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To cite this article: Shayna Sarosiek, David Sermer, Andrew R. Branagan, Steven P. Treon & Jorge J. Castillo (2022) Zanubrutinib for the treatment of adults with Waldenstrom macroglobulinemia, Expert Review of Anticancer Therapy, 22:5, 471-478, DOI: [10.1080/14737140.2022.2064849](https://doi.org/10.1080/14737140.2022.2064849)

To link to this article: <https://doi.org/10.1080/14737140.2022.2064849>



Published online: 22 Apr 2022.



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REVIEW



Zanubrutinib for the treatment of adults with Waldenström macroglobulinemia

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ABSTRACT

Introduction: The development of Bruton tyrosine kinase (BTK) inhibitors has significantly changed the treatment landscape for patients with Waldenström macroglobulinemia (WM). Ibrutinib was the first BTK inhibitor to receive FDA approval for this disease, but in recent years additional more selective BTK inhibitors have become available. Zanubrutinib, the most recently FDA-approved therapy for WM, has demonstrated comparable efficacy regarding hematologic response, but with an improved side effect profile compared to other BTK inhibitors.

Areas covered: In this review, we highlight the pivotal studies that have formed the foundation for the use of zanubrutinib in WM, including safety and efficacy data from prospective clinical trials of the currently available BTK inhibitors.

Expert opinion: BTK inhibitors are very effective in WM and have an overall response rate higher than 90%. The side effect profile of these medications is manageable but does include a risk of atrial fibrillation, infection, and bleeding. The newer BTK inhibitors, such as acalabrutinib and zanubrutinib, are known to have less off-target effects and are potential treatment options. BTK inhibitors should be considered as a treatment option in treatment-naïve and previously treated disease depending on the individual patient preferences, comorbidities, and molecular profile.

ARTICLE HISTORY

Received 25 January 2022
Accepted 7 April 2022

KEYWORDS

Acalabrutinib; Bruton tyrosine kinase; BTK; ibrutinib; Waldenström macroglobulinemia; zanubrutinib

1. Introduction

Waldenström macroglobulinemia (WM) is an indolent B-cell lymphoma characterized by the presence of an IgM monoclonal gammopathy and a bone marrow infiltrate of clonal lymphoplasmacytic cells [1]. Whole genome sequencing has revealed an activating mutation in *MYD88*, which is present in higher than 90% of patients with WM [2,3]. This mutation is the result of a substitution of leucine to proline in position 265 of *MYD88* (*MYD88*^{L265P}) and results in the downstream activation of nuclear factor- κ B (NF- κ B) through Bruton tyrosine kinase (BTK) and interleukin-1 receptor-associated kinases in the B-cell receptor pathway. Dysregulation of this pathway can lead to unregulated cell survival, proliferation, and migration and has been implicated in the development of many lymphoid disorders.

In addition to the *MYD88* mutation, more than 30 distinct activating mutations in the C-terminal domain of *CXCR4* have been reported in WM [4,5]. These mutations lead to activation of the pro-survival factors AKT and ERK. *CXCR4* mutations (*CXCR4*^{MUT}) include both frameshift and nonsense variants and are found in 30–40% of patients with WM [6]. The presence or absence (wild-type, WT) of these mutations has enabled the identification of three specific molecular groups of patients with WM, including *MYD88*^{L265P}*CXCR4*^{WT} (50–60%), *MYD88*^{L265P}*CXCR4*^{MUT} (30–40%), and *MYD88*^{WT}*CXCR4*^{WT} (5–10%). Distinct clinical phenotypes, survival patterns, and treatment responses have been delineated for each of these

subtypes [7–11]. Therefore, the method of evaluating these mutations is important to ensure accurate results [9]. Allele-specific PCR is the optimal manner of detecting *MYD88*^{L265P} mutations in WM. Next generation sequencing (NGS) is also commonly used but has a lower sensitivity than PCR techniques [12]. Allele-specific PCR probes have been developed for the detection of nonsense *CXCR4* mutations, but this testing is not routinely available so targeted NGS, which also has a lower sensitivity, is typically used [13]. CD19 selection also increases the sensitivity of PCR and NGS, especially in cases with low bone marrow disease burden [12,13]; however, this step might not be available outside of research settings.

The B-cell signaling pathways associated with *MYD88* and *CXCR4* mutations have been studied to advance the treatment of WM. Targeted therapies for WM, including the initial BTK inhibitor ibrutinib, have been developed from this research. Ibrutinib became the first FDA-approved treatment for WM in 2015 and since that time more selective BTK inhibitors have been developed, including the newly FDA-approved agent zanubrutinib.

2. Ibrutinib

The safety of the first BTK inhibitor, ibrutinib, was initially evaluated in a phase I clinical trial of relapsed and refractory non-Hodgkin lymphoma, including four patients with WM [14]. The objective response rate (defined as the achievement of

Article highlights

- Bruton tyrosine kinase (BTK) inhibition plays an important role in the treatment of patients with Waldenström macroglobulinemia.
- The currently available BTK inhibitors share a side effect profile that includes infection, cytopenias, bleeding, and atrial arrhythmia.
- Ibrutinib was the first FDA-approved treatment for Waldenström macroglobulinemia (WM).
- Zanubrutinib, also FDA-approved for the treatment of WM, offers an equivalent hematologic response rate with an improved side effect profile.

a partial response or better) was 60%, including a hematologic response in three of the four patients with WM. Based on these early data, additional clinical trials in WM were developed. The success of BTK inhibition with ibrutinib in WM was then demonstrated in patients with previously treated disease in a prospective trial of 63 symptomatic patients (Table 1) [15–22]. The patients enrolled in this trial were treated with ibrutinib 420 mg orally once daily until the time of disease progression or unacceptable toxicity. The overall response rate (ORR) was 91%, with an ORR of 100% in patients with *MYD88*^{L265P}*CXCR4*^{WT}. The ORR in patients with *MYD88*^{L265P}*CXCR4*^{MUT} and *MYD88*^{WT}*CXCR4*^{WT} were 86% and 60%, respectively. The median time to a minor response was 4 weeks with a shorter time to major response (1.8 vs 4.7 months) for those with *MYD88*^{L265P}*CXCR4*^{WT} compared to those with *MYD88*^{L265P}*CXCR4*^{MUT} disease. The median 5-year progression-free survival (PFS) rate was 54% overall; 70% and 38%, respectively, for patients with *MYD88*^{L265P}*CXCR4*^{WT} and *MYD88*^{L265P}*CXCR4*^{MUT} [17]. Treatment was well tolerated with grade ≥3 adverse events including neutropenia,

thrombocytopenia, and pneumonia. Eight patients (13%) experienced an atrial arrhythmia. All but one of these patients were able to continue treatment with ibrutinib despite the development of the arrhythmia.

The efficacy of ibrutinib was again demonstrated in 30 treatment-naïve patients with WM treated with ibrutinib 420 mg orally once daily as a single agent (Table 1) [23]. In this study, the ORR was 100%, and 83% of patients attained a major response (defined as a partial response or better). Lower major response rates were seen in those patients with *CXCR4*^{MUT} compared with those with *CXCR4*^{WT} at 78% and 94%, respectively. The time to major response was also longer in those with *MYD88*^{L265P}*CXCR4*^{MUT} disease compared with those with *MYD88*^{L265P}*CXCR4*^{WT} disease (7.3 v. 1.8 months, respectively) with an overall median time to major response of 1.9 months. With long-term follow-up, the median PFS in the whole cohort was not reached, and the 4-year PFS rate was 76% [19]. Although it was not statistically significant, the 4-year PFS rate was lower in patients with *CXCR4*^{MUT} compared to those with *CXCR4*^{WT} disease (59% v. 92%, respectively). The most common adverse events of grade ≥3 included increases in alanine and aspartate aminotransferase, neutropenia, hypertension, anemia, rash, thrombocytopenia, and urinary tract infections (Table 2) [16,17,19,21,22,24,25]. Atrial arrhythmias occurred in 20% of patients, and all patients were able to continue ibrutinib therapy. Based on the results of these trials, ibrutinib became the first drug to be FDA-approved for the indication of WM in 2015. Ibrutinib is also FDA-approved for the treatment of chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL).

Subsequently, an open-label subset of the iNNOVATE trial (Arm C) evaluated the use of ibrutinib in patients with

Table 1. Pivotal trials evaluating the efficacy of Bruton tyrosine kinase-inhibitors in Waldenström Macroglobulinemia.

Study	Patient population	Complete response rate	Overall response rate ^a	Progression Free Survival (PFS) Overall Survival (OS)
Ibrutinib				
Tam [16]	18 TN	0%	89%	18-month PFS: 94%
	81 R/R	0%	94%	18-month PFS: 82%
Treon [15,17]	63 R/R	0%	91%	5-year PFS: 54%
				5-year OS: 87%
Trotman [18]	31 R/R ^b	0%	87%	5-year PFS: 40%
				5-year OS: 73%
Castillo [19]	30 TN	0%	100%	4-year PFS: 76%
				4-year OS: 100%
Buske ^c [20]	34 TN	3%	91%	4-year PFS: 70%
	41 RR	0%	93%	4-year PFS: 71%
Acalabrutinib				
Owen [21]	14 TN	0%	93%	2-year PFS: 90%
				2-year OS: 92%
	92 R/R	0%	93%	2-year PFS: 82%
				2-year OS: 89%
Zanubrutinib				
Tam [16]	19 TN	0%	95%	18-month PFS: 78%
	83 R/R	0%	94%	18-month PFS: 86%
Trotman [22]	24 TN	0%	100%	2-year PFS: 92%
				2-year OS: 100%
	53 R/R	2%	94%	2-year PFS: 76%
				2-year OS: 92%

R/R, relapsed/refractory; TN, treatment-naïve.

^aOverall response rate = Complete response + very good partial response + partial response + minor response.

^bprior rituximab treatment required.

^crituximab + ibrutinib.

Table 2. Summary of select grade 3–4 adverse events with Bruton tyrosine kinase-inhibitors in Waldenström Macroglobulinemia.

Adverse Event	Ibrutinib (Tam, 2020) [16] Grade 3–4 (%)	Ibrutinib (Dimopoulos, 2017) [25] Grade 3–4 (%)	Ibrutinib (Treon, 2021) [17] Grade 3–4 (%)	Ibrutinib (Castillo, 2022) [19] Grade 3–4 (%)	Ibrutinib-Rituximab (Dimopoulos, 2018) [24] Grade 3–4 (%)	Acalabrutinib (Owen, 2020) [21] Grade 3–4 (%)	Zanubrutinib (Tam, 2020) [16] Grade 3–4 (%)	Zanubrutinib (Trotman, 2020) [22] Grade 3–4 (%)
Cytopenias								
Neutropenia	8	10	16	10	9	16	20	16
Thrombocytopenia	3	3	11	7	0	4	6	-
Cardiac								
Atrial fibrillation	4	0	2	0	12	1	0	-
Hypertension	11	10	0	10	13	3	6	4
Infections								
Lung	7	3	3	3	9	7	1	4
Skin	-	3	2	0	-	3	-	5
Urinary tract	2	-	0	7	-	2	0	1
Gastrointestinal								
Diarrhea	1	6	0	0	-	2	3	3
Nausea	1	0	-	0	-	2	0	0
Musculoskeletal								
Arthralgia	0	3	0	0	-	1	3	1
Myalgia	-	0	0	3	-	-	-	-
Rash	0	-	0	7	-	0	0	0
Fatigue	1	3	-	0	-	2	1	0
Bleeding/bruising								
Epistaxis	0	-	0	-	-	1	0	0
Bruising	0	0	-	3	-	0	0	0

"-" means not reported.

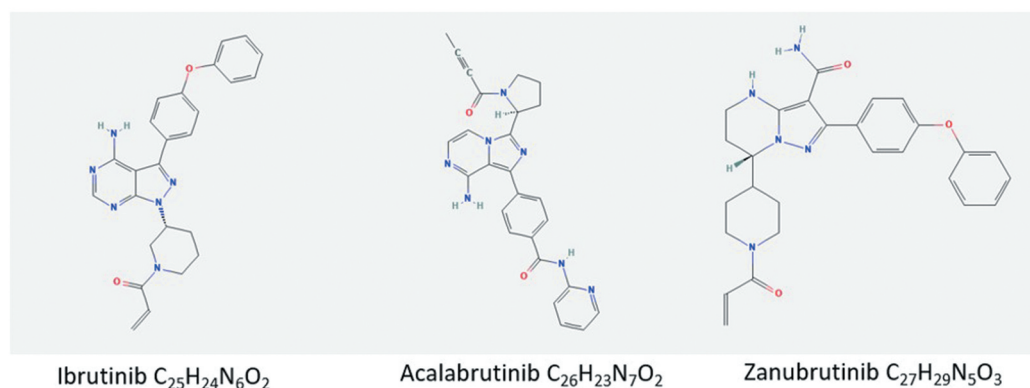
rituximab-refractory WM (Table 1) [25]. Thirty-one patients that had relapsed within 12 months or had not achieved a minor response to rituximab therapy were enrolled. Ibrutinib was administered at 420 mg orally once daily until disease progression or unacceptable toxicity. The ORR was 90% with 71% of patients achieving a major response. Long-term follow-up at a median of 58 months revealed a median PFS of 39 months with a 60-month PFS rate of 40%. The median PFS was not reached in patients with *MYD88*^{L265P}/*CXCR4*^{WT}, and it was 18 months in patients with *MYD88*^{L265P}/*CXCR4*^{MUT} disease [18]. The median overall survival (OS) was not reached. Eighty-one percent of patients had a grade ≥3 adverse event, the most common of which were infections, neutropenia, hypertension, anemia, thrombocytopenia, and diarrhea (Table 2). No atrial fibrillation was reported in this study.

In the main study of the phase III INNOVATE trial, 150 patients with either treatment-naïve or relapsed WM were randomly assigned to receive treatment with a combination of the anti-CD20 monoclonal antibody rituximab at 375 mg/m² on weeks 1 to 4 and 17 to 20 with either ibrutinib 420 mg daily (Arm A) or with placebo (Arm B) (Table 1). The ORR (92% and 72%, respectively) and the major response rate (47% and 32%, respectively) were higher in Arm A compared to Arm B [24]. At a median follow-up of 50 months, the median PFS was not reached with ibrutinib-rituximab and was 20 months in the placebo-rituximab arm [26]. For patients with *MYD88*^{L265P}/*CXCR4*^{MUT}, the major response rate for those receiving ibrutinib-rituximab was 73% compared to 48% in the placebo-rituximab arm. For patients with *MYD88*^{L265P}/*CXCR4*^{WT} the major response rate was 78% for those on the ibrutinib-rituximab arm and 29% for the placebo-rituximab arm. The time to response in patients with *CXCR4*^{MUT} was 3 months, which compares favorably to the time to response with ibrutinib monotherapy in *CXCR4*^{MUT} patients in the previously mentioned trials. The most common grade ≥3 adverse events that occurred in the ibrutinib-rituximab arm compared to

the placebo-rituximab arm included atrial fibrillation (12% v. 1%) and hypertension (13% v. 4%), with lower rates of infusion reactions (1% v. 16%) and IgM flare (8% v. 47%) (Table 2). Although this study demonstrated a high ORR and prolonged PFS with ibrutinib plus rituximab, a direct comparison of ibrutinib plus rituximab and ibrutinib monotherapy has not yet been performed. Based on these findings, the FDA approved the combination of ibrutinib-rituximab for WM in 2018.

3. Acalabrutinib

Soon after the development of ibrutinib, next-generation, more selective BTK inhibitors, were developed. An initial success of acalabrutinib was seen in patients with relapsed or refractory CLL [27]. Acalabrutinib is currently FDA-approved for the treatment of CLL and MCL. A dedicated phase II trial in patients with WM was developed by Owen et al. (Table 1) [21]. In this trial, 106 patients received treatment with acalabrutinib 100 mg by mouth twice daily. Fourteen patients were treatment-naïve, and 92 patients had relapsed or refractory disease. The median time to best response was 5 months. At a median follow-up of 27 months, the ORR was 93%. A major response was seen in 79% of those with treatment-naïve disease and in 72% of those with relapsed or refractory disease. Of the 50 patients with genotyping performed, the *MYD88*^{L265P} mutation was found in 36 patients (72%). The ORR was 94% in the 36 patients with *MYD88*^{L265P} disease, and 57% of the 14 patients with *MYD88*^{WT} disease. No patients with *MYD88*^{WT} disease attained a very good partial response (VGPR) or complete response (CR). *CXCR4* status was not analyzed in this study, and thus efficacy data of acalabrutinib for *CXCR4*^{MUT} disease are not available. At 24 months of follow-up, 90% of treatment-naïve patients and 82% of those with relapsed or refractory disease had maintained their disease response. The median PFS and OS were not reached at the



	Ibrutinib (nM)	Acalabrutinib (nM)	Zanubrutinib (nM)
IC ₅₀ against BTK	1.5	5.1	0.5
IC ₅₀ against ERBB2	6.4	~1000	88
IC ₅₀ against ERBB4	3.4	16	6.9
IC ₅₀ against EGFR	5.3	>1000	21
IC ₅₀ against ITK	4.9	>1000	50
IC ₅₀ against TEC	10	126	44

Figure 1. 2-D structure and molecular formula of the BTK-inhibitors.

Ibrutinib PubChem URL: <https://pubchem.ncbi.nlm.nih.gov/compound/24821094#section=2D-Structure>.

Acalabrutinib PubChem URL: <https://pubchem.ncbi.nlm.nih.gov/compound/71226662#section=2D-Structure>.

Zanubrutinib PubChem URL: <https://pubchem.ncbi.nlm.nih.gov/compound/135565884#section=2D-Structure>.

time of study publication. Grade 3 or higher adverse events that occurred in more than >5% of patients included neutropenia and pneumonia (Table 2). Atrial fibrillation occurred in five of the 106 patients (5%) and was limited to grade 1 or 2 events, except in one patient with a grade 3 atrial fibrillation treated with cardioversion. No patients needed to stop acalabrutinib due to atrial arrhythmia. Bleeding occurred in 61 patients (58%), and most events were grade 1 or 2. Based on this study, acalabrutinib is an effective and well-tolerated BTK inhibitor for WM, although no direct comparison to ibrutinib is available in WM patients.

4. Zanubrutinib

4.1. Zanubrutinib selectivity and dosing

Zanubrutinib, a more potent and selective BTK inhibitor than ibrutinib, was then developed. Zanubrutinib is a covalent, non-reversible BTK inhibitor, which binds at the same Cys481 binding site as ibrutinib and acalabrutinib. Although the binding site is the same, zanubrutinib has a slightly different structure, binds with more affinity, and has an IC₅₀ of 0.5 nM compared with an IC₅₀ of 1.5 nM for ibrutinib and 5.1 nM for acalabrutinib [28]. Due to the lower IC₅₀ against BTK and higher IC₅₀ for multiple other tyrosine kinases, as demonstrated in Figure 1, zanubrutinib has fewer off-target effects [28].

Zanubrutinib dosing was established in an early phase I/II trial for patients with various B-cell malignancies, including 77 patients with WM (Table 2) [22,29]. This trial included a dose escalation study, in which 320 mg total daily was the recommended phase II dose. Analyses from this study revealed no

difference in safety or efficacy between 320 mg once daily dosing and 160 mg twice daily. Additionally, there was no significant difference in BTK occupancy (>95% with both doses) in peripheral blood mononuclear samples, although BTK occupancy in lymph nodes was different (89% v. 50% $p = 0.03$ for 160 mg twice daily and 320 mg once daily, respectively); therefore, 160 mg twice daily was then utilized for the remainder of the study. Since this original study subsequent trials have continued to demonstrate no difference in objective response rates, safety or tolerability between either 320 mg once daily or 160 mg twice daily [30]. Based on this data, zanubrutinib has been FDA approved at either dose regimen.

4.2. Zanubrutinib clinical data

The initial phase I/II clinical trial of zanubrutinib included 24 patients with treatment-naïve WM and 53 patients with relapsed or refractory WM. During this trial, 50 patients were treated with zanubrutinib 160 mg orally twice daily and 23 patients received 320 mg once daily. The median time to treatment response was 2.8 months. The ORR and major response rates were 96% and 82%, respectively. A VGPR occurred in 45% of patients with the response deepening from 21% at 6 months to 44% at 24 months. At the median follow-up of 36 months in the patients with relapsed or refractory disease and 24 months in the treatment-naïve patients 73% of patients remained on therapy. The PFS rate at 3 years was 82%. Of the 65 patients with a known genotype, a VGPR was achieved in 49% of those with *MYD88*^{L265P} and 25% of those with *MYD88*^{WT} disease.

A VGPR was seen in 59% of those with *MYD88*^{MUT}*CXCR4*^{WT} and 27% of those with *MYD88*^{MUT}*CXCR4*^{MUT}. Major response rates were similar in patients without and with *CXCR4* mutations (87% and 91%, respectively) highlighting a potential benefit of this therapy over ibrutinib in patients with *CXCR4* mutations. The grade 3 or higher adverse events that occurred in more than 1 patient included neutropenia, anemia, basal cell carcinoma, cellulitis, hypertension, pneumonia, diarrhea, headache, falls, and actinic keratosis (Table 2).

After the success of the phase I/II trial, the phase III ASPEN trial confirmed the efficacy and safety of zanubrutinib specifically in WM (Table 1). This randomized trial of 201 patients with treatment-naïve or relapsed/refractory disease compared the previously available ibrutinib 420 mg daily with zanubrutinib 160 mg orally twice daily [16]. One hundred and ninety-nine patients received at least one dose of the study treatment. The main outcome of the study was VGPR attainment. The ORR in both arms was similar with 94% for zanubrutinib and 93% for ibrutinib. This is similar to the ORR reported with acalabrutinib, although no direct comparison has been made [21]. No patients achieved a complete response. The difference in rate of VGPR was not statistically significant between the two arms, although numerically more patients in the zanubrutinib achieved a VGPR (28%) compared with those on the ibrutinib arm (19%) ($p = 0.09$). Also, there was no significant difference in the major response rates between zanubrutinib and ibrutinib (77% v. 78%). The median time to major response in both arms was 2.8 months, independent of whether a patient had treatment naïve or relapsed/refractory disease. At 18 months of follow-up, the median PFS was not reached, and the 18-month PFS rates were 84% and 85% for patients receiving ibrutinib and zanubrutinib, respectively. In a *post-hoc* analysis in which 20 of 92 (22%) patients exposed to ibrutinib and 33 of 98 (34%) patients exposed to zanubrutinib had *CXCR4* mutations, patients with and without *CXCR4* mutations had VGPR rates of 10% and 24% to ibrutinib, respectively, and 18% and 34% to zanubrutinib, respectively. In those with and without *CXCR4* mutations the major response rates to ibrutinib were 65% and 82%, respectively, and to zanubrutinib 70% and 82%, respectively. The median time to major response to ibrutinib based on *CXCR4* mutation was 6.5 and 2.8 months, respectively, and 3.0 and 2.8 months, respectively, to zanubrutinib, suggesting that VGPR and major response attainment to zanubrutinib was affected by *CXCR4* mutations, but the median time to major response was not.

Although the primary endpoint of this trial, attainment of VGPR or better, was not reached, zanubrutinib was associated with a similar ORR compared to ibrutinib as well as a lower incidence of atrial fibrillation, bleeding, diarrhea, edema, muscle spasms, and pneumonia (Table 2) and was therefore granted FDA approval in 2021. The incidence of neutropenia was higher in the zanubrutinib arm, but this did not translate to a significantly increased risk of infection.

4.3. Zanubrutinib in *MYD88*^{WT} disease

As demonstrated in the previous studies, the ORR with ibrutinib was lower in patients with *MYD88*^{WT} disease. Recent data demonstrated that zanubrutinib may have

efficacy in this group of patients based on a 28-patient cohort of the ASPEN study, which included only patients with *MYD88*^{WT} WM. Of these patients, 23 had relapsed or refractory disease and five were treatment naïve [31]. All patients received treatment with zanubrutinib. Of those patients, 26 had *MYD88*^{WT} disease confirmed centrally. Seven of these patients (27%) attained a VGPR and 13 patients (50%) attained a major response rate by 18 months. There were no CRs demonstrated. The median time to major response was 2.9 months and median time to minor response was 1 month. Eighteen-month PFS and OS rates were 68% and 88%, respectively. The most common adverse events were diarrhea, upper respiratory infection, contusion, fever, and anemia. The etiology for improved observed responses on zanubrutinib than ibrutinib in patients with *MYD88*^{WT} disease is not well understood. In this study, several patients had a low burden of disease in the bone marrow, which might have biased the results by including false *MYD88*^{WT} patients.

5. Expert opinion

BTK inhibitors are arguably the most effective monotherapy agents for patients with WM. Zanubrutinib has shown to be safe and effective in patients with WM in prospective clinical trials, and based on the results of the ASPEN study, zanubrutinib was approved by the FDA for the treatment of WM in 2021 [32]. The National Comprehensive Cancer Network has included zanubrutinib as a Category 1, preferred regimen in treatment-naïve and relapsed or refractory patients with WM [33]. Zanubrutinib has also shown to be effective in WM patients without *MYD88* mutations, in whom ibrutinib therapy has been associated with lower rates of response and shorter PFS.

The open-label ASPEN study was designed to show a superiority of zanubrutinib over ibrutinib in attaining higher rates of VGPR or better. The design of the study had salient limitations. Although a higher rate of VGPR is desirable in WM, VGPR attainment is not an established surrogate of PFS or overall survival, and therefore it was an unusual choice of a primary outcome measure for a randomized phase III study. In addition to randomization, blinding of participants and investigators to the interventions provided minimizes bias. Open-label studies have been associated with an overestimation of adverse events, and participants and investigators could be more likely to report or inquire on adverse events in one arm over the other. Finally, the method of detection of *MYD88* and *CXCR4* mutations was performed using non-selected bone marrow cells with low burden of disease in some patients, especially in the sub-study in patients without *MYD88* mutations, which could have affected the sensitivity of the tests [12,34]. Despite these limitations, current data suggest that zanubrutinib is associated with higher rates of VGPR and major response in patients with *CXCR4* mutations compared with those patients on ibrutinib and, therefore, may be preferred over single-agent ibrutinib in this setting.

Although the ASPEN study did not meet its primary endpoint, the data from this trial demonstrated that the safety

profile of this new, more selective BTK inhibitor was improved compared with ibrutinib with lower rates of atrial fibrillation, bleeding, hypertension, and gastrointestinal toxicity, but with higher rates of neutropenia. It is possible the favorable adverse event profile of zanubrutinib is related to a kinase profiling with less off-target effects than ibrutinib. Recent data have also supported the improved tolerance of zanubrutinib in a study of 57 patients with multiple types of non-Hodgkin lymphoma [35]. Patients enrolled in this study were intolerant to either ibrutinib or acalabrutinib and were transitioned to treatment with zanubrutinib. After transitioning to zanubrutinib, 73% of patients did not have recurrence of the intolerance previously demonstrated on acalabrutinib or ibrutinib. Of those who had recurrence of the intolerance event, 79% had recurrence at a lower severity. This study also demonstrated that 41% of patients maintained their hematologic response and 53% of patients had improved hematologic response after transitioning to zanubrutinib.

6. Future research

Future studies should focus on inducing durable deeper responses, and hopefully attain complete responses, with fixed-duration regimens maximizing efficacy while decreasing long-term toxicity and cost. Potential next steps could include the combination of zanubrutinib with proteasome inhibitors or alkylating agents with and without anti-CD20 monoclonal antibodies. As examples, prospective studies evaluating ibrutinib in combination with bortezomib and rituximab (NCT03620903), carfilzomib (NCT04263480), and ixazomib (NCT03506373) are underway in Europe and the United States. A Canadian study will evaluate the combination of six cycles of bendamustine and rituximab and 1-year course of acalabrutinib (NCT04624906). Other combinations of interest include ibrutinib and daratumumab (NCT03679624), ibrutinib and venetoclax (NCT04273139), and ibrutinib, venetoclax and rituximab (NCT04840602). There is also a dearth of data available for the treatment of patients with WM involving the central nervous system, known as Bing-Neel syndrome. The current standard of care in these patients is treatment with ibrutinib and other chemotherapy agents that penetrate the blood–brain barrier. Zanubrutinib may offer an effective therapeutic option in this setting with an improved side effect profile, but at this time only one published case report is available demonstrating the efficacy in this setting [36]. Future studies will hopefully determine the role of zanubrutinib in this patient population.

Additional covalent, BTK inhibitors, such as orelabrutinib and tirabrutinib, are also in development in WM and other hematologic malignancies [37–40]. These BTK inhibitors have not yet been compared to zanubrutinib but may play a role in future therapies depending on their specific safety and efficacy.

Future research will also need to include investigation into BTK inhibitor resistance, which has been reported in patients treated with ibrutinib and zanubrutinib, especially at the C481 binding site. This binding site is the same for

ibrutinib, zanubrutinib, and other covalent BTK inhibitors, so alternative covalent BTK inhibitors are generally not recommended when resistance develops. BTK C481S is the most common mutation in ibrutinib, but additional mutations in the BTK gene and in phospholipase C gamma 2 (PLCγ2) have also been reported [41,42]. Currently, there are non-covalent BTK inhibitors, such as pirtobrutinib, which are in clinical trials and early data have demonstrated the ability to overcome resistance to covalent BTK inhibitors, but additional investigation is needed as some mutations may portend resistance to all currently available covalent and non-covalent BTK inhibitors [43,44]. In the absence of an available non-covalent BTK inhibitor for a patient with resistance to a covalent BTK inhibitor, additional well-established treatments, such as bendamustine-rituximab, proteasome-based inhibitor therapies, or venetoclax could be administered [45–48].

7. Conclusion

Based on the data from the ASPEN study, zanubrutinib received FDA approval for the treatment of patients with WM in 2021. Due to the high efficacy rate and favorable adverse event profile, zanubrutinib has the potential of becoming a standard of care in patients with WM. Additional data in select WM populations, as well as in combination therapies, are needed to further delineate the role of zanubrutinib in WM.

Declaration of interest

S Sarosiek has received research funding from Acrotech Biopharma and ADC Therapeutics, JJ Castillo has received research funding and consulting fees from Abbvie, AstraZeneca, Beigene, Janssen, Pharmacyclics, Polyneuron, Roche and TG Therapeutics. AR Branagan has received research funds and consulting fees from Pharmacyclics/Janssen, Genzyme, Adaptive Biotechnologies, BeiGene, Karyopharm Therapeutics and CSL Behring. SP Treon has received research funds or consulting fees from Abbvie, Beigene, BMS, Janssen, Lilly, Pharmacyclics and X4. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

The authors have no funding to report.

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