypertension (14.9% versus 25.5%) was significantly lower as compared with ibrutinib.[14] The safety profile of zanubrutinib in patients with WM is consistent with that reported in other B-cell malignancies.[16]

Phase 2 expanded access study (BGB-3111–216)

Fifty patients with WM (17 treatment naïve and 33 relapsed/refractory with a median of 2 earlier therapies) were treated with zanubrutinib 160 BID or 320 mg OD across 10 academic and community medical centers in the United States. Median age was 72 year and most were classified as intermediate (54%) or high-risk (40%) disease. Overall, major, and VGPR were observed in 85%, 73%, and 39% of patients, respectively. Despite older age and high proportion of intermediate-high risk patients, efficacy and safety results were comparable to those reported in ASPEN trial.[17]

Acalabrutinib

Acalabrutinib is a highly selective second-generation irreversible BTK and does not affect other kinases, such as EGFR, Tec, or interleukin-2-inducible kinase, associated with side effects such as rash, atrial fibrillation, or suppression of Natural killer (NK) cell activity. The Food and Drug Administration (FDA) has approved this agent for relapsed or refractory MCL. The safety and efficacy of acalabrutinib in patients with WM was investigated in a phase II study including 106 patients with WM, 92 R/R and 14 TN

patients.[18] Patients received 100 mg oral acalabrutinib bid until disease progression or unacceptable toxicity. The study's primary endpoint was the overall response rate (ORR). The ORR was 93% in both groups, with an MRR of 79% in TN patients and 80% in relapsed/refractory patients. In MYD88-mutated patients, the ORR was 94%, including 81% MRR and 11% VGPR. Corresponding response rates in MYD88 wild-type patients were 79%, 64%, and no VGPR or better was observed. PFS at 24 months was, respectively, 90% (95% CI 47.3–98.5) and 81.9% (95% CI 72.1–88.5). CXCR4 mutation status was not assessed in this trial.

At a median follow-up of 27.4 months (range = 4.6–40.7 months), 72% of patients remained on treatment. Treatment discontinuation due to adverse events was 21% in TN patients and 4% in relapsed/refractory patients, respectively. The most common treatment-related adverse events were bleeding (56%) mostly of grade 1 to 2, headache (39%), diarrhea (31%), contusion (29%), and dizziness (25%). Grade 3/4 neutropenia was observed in 16% of patients. Atrial fibrillation occurred in 3% of patients.

Tirabrutinib

Tirabrutinib is a second-generation, irreversible, BTKi that was approved in 2020 for the treatment of patients with WM in Japan, based on the results of a multicenter, open-label, single-arm, phase II study (ONO-4059–05) including 27 patients, 18 not previously treated and 9 who had received one or more systemic treatment.[19] Patients received tirabrutinib orally at a daily dose of 480 mg under fasting conditions until disease progression or unacceptable toxicity. MRR was 93%, including a VGPR + CR rate of 22% after the primary analysis. In an updated analysis, with a median follow-up of 24.8 months, the PFS and OS rates at 24 months were 92.6% and 100%, respectively. Treatment-related skin adverse events were observed in 52% of patients. Bleeding was reported in 33% of patients (all grade 1–2), whereas atrial fibrillation and hypertension were reported in 4% of patients each.

Zanubrutinib in Patients Intolerant to Ibrutinib or Acalabrutinib

A phase 2, multicenter, open-label, single-arm study conducted in the United States investigated treatment with zanubrutinib in 67 patients with CLL/small lymphocytic lymphoma, MCL, WM, or MZL who became intolerant to ibrutinib, acalabrutinib, or both. The primary endpoint was recurrence and change in severity of ibrutinib or acalabrutinib intolerance events based on investigator-assessed adverse events. Most intolerance events (70% for ibrutinib and 83% for acalabrutinib) did not recur with zanubrutinib. Of the recurring events, 79% of ibrutinib intolerance events and 33% of acalabrutinib intolerance event recurred at a lower severity with zanubrutinib. Moreover, no events recurred at higher severity. These data suggest that zanubrutinib may represent a viable treatment option for patients intolerant to ibrutinib and/or acalabrutinib.[20]

Withdrawal Syndrome and IgM Rebound after Discontinuation of BTK Inhibitors

Clinicians must be aware of the possible onset of withdrawal symptoms including fever, pain, and fatigue following interruption of BTK inhibitors, which is sometimes needed to manage toxicities or perioperatively to reduce the risk of bleeding. Symptoms have been reported to occur in about 20% of patients with WM who hold ibrutinib, generally within 2 days of hold, and resolve rapidly after reinitiation of therapy. Steroids may be useful to control withdrawal symptoms while waiting to resume treatment.[21]

Discontinuation of BTK inhibitors may also be followed by an IgM rebound that was reported in 25% of patients at 3 weeks and 65% at 5 weeks. The IgM rebound is

normally asymptomatic but sometimes may be abrupt and complicated by hyperviscosity syndrome requiring emergent plasmapheresis. For those patients with progression, timely initiation of salvage therapy diminishes the risk of IgM rebound.[22,23]

BTK Inhibitors as Primary Therapy for Waldenström Macroglobulinemia

There are no published prospective randomized studies comparing efficacy and safety of BTK inhibitors with chemoimmunotherapy, which has been considered the standard frontline approach in the past 2 decades, until BTK inhibitors became available. The ongoing RAINBOW trial (NCT04061512) is comparing rituximab-ibrutinib with dexamethasone–rituximab-cyclophosphamide. Furthermore, data on the optimal sequencing of available therapies are currently limited to a single retrospective study showing comparable outcomes of patients receiving chemoimmunotherapy frontline and BTK inhibitors at first relapse as compared with patients treated with the opposite sequencing (Tawqif and colleagues.[24] EHA 2022). While waiting to get more evidence on the best sequencing, the choice between BTK inhibitors or chemoimmunotherapy frontline is mainly driven by patients' characteristics (age, fitness, comorbidities) and practical considerations (indefinite oral versus fixed-duration parenteral therapy, costs, and drug reimbursement). A therapeutic algorithm based on genomic profile was proposed some years ago, indicating ibrutinib as the first-choice for MYD88-mutated/CXCR4 wild-type patients and for MYD88-mutated/CXCR4-mutated patients for whom a rapid response is not needed, whereas chemoimmunotherapy was considered the preferred option in MYD88-mutated/CXCR4-mutated patients in need of a rapid response and in MYD88 wild-type subjects.[25] However, this scenario has changed with the approval of second-generation BTKi zanubrutinib, which has demonstrated remarkable activity also in CXCR4-mutated patients and in MYD88 wild-type ones.

Preliminary data from retrospective studies suggest that TP53 aberrations are associated with chemoresistance in WM,[26] as in other lymphoproliferative disorders. With the availability of an alternative to chemotherapy, these abnormalities could become relevant as a driver of treatment choice in the next future.

SUMMARY

BTK inhibitors have demonstrated clinically meaningful efficacy in patients with previously untreated WM. In a head-to-head comparison with ibrutinib, zanubrutinib was not significantly superior to ibrutinib but provided faster and deeper response in CXCR4-mutated patients. Furthermore, unlike ibrutinib, second-generation BTK inhibitors acalabrutinib and zanubrutinib showed activity also in MYD88 WT patients.

The safety advantages of second-generation BTK inhibitors are consistent with less off-target activity compared with ibrutinib. In a head-to-head comparison with ibrutinib, fewer adverse events leading to treatment discontinuation, dose reductions, and deaths occurred in the zanubrutinib arm. The cumulative incidences of atrial fibrillation, diarrhea, and hypertension were lower in patients receiving zanubrutinib. Despite a higher rate of neutropenia in the zanubrutinib arm, infection rates were similar. Real-world data are eagerly awaited to confirm the efficacy and safety of BTK inhibitors in unselected patients with WM.

CLINICS CARE POINTS

- BTK inhibitors are highly effective and well tolerated as front-line treatment of WM.

- Clinical responses to BTK inhibitors are influenced by both MYD88 and CXCR4 mutational status.
- Complete response is quite rare with BTK inhibitors, despite their robust clinical activity.
- In selected situations, there are data supporting adding rituximab to ibrutinib.
- The next-generation BTK inhibitors have fewer off-target effects because of their higher selectivity compared with ibrutinib.
- While BTK inhibitors have a well-established role in patients relapsing after chemoimmunotherapy, evidence in the frontline setting is more limited. Studies comparing BTK inhibitors with chemoimmunotherapy in TN patients with WM are ongoing and will determine whether BTK inhibitors should be considered the standard of care for all or for definite subsets of patients.

DISCLOSURE

M. Varettoni: ABBVIE: advisory board, speaker honoraria; AstraZeneca: advisory board, speaker honoraria; Beigene: advisory board; Janssen: advisory board.J.V. Matous: Beigene: advisory board; Janssen: advisory board.

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