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Current and novel BTK inhibitors in Waldenström's macroglobulinemia

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***Abstract*:** The current therapeutic approach in Waldenström's macroglobulinemia (WM) is being driven by insights in disease biology and genomic landscape. Bruton's tyrosine kinase (BTK) plays a key role in signaling pathways for the survival of WM clone. BTK inhibition has changed the treatment landscape of the disease. Ibrutinib has resulted in deep and durable responses both as an upfront and salvage treatment with a manageable toxicity profile. However, the need for fewer off-target effects and deeper responses has resulted in the clinical development of second-generation BTK inhibitors. Zanubrutinib has resulted in clinically meaningful antitumor activity, including deep and durable responses, with a low discontinuation rate due to treatment-related toxicities. Cardiovascular adverse events seem to be milder compared with ibrutinib. Interestingly, the efficacy of zanubrutinib in WM is significant both for $MYD88^{L265P}$ and $MYD88^{WT}$ patients. Although the randomized, phase III ASPEN clinical trial did not meet its primary endpoint in terms of showing a superiority of zanubrutinib in deep responses compared with ibrutinib, secondary efficacy and safety endpoints underscore the potential clinical role of zanubrutinib in the treatment algorithm of WM independent of the MYD88 mutational status. Combination regimens and non-covalent BTK inhibitors are emerging as promising treatment strategies. Long-term data will determine whether next-generation BTK inhibitors are more potent and safer compared with ibrutinib, and whether they are able to overcome resistance to ibrutinib, either alone or in combination with inhibitors of other interrelated molecular pathways.

Keywords: Bruton's tyrosine kinase, ibrutinib, MYD88, Waldenstrom's macroglobulinemia, zanubrutinib

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Introduction

Waldenström's macroglobulinemia (WM) is an indolent B-cell lymphoma characterized by lymphoplasmacytic cell infiltration of the bone marrow and/or lymphatic tissue, along with secretion of monoclonal immunoglobulin M (IgM) in the serum. WM is a rare malignancy accounting for 1–2% of all hematological cancers.[1–5] The disease incidence is estimated approximately at five cases per 1 million person-years.[6] It increases with age,[7,8] and there is a higher prevalence among White males. Interestingly, a significant familial predisposition has been also reported.[9,10]

Any lymphoplasmacytic infiltration is sufficient for the diagnosis of WM,[1,11] whereas a lower BM clonal cell infiltration is associated with a more indolent disease course.[12,13] Risk stratification in symptomatic WM patients is based on the International Prognostic Scoring System for WM. A three-level risk category is defined based on age, b2-microglobulin, hemoglobin, platelet, and IgM levels.[14,15]

Compared with healthy individuals, patients with WM present with a distinct molecular profile including but not limited to enhanced expression

of the VDJ recombination genes DNTT, RAG1, and RAG2, as well as upregulation of genes involved in MYD88 and CXCR4 signaling.[16,17] Patterns of aberrant methylation and unique epigenomics signatures have been also described in patients with WM.[18]

The diverse clinical presentation of patients with WM is attributed to the diverse bone marrow and/or organ infiltration by clonal cells and the immunological and physiochemical properties of monoclonal IgM that are primarily present in each patient. It has to be noted that treatment will not be required at the time diagnosis in up to one third of patients. The median time of asymptomatic patients to acquire features of symptomatic disease has been estimated at 5–10 years.[13,19,20] Validated scoring systems are useful in stratifying asymptomatic patients with WM based on risk of progression to symptomatic disease.[12] The consensus criteria for treatment initiation should be evaluated in combination with individualized clinical judgment, taking into consideration the disease complexity.[21–23]

Currently, WM remains incurable with an estimated median overall survival of 10–12 years.[24] Taking into consideration the indolent course of the disease and the advanced age of patients, almost half of the patients with WM die of causes unrelated to the disease. Furthermore, estimates of median survival may not reflect the survival benefit of novel therapies that have been introduced in the therapeutic armamentarium during the recent years. Although WM is an orphan disease, there are several treatment options for both newly diagnosed and relapsed WM patients. Chemoimmunotherapy, including the anti-CD20 antibody rituximab in combination with cyclophosphamide, bendamustine, or bortezomib and dexamethasone, has been considered the standard of care for many years. These treatment regimens have high response rates, induce durable responses, and present a manageable toxicity profile.[22,25] Novel treatment options are imperative due to either treatment intolerance or disease refractoriness.[26,27] In this context, inhibition of Bruton's tyrosine kinase (BTK) has come to the foreground of research efforts. Ibrutinib, a first-in-class BTK inhibitor, has been the first (and only) agent to receive USA Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for the treatment of patients with WM. However, acquired resistance and intolerance to ibrutinib have led to the clinical development of next-generation BTK inhibitors.

BTK inhibition in WM

BTK was discovered in 1993[28] and received its name after Ogden Bruton, a pediatrician who described Bruton's agammaglobulinemia (X-linked agammaglobulinemia), a primary immunodeficiency syndrome which involves a mutation in BTK.[29] BTK is a non-receptor tyrosine kinase, which plays a central role in B-cell signaling and is necessary for normal B-cell development in the bone marrow involved in adaptive and innate receptor-mediated signals. It has an upstream role in the molecular cascade that follows the activation of the B-cell receptor (BCR) and leads to downstream pathway activation of phosphoinositide-3-kinase (P13K)–protein kinase B (AKT) pathway, phospholipase C (PLC), protein kinase C (PKC), and nuclear factor κB (NF-κB). This signaling cascade promotes B-cell differentiation, proliferation, and survival.[30–32] BTK also has a role in the signaling of G-coupled chemokine receptors (like CXCR4), cytokine receptors (CD19, CD38 CD40), tumor necrosis family receptors (TNFRs), integrins and toll-like receptors (TLRs), such as TLR/MYD88.[33,34]

In WM, there is constitutive activation of BTK secondary to multiple mutations, detected by multiple methods in whole bone marrow, CD19+ selected cells, peripheral blood and cell-free deoxyribonucleic acid (DNA).[35–39] The first mutation described using whole-genome sequencing of CD19+ bone marrow cells, which is found in up to 90% of WM patients, is the somatic activating mutation of myeloid differentiation factor, $MYD88^{L265P}$ Leu265Pro.[40–42] MYD88-activating mutations promote Myddosome self-assembly and trigger TLR activation *via* BTK interaction and signaling of interleukin 1 (IL-1), IRAK4/IRAK1 and NF-κB.[43–45] Around 5–10% patients will have other MYD88 mutations or wild-type MYD88.[46] $MYD88^{WT}$ often has mutations in the NF-κB pathway, which are downstream to BTK and therefore show different response patterns to BTK inhibition.[47,48] In addition to BTK, MYD88 mutations transactivate another tyrosine kinase, hematopoietic cell kinase (HCK) which is also involved in pro-survival signaling.[49] Interestingly, HCK is also found to be a highly relevant target molecule of ibrutinib.[49]

In 20–40% of patients with WM, the somatic, subclonal, activating mutation in the CXCR4 gene (C-terminal of the C-X-X chemokine receptor type 4) is identified. It is analogous to the germline mutation observed in patients with WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome ($CXCR4^{WHIM}$).[50,51] The same patient may harbor different CXCR4 mutations, and this is most likely linked to genomic instability.[52,53] The mutations in the C-terminal domain of the CXCR4 receptor lead to a permanently activated state by blocking the internalization of the receptor that normally occurs after SDF-1α stimulation.[54] CXCR4 activation promotes AKT kinase and extracellular-regulated kinase (ERK) function, which may be associated with resistance to ibrutinib therapy.[55] $CXCR4^{WHIM}$ status is associated with lower responses to BTK inhibition,[55,56] which has provided the rationale for the clinical development of anti-CXCR4 monoclonal antibodies, such as ulocuplumab, and small molecules, such as mavorixafor.[57,58] Combining BTK and CXCR4 inhibition has resulted in disease responses independent of mutational status in preclinical studies.[59]

Overall, patients with different MYD88 and CXCR4 mutational status have distinct clinical presentations and sensitivity to BTK inhibition. $MYD88^{L265P}$/$CXCR4^{MUT}$ patients have higher levels of bone marrow infiltration, and serum IgM and $MYD88^{WT}$/$CXCR4^{WT}$ have the lowest levels of IgM, bone marrow infiltration and respond less well to BTK inhibition.[53,60]

Ibrutinib

Ibrutinib is a first-in-class, orally administered BTK inhibitor. It binds irreversibly and covalently with a cysteine residue on site 481 within the binding site of BTK. In several B-cell lymphomas ibrutinib has shown potent and sustained single-agent activity.[61] Ibrutinib, like all BTK inhibitors, activates apoptosis, inhibits DNA replication, and blocks pro-survival signaling pathways. It also exerts immunomodulatory effects on macrophages and the tumor microenvironment. It inhibits HCK and causes inactivation of downstream transcription factors including NF-κB, STAT3, and AL-1 and downregulation of cytokines and chemokines.

Ibrutinib is indicated for the treatment of chronic lymphocytic leukemia/small lymphocytic leukemia, marginal zone, and mantle-cell lymphoma.[62] It is indicated for the treatment of patients with relapsed/refractory WM, but also for treatment-naïve, newly diagnosed patients with WM. In Europe, ibrutinib is indicated in the first line only for patients who are considered unsuitable for chemoimmunotherapy. It should be administered continuously until disease progression or unacceptable toxicity. MYD88 and CXCR4 testing is recommended before treatment initiation. Drug interruption or dose modifications are required when potent CYP3A inhibitors or inducers are co-administered or in the case of hepatic impairment, due to the fact that ibrutinib is primarily metabolized in the liver by CYP3A.[63] Ibrutinib is the only FDA- and EMA-approved drug for WM, which has changed the treatment and outcome landscape for the disease.

Table 1 summarizes the most important clinical data of ibrutinib in patients with WM. Following encouraging initial preliminary results, a phase II trial demonstrated the efficacy of ibrutinib in the relapsed/refractory disease setting.[64,65] The median time to first response was 4 weeks and the response rates increased with increased follow up, whereas no IgM flares were reported. The mutational status was a predictor of response. The overall response rates were higher among patients with $MYD88^{L265P}CXCR4^{WT}$ (100%) and lowest for those with $MYD88^{WT}CXCR4^{WT}$ (71%). The progression-free survival (PFS) at 47 months was inferior for $MYD88^{L265P}CXCR4^{WHIM}$ (45 months) compared with patients with $MYD88^{L265P}CXCR4^{WT}$ (not reached) and lowest (21 months) for those with $MYD88^{WT}CXCR4^{WT}$.[66] In addition to the above, a sub-analysis of the phase III iNNOVATE trial confirmed the efficacy of ibrutinib in rituximab refractory patients ($n=31$).[67] The response rates were similar for $MYD88^{L265P}CXCR4^{WHIM}$ and $MYD88^{L265P}CXCR4^{WT}$ patients, but the time to response was prolonged in the latter group.[68] Furthermore, ibrutinib monotherapy showed high efficacy and safety among newly diagnosed patients ($n=30$), who were all $MYD88^{L265P}$, in a prospective phase II study. Patients with $CXCR4^{WHIM}$ had inferior responses compared with those with $CXCR4^{WT}$.[69]

iNNOVATE is a double-blind, randomized, placebo-controlled trial that included 150 treatment-naïve and relapsed/refractory patients with WM who were randomized (1:1) to receive either rituximab with placebo or rituximab with ibrutinib. All

Table 1. Clinical trials of ibrutinib in WM patients.

	Patients (*n*)	Design/ disease setting	Treatment	Outcomes	Comments
Advani *et al.*[64]	4 RR	Phase I prospective	PO ibrutinib	ORR: 3/4 patients MRR: not reported PFS: not reported OS: not reported	
Treon *et al.*[65,66]	63 RR	Phase II prospective	PO ibrutinib	At 47.1 months: ORR: 90.5% MRR: 73% PFS: 2 years 69.1% OS: 2 years 95.2% Median time to response: 4 weeks	Response and PFS lower in $CXCR4^{WHIM}$ and $MYD88^{wt}$ Median PFS at 47.1 months: not reached for $MYD88^{L265P}$, 45 months for $MYD88^{L265P}$/ $CXCR4^{WHIM}$, and 21 months for $MYD88^{WT}$/$CXCR4^{WT}$
Dimopoulos *et al.*[68]	31 RR (rituximab refractory)	Phase III open label	PO ibrutinib	ORR: 90% MRR: 71% PFS: 18 months 86% OS: 18 months 97%	Response and PFS similar, in $MYD88^{L265P}$ $CXCR4^{WHIM}$, but slower ORR and MRR 88% for $CXCR4^{WT}$/$MYD88^{L265P}$ *versus* 71% for $CXCR4^{WHIM}$/ $MYD88^{L265P}$
Dimopoulos *et al.*[70]	150 (TN and RR)	Phase III double blind, randomized 1:1	Ibrutinib + rituximab (Ibr/R) *versus* placebo + rituximab (Pcb/R)	At 30-month FU: ORR: 92% in Ibr/R arm *versus* 72% in Pcb/R arm MRR: 47% in Ibr/R arm *versus* 32% in Pcb/R OS: 94% in Ibr/R arm *versus* 92% in Pcb/R 30-month PFS: 82% in Ibr/R *versus* 25% in Pcb/R Median PFS: not reached in Ibr/R *versus* 20.3 months in Pcb/R	PFS and RR not affected by MYD88/CXCR4 mutation status but major response lower in $CXCR4^{WHIM}$
Treon *et al.*[69]	30 TN $MYD88^{L265P}$	Phase II prospective	PO ibrutinib	ORR:100% MRR: 83% PFS: 18 months 92% OS: 18 months 100%	Median time to response 4 weeks MRR was 94% in WT CXCR4 MRR was 71% in CXCR4 mutated

MRR, major response rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, per os (orally); RR, relapsed/ refractory; TN, treatment naïve; WM, Waldenström's macroglobulinemia; WT, wild type.

previously treated patients were rituximab sensitive, whereas 45% had not received any prior treatment. Among the patients receiving ibrutinib–rituximab, ibrutinib prevented the rituximab-induced IgM flare, whereas IgM levels showed a rapid reduction, and hemoglobin level increases were sustainable.[70] The addition of ibrutinib to rituximab resulted in a significant PFS benefit both in treatment-naïve and relapsed/refractory patients with WM, independently of the MYD88/CXCR4 mutational status. However, major response rates were lower in patients with $CXCR4^{WHIM}$. No novel

toxicities emerged, whereas the treatment discontinuation rate due to toxicity was similar between the two treatment groups. Furthermore, there are still unanswered questions regarding the role of ibrutinib in the therapeutic algorithm of WM.[71] Despite the superiority of ibrutinib–rituximab compared with rituximab, there are no data available regarding the comparison of ibrutinib–rituximab with ibrutinib. Further studies evaluating the efficacy of ibrutinib–rituximab compared to other established regimens for WM both in the upfront and in the relapsed/refractory setting are needed.

Ibrutinib is also an effective treatment option for Bing–Neel syndrome as it crosses the blood–brain barrier into the central nervous system.[72] A recent multicenter study enrolled 28 patients with Bing–Neel who received ibrutinib. A total of 85% of patients showed improvement or resolution of their symptoms, and 83% of them showed improvement in the associated abnormalities in the imaging studies, as well.[73]

Ibrutinib has a favorable toxicity profile; however, it has multiple off-target effects because it is a non-selective agent and inhibits other molecules beyond BTK including epidermal growth-factor receptor (EGFR), ErbB2, proto-oncogene tyrosine-protein kinase (SRC), interleukin-2-inducible T-cell kinase (ITK), tyrosine-protein kinase (TEC), and HCK. Common adverse events are gastrointestinal disturbances, upper respiratory-tract infections, rash, fatigue, and dyspnea.[74] Severe neutropenia and thrombocytopenia have been reported in up to 15% of the patients receiving ibrutinib in the abovementioned clinical trials, whereas less than 10% of the patients experienced severe infections, bleeding and arrhythmias, especially atrial fibrillation.[75] The arrhythmogenic potential of ibrutinib seems to be mediated by the inhibition of the PI3K–AKT cardioprotective pathway.[76–78] Systematic reviews of ibrutinib studies in patients with B-cell malignancies suggest a relative risk for atrial fibrillation and hypertension of 4.69 [95% confidence interval (CI): 2.17–7.64] and 2.82 (95% CI: 1.52–5.23), respectively, whereas cases of life-threatening arrhythmias have been also reported.[79,80] Treatment discontinuation due to new onset of atrial fibrillation is not recommended, but patients should receive cardiologic consultation and proper anticoagulation prophylaxis.[81] Another pooled analysis of clinical trial data has suggested an increased relative risk of bleeding with ibrutinib (2.93, 95% CI: 1.14–7.52).[82–84] Ibrutinib may affect platelet aggregation by interfering with integrin signaling and von Willebrand signaling cascade.[85,86] For this reason, perioperative interruption of ibrutinib is advised for 3–7 days. Importantly, the combination of ibrutinib with rituximab did not result in an excess of reported toxities.[87] However, the adverse events raise concern in the context of long-term, continuous treatment with ibrutinib.[65]

Ibrutinib therapy may be interrupted to manage or prevent toxicities; however, 20% of the patients may develop withdrawal symptoms within 2 days, which typically resolve with treatment re-initiation.[88] Ibrutinib interruption may induce a rebound effect and a hyperactive immune state similar to cytokine-release syndrome.[89–91] IgM rebound may be also observed in up to 80% of patients with WM during the first 2 months following ibrutinib discontinuation.[92] Re-initiation of treatment usually restores IgM levels and any related symptoms.[93] The optimal strategy of interrupting ibrutinib and assuring persistence of disease response has to be determined in future studies.

Resistance to ibrutinib has been associated with poor prognosis.[94] Mutations in the binding site of ibrutinib BTK^{Cys481} have been identified in MYD88 mutated WM cells derived from patients progressing while on ibrutinib therapy. Interestingly, these mutations are mainly subclonal and demonstrate a variable clonal distribution. There has been evidence that these mutations occur *de novo* during treatment with ibrutinib.[95] Sustained ERK 1/2 activation has also emerged as a principal mediator of ibrutinib resistance. The activation of ERK 1/2 pathway may also provide protection from BTK inhibition through a paracrine mechanism to BTK wild-type WM cells.[48] In this context, ERK1/2 inhibition may overcome resistance. Furthermore, there have been reports of ibrutinib-resistant WM cell lines that lack BTK^{Cys481} mutation or $CXC4^{WHIM\text{-}like}$ mutations, which suggest the existence of BTK-independent survival signals. Whole-exome sequencing of ibrutinib-resistant WM cells has revealed a diverse panel of both BTK-related and BTK-independent genomic abnormalities, including chromosomal deletions affecting regulators of BTK signaling, recurring mutations in ubiquitin ligases, innate immune signaling, TLR/MYD88 pathway regulators, AKT and Bcl-2 associated pathways.[96,97]

Zanubrutinib

The need for more selective BTK inhibitors in order to minimize the off-target effects and the associated toxicity has led to the clinical development of second-generation BTK inhibitors.[98]

Zanubrutinib (BGB-3111) is an oral, second-generation BTK inhibitor. It binds irreversibly to the Cys481 residue of the adenosine triphosphate (ATP)-binding pocket of the BTK active site. Importantly, it has minimal off-target activity. It has a half-maximal inhibitory concentration for inhibition of off-target kinases, such as ITK, TEC, EGFR, human epidermal growth-factor receptor 2, and Janus kinase 2, 2- to 70-fold higher than ibrutinib.[99–101] Zanubrutinib is currently approved by the FDA for the treatment of relapsed/refractory mantle-cell lymphoma. The recommended dose is 160 mg twice daily.[102] Table 2 summarizes the results of the most important clinical trials of zanubrutinib in the treatment of WM.

The initial phase I trial enrolled 42 patients with WM, of whom nine were treatment-naïve and 33 had relapsed/refractory disease. The overall response rate was 90%, including a 75% of major response rates, whereas 1-year PFS was 91.7%. Four patients harbored MYD88^{L265}CXCR4^{WHIM} and all responded to treatment. Four out of five MYD88^{wt} patients also showed responses. Regarding the safety profile, 20% of the patients experienced grade 1/2 toxicities, 35% purpura/petechia, 31% upper respiratory-tract infections and 25% constipation. Hematological toxicities (anemia and neutropenia, each in 8% of the patients) were the two most frequent grade 3/4 adverse events. Atrial fibrillation grade 2 or less was reported in 6% of the patients.[101,102] Interestingly, severe hemolysis and reaction to blood tranfusions have been reported in two patients receiving zanubrutinib in combination with an anti-programmed-cell-death-1 antibody in a phase I clinical trial.[108]

The previous study was subsequently expanded to a phase I/II trial design and included 77 patients with WM (nine treatment-naïve and 33 previously treated).[103] A total of 50 patients received zanubrutinib at 160 mg twice daily and 23 were treated at 320 mg once daily. The overall response rate was 96%, whereas the rate of very good partial response or complete remission (VGPR/CR) was 45.2% after a median follow up of 36 months for the patients with relapsed/refractory disease, and 24 months for the treatment-naïve patients. Interestingly, the depth of response increased over time with 21% of the patients achieving VGPR/CR at 6 months, 33% at 12 months, and 44% at 24 months from treatment initiation. The estimated 3-year PFS rate was 81%, and the overall survival (OS) rate was 85%. The toxicity profile was considered acceptable and included contusion in 32.5% of the patients, neutropenia in 18%, major hemorrhage in 4%, atrial fibrillation/flutter in 5.2%, and diarrhea in 3%.[103]

Recently, the results of the phase III ASPEN clinical trial comparing zanubrutinib with ibrutinib monotherapy were reported.[109,104] The study included 201 previously treated and non-eligible for chemoimmunotherapy treatment-naïve patients with WM, who were randomized to receive one of the two BTK inhibitors. All patients harbored the MYD88^{L265P} mutation. The rate of deep responses (VGPR/CR) was 28% ($n=29$) in the zanubrutinib compared with 19% ($n=19$) in the ibrutinib patient group ($p=0.09$). Therefore, the primary endpoint of statistical superiority in relation to deep responses (VGPR or better) was unmet. Furthermore, the major response rate among patients receiving zanubrutinib was 78% and 80% among those receiving ibrutinib, whereas the overall response rates were over 90% in both treatment groups. The 18-month PFS rate was 85% and 84%, respectively, and the 12-month OS rate was 97% and 94%, respectively. Overall, 58.4% patients experienced grade 3 or higher toxicities with zanubrutinib compared with 63.3% with ibrutinib. Patients with WM receiving zanubrutinib had a lower incidence of atrial fibrillation (3% *versus* 18% with ibrutinib, $p<0.05$), contusion, diarrhea, peripheral edema, hemorrhage, muscle spasms, and pneumonia. The adverse events leading to treatment discontinuation were also fewer among zanubrutinib recipients. Although the incidence of neutropenia was higher with zanubrutinib (32% *versus* 15% with ibrutinib, $p<0.05$), the rates of grade 3 or higher infections were similar in both treatment groups.[109,104]

The ASPEN study had also a non-randomized patient group who harbored MYD88^{wt}. All 26 WM patients included received zanubrutinib until disease progression or unacceptable toxicity. Five patients were treatment naïve and 23 had received at least one prior line of treatment. Interestingly, the overall response rate reached

Table 2. Clinical trials of novel BTK inhibitors in WM patients.

	Patients (*n*)	Design/ disease setting	Treatment	Outcomes	Comments
Trotman *et al.*[102], 2020[103]; Tam *et al.*[101]	77 (24 TN; 53 RR)	Phase I/II prospective	PO zanubrutinib	ORR: 96% VGPR/CR: 45.2% 3-year PFS: 80.5% 3-year OS: 84.8%	VGPR/CR rate increased over time: 20.5% at 6 months, 32.9% at 12 months, and 43.8% at 24 months AEs of interest: contusion (32.5%, grade 1), neutropenia (18.2%), major hemorrhage (3.9%), atrial fibrillation/ flutter (5.2%), grade 3 diarrhea (2.6%)
Tam *et al.*[104]; Garcia-Sanz *et al.*[105]	201 $MYD88^{L265P}$ (cohort 1) 26 $MYD88^{WT}$ (cohort 2)	Phase III prospective, randomized (cohort 1)	PO zanubrutinib *versus* ibrutinib (cohort 1), PO zanubrutinib (cohort 2)	Cohort 1 VGPR/CR: 28.4% *versus* 19.2% ORR: 78% *versus* 78% MRR: 77.5% *versus* 77.8% 18-month PFS: 85% *versus* 84% Cohort 2 VGPR:26.9% ORR: 80.8% MRR: 50% 12-month PFS: 72.4%	Incidence of atrial fibrillation, contusion, diarrhea, peripheral edema, hemorrhage, muscle spasms, and pneumonia, as well as adverse events leading to treatment discontinuation, were all lower among zanubrutinib recipients; incidence of neutropenia was higher with zanubrutinib, although grade 3 or higher infection rates were similar in both groups
Owen *et al.*[106]	106 (14 TN, 92 RR)	Phase II, prospective	PO acalabrutinib	ORR: 93% MRR: 78% 24-month PFS: 90% TN, 82% RR	Common AEs: headache, diarrhoea, bruising, fatigue, nausea, arthralgia Most common grade 3 (or higher) AEs: neutropenia and lower respiratory tract infections Atrial fibrillation: 5% MYD88 wild type ($n = 14$): PR rate = 64%
Sekiguchi *et al.*[107]	27 (18 TN, 9 RR)	Phase II, prospective	PO tirabrutinib	TN: ORR, 94.4%, MRR, 88.9% RR: ORR, 100%, MRR, 88.9% Median PFS and OS not reached	96.2% MYD88L265P mutated Most common AEs: rash (44.4%), neutropenia (25.9%), leukopenia (22.2%) Grade ⩾3 AEs: neutropenia (11.1%), lymphopenia (11.1%), leukopenia (7.4%)

AEs, adverse events; BTK, Bruton's tyrosine kinase; CR, complete remission; MRR, major response rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, per os (orally); RR, relapsed/refractory; TN, treatment naïve; VGPR, very good partial response; WM, Waldenström's macroglobulinemia.

81%, including a major response rate of 50%, and a very good partial response rate of 27%. The PFS rate at 12 months was 72%. The most frequently reported toxicities included diarrhea, anemia, contusion, pyrexia, and upper respiratory-tract infection. Major hemorrhage and atrial fibrillation were reported in two patients and one patient, respectively. Following a median follow-up of 17.9 months, two patients discontinued zanubrutinib due to adverse events, whereas there were no cases of disease transformation to high-grade lymphoma.[105]

Acalabrutinib

Acalabrutinib (ACP-196), is another highly selective, potent covalent BTK inhibitor. Its off-target activity is minimal.[110] It has received accelerated FDA approval as monotherapy for the treatment of relapsed/refractory mantle-cell lymphoma and chronic lymphocytic leukemia.[111,112] Acalabrutinib monotherapy has showed high response rates of 93% both among treatment-naïve ($n=14$) and previously treated ($n=92$) patients with WM. Regarding 50 patients with available mutational status, the overall response rate was 94% among $MYD88^{L265P}$ patients compared with 79% among $MYD88^{WT}$ patients, and no very good partial responses were observed in the wild-type patient group. Overall, the responses were similar to those reported with ibrutinib, with a possible superior benefit for the patients with $MYD88^{wt}$. Acalabrutinib showed a similar toxicity profile with ibrutinib.[113,106]

Tirabrutinib

Tirabrutinib (GS-4059/ONO) is an irreversible, selective BTK inhibitor. In a phase II trial, tirabrutinib resulted in an overall response rate of 94% and 100% among treatment-naïve and previously treated patients with WM after a median follow up of 6.5 and 8.3 months, respectively.[107] Interestingly, the median time to major response was 1.87 months. Among the whole study population, the MYD88L265P mutation was detected in 96% of the patients. The toxicity profile was manageable, whereas the most common adverse effects included rash, neutropenia, and leukopenia.[107]

Non-covalent BTK inhibitors

Next-generation BTK inhibitors do not rely on covalent binding at the C481 site of the BTK molecule and, thus, they may bypass resistant mechanisms mediated by mutations in the C481 site.[114] Two non-covalent, reversible BTK inhibitors that are being currently evaluated in WM are LOXO-305 and ARQ531. Promising preclinical data on the pharmacokinetic properties of LOXO-305 have led to an ongoing phase I/II clinical trial evaluating the maximum tolerated dose in patients with B-cell malignancies including WM [ClinicalTrials.gov identifier: NCT03740529].[115] ARQ-531 is another reversible inhibitor that binds to the ATP binding region within the kinase domain of BTK without interacting with the C481 region. Interestingly, ARQ-531 also inhibits downstream effector of B-cell receptor signaling cascade including MEK, ERK, MYC and members of the SRC family kinases.[116,117] In preclinical models of ibrutinib-resistant chronic lymphocytic leukemia and Richter's transformation, ARQ-531 has shown significant activity.[116,118] The results of the phase I part of the ongoing phase I/II study [ClinicalTrials.gov identifier: NCT03162536] evaluating ARQ-531 in relapsed/refractory B-cell malignancies indicated an acceptable toxicity profile and promising efficacy. The most common adverse events included gastrointestinal complaints, rash, and hematological toxicity. Ten partial responses were shown in all dose escalation levels ($n=40$). A daily dose of 65 mg has been selected as the recommended dose for further evaluation in the phase II part of the study.[119]

Concluding remarks

The therapeutic approach in WM is increasingly being driven by insights in disease biology and genomic landscape. BTK plays a central role in signaling pathways for the WM clone and is constitutively activated secondary to MYD88 mutations. BTK inhibition has changed the treatment landscape of the disease. Ibrutinib has resulted in deep and durable responses both as an upfront and salvage treatment with a manageable toxicity profile. However, several challenges have emerged in order to optimize the treatment strategy including the development of more selective agents with fewer off-target effects and deeper responses, therapeutic approaches to overcome or even prevent resistance, the potential for a fixed-duration treatment regimen.[120] Zanubrutinib has resulted in clinically meaningful antitumor activity, including deep and durable responses, with a low discontinuation rate due to treatment-related toxicities. Cardiovascular adverse events seem to be milder compared with ibrutinib. Interestingly, the efficacy of zanubrutinib in WM is significant both for $MYD88^{L265P}$ and $MYD88^{WT}$ patients. Furthermore, ongoing studies with non-covalent BTK inhibitors [ClinicalTrials.gov identifiers: NCT03740529 and NCT03162536] have shown promising efficacy and a tolerable toxicity profile in B-cell malignancies, whereas they bypass resistance mediated by mutations in the C481 site of the BTK. In an effort to enhance and optimize our current treatment strategies in WM, combinatory regimens including BTK inhibitors with CXCR4 antagonists (ulocuplumab, mavorixafor)

[ClinicalTrials.gov identifiers: NCT03225716 and NCT04274738, respectively], or proteasome inhibitors (bortezomib with anti-CD20 monoclonal antibody rituximab, carfilzomib, ixazomib) [ClinicalTrials.gov identifiers: NCT03620903, NCT04263480, and NCT03506373, respectively], or bcl2 antagonists (venetoclax, APG-2575) [ClinicalTrials.gov identifiers: NCT04273139 and NCT04260217, respectively], or anti-CD38 monoclonal antibodies (daratumumab) [ClinicalTrials.gov identifier: NCT03679624], or programmed cell-death ligand-1 inhibitors (pembrolizumab) [ClinicalTrials.gov identifier: NCT02332980], are being currently evaluated in ongoing clinical trials.[120] Long-term data will determine whether next-generation BTK inhibitors are more potent, safer, and able to overcome resistance to ibrutinib in WM, either alone or in combination with inhibitors of other interrelated intracellular cascades.

Conflict of interest statement

MAD declares honoraria from Beigene and Janssen. INS, MG, and DF declare that there is no conflict of interest.

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