Current Hematologic Malignancy Reports
https://doi.org/10.1007/s11899-024-00731-0

Bruton Tyrosine Kinase Inhibition: an Effective Strategy to Manage Waldenström Macroglobulinemia

Reema K. Tawfiq[1] · Jithma P. Abeykoon[2,3] · Prashant Kapoor[2,3]

Accepted: 26 February 2024

Abstract

Purpose of Review The treatment of Waldenström macroglobulinemia (WM) has evolved over the past decade. With the seminal discoveries of *MYD*88 and *CXCR* warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) mutations in WM cells, our understanding of the disease biology and treatment has improved. The development of a new class of agents, Bruton tyrosine kinase inhibitors (BTKi), has substantially impacted the treatment paradigm of WM. Herein, we review the current and emerging BTKi and the evidence for their use in WM.

Recent Findings Clinical trials have established the role of covalent BTKi in the treatment of WM. Their efficacy is compromised among patients who harbor $CXCR4^{WHIM}$ mutation or $MYD88^{WT}$ genotype. The development of BTK^{C481} mutation-mediated resistance to covalent BTKi may lead to disease refractoriness. Novel, non-covalent, next-generation BTKi are emerging, and preliminary results of the early phase clinical trials show promising activity in WM, even among patients refractory to a covalent BTKi.

Summary Covalent BTK inhibitors have demonstrated meaningful outcomes in treatment-naïve (TN) and relapsed refractory (R/R) WM, particularly among those harboring the $MYD88^{L265P}$ mutation. The next-generation BTKi demonstrate improved selectivity, resulting in a more favorable toxicity profile. In WM, BTKi are administered until progression or the development of intolerable toxicity. Consequently, the potential for acquired resistance, the emergence of cumulative toxicities, and treatment-related financial burden are critical challenges associated with the continuous therapy approach. By circumventing BTK C481 mutations that alter the binding site to covalent BTKi, the non-covalent BTKi serve as alternative agents in the event of acquired resistance. Head-to-head comparative trials with the conventional chemoimmunotherapies are lacking. The findings of the RAINBOW trial (NCT046152), comparing the dexamethasone, rituximab, and cyclophosphamide (DRC) regimen to the first-generation, ibrutinib are awaited, but more studies are needed to draw definitive conclusions on the comparative efficacy of chemoimmunotherapy and BTKi. Complete response is elusive with BTKi, and combination regimens to improve upon the efficacy and limit the treatment duration are also under evaluation in WM.

Keywords IgM lymphoplasmacytic lymphoma · MYD88 mutation · CXCR4 mutation · Monoclonal gammopathy · Lymphoproliferative disorder

Introduction

Waldenström macroglobulinemia (WM) is a rare indolent, low-grade B cell lymphoma that accounts for 1–2% of hematologic malignancies and is characterized by lymphoplasmacytic infiltration of the bone marrow and circulating monoclonal immunoglobulin M (IgM) [1]. The incidence is approximately three per million people per year, with nearly 1,400 new cases diagnosed in the United States annually [2]. WM is a disease affecting the elderly, with the median age at diagnosis being 70 years [3]. The incidence increases with age and is more common in Caucasian men [1, 4]. Like

✉ Prashant Kapoor
kapoor.prashant@mayo.edu

[1] Department of Hematology-Oncology, Mayo Clinic, Jacksonville, FL, USA

[2] Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

[3] Division of Hematology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Published online: 27 March 2024

other low-grade lymphoproliferative malignancies, WM is currently an incurable disease. However, with the advent of new treatments, the median overall survival (OS) of patients with WM has improved in recent years [5].

Although the exact etiology of WM remains unclear, whole-genome sequencing (WGS) has identified important pathogenic mutations. A commonly recurrent somatic variant (T → C) at position 38,182,641 in chromosome 3p22.2 that harbors the myeloid differentiation factor 88 (*MYD88*) gene was identified in WM [6]. The variant leads to an amino acid change from leucine to proline (L265P) in the *MYD88* structure. MYD88 is an adaptor protein that dimerizes upon interaction with the activated toll like receptor (TLR) and IL-1 receptor and facilitates cross talk between TLR and the B cell receptor. The $MYD88^{L265P}$ mutation affects the toll/interleukin-1 receptor (TIR) domain of the MYD88 protein and leads to its constitutive activation. As a result, a myddosome complex spontaneously forms and, in turn, activates downstream pro-survival signals through transcription factors, including nuclear factor κB (NF-κB) via Bruton's tyrosine kinase (BTK) and IL-1R-associated kinase-1 (IRAK1) activation as well as hematopoieses cellular kinase (HCK) transactivation [7–9]. While not exclusive to WM, the $MYD88^{L265P}$ mutation has been identified in over 90% of patients with WM [6, 8]. BTK activation additionally results in phosphorylation of phospholipase C gamma 2 (PLCγ2) triggering calcium flux and gene transcription regulation.

The other somatic mutation(s) frequently involved in the pathogenesis of WM affects the C-terminal domain of the C-X-C chemokine receptor type 4 (CXCR4), also known as Fusin or CD184, encoded by the *CXCR4* gene [10]. This alteration is similar to the germline mutation in the *CXCR4* gene of the patients with WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome [11, 12]. Over 40 *CXCR4* mutations have been identified. These mutations are present in 23% to 40% of patients with WM [10, 13, 14] and may be either nonsense ($CXCR4^{NS}$) or frameshift ($CXCR4^{FS}$) type. Nonsense mutation results in a truncated receptor protein associated with the loss of the regulatory serines which leads to persistent upregulation of the transmembrane CXCR4 receptor due to lack of its internalization. Consequently, sustained downstream activation of the AKT and ERK signaling pathways occurs [11].

The clinical presentation can be vastly variable in patients with WM [15]. Clinical features of WM may include anemia, thrombocytopenia, lymphadenopathy, hepatosplenomegaly, peripheral neuropathy, hyperviscosity, and cryoglobulinemia [16]. Given the heterogeneous clinical presentation, we evaluate and diagnose patients with WM by utilizing the Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines and the Second International Workshop on WM (IWWM) consensus criteria to initiate therapy [17–19]. The absence of symptomatic disease or end-organ damage, as observed in smoldering WM (SWM), requires careful observation. The median time from SWM to symptomatic WM has been estimated to be 5 to 10 years [20]. However, the progression risk in SWM is affected by several prognostic factors [21–24]. Therefore, validated scoring systems can help stratify asymptomatic patients with WM based on the risk of progression to symptomatic disease [22]. More recently, the Mayo Group proposed a simple model to predict the time-to-progression to active (symptomatic) disease based on hemoglobin and beta-2 microglobulin values obtained at the diagnosis of SWM [25•].

Symptomatic patients who require treatment are risk-stratified as either low, intermediate, or high, based on the International Prognostic Scoring System for WM (IPSSWM). The level of risk is based on the patient's age, beta-2-microglobulin, hemoglobin, platelet, and IgM levels [26]. In recent years, more staging systems have been proposed and the treatment of WM has evolved [27, 28]. There are currently several treatment options for treatment naïve (TN) and relapsed/refractory (R/R) WM patients. Since WM still remains incurable, its treatment is aimed at controling symptoms, preventing further end-organ damage, and maximizing the quality of life.

The choice of therapy should be guided by the WM-associated complications and symptomology, genomic features, patient co-morbidities, access to novel therapies, and patient preference [29]. Treatment options include fixed-duration chemoimmunotherapy regimens like bendamustine plus rituximab (BR), or dexamethasone, rituximab, and cyclophosphamide (DRC) both of which have high response rates in both TN and R/R WM, although BR was more effective in retrospective series [30–33]. Also, proteasome inhibitors like bortezomib, carfilzomib, and ixazomib, in combination with rituximab, have been shown in prospective studies to be effective with high response rates [34–39]. Despite the efficacy of conventional chemoimmunotherapy and proteasome inhibitor-based regimens, additional novel therapies with substantial efficacy have emerged as alternative options. Chiefly, the development and utilization of BTK inhibitors (BTKi) have revolutionized the management of WM.

BTK, a member of the tyrosine-protein kinase (TEC) family, is a cytoplasmic, non-receptor tyrosine kinase, encoded by a gene located on the X chromosome and expressed in most cells of hematopoietic lineage [40]. In X-linked agammaglobulinemia, an antibody deficient state, characterized by marked immunodeficiency, the pre-B cells fail to mature because of the mutated BTK gene, leading to recurrent bacterial infections. BTK plays a central role in signaling cascades responsible for B-cell differentiation, proliferation, and survival [41, 42]. It also plays an integral role in cytokine receptor pathways.

The development and utility of BTKi in WM paralleled the discovery and a deeper understanding of the underlying recurrent somatic mutations that play a crucial role in the disease. Activation of BTK occurs secondary to constitutive activation of the upstream proteins, including the frequently occurring *MYD88*^{L265P} mutation [9]. By impairing crosstalk between MYD88 and BTK, BTKi interferes with the critical survival pathways of WM cells [43]. Hence, BTK has become a promising therapeutic target in WM.

Currently, there is no standard therapy for WM and there are limited data from randomized trials comparing different treatment approaches. The approach to herapy selection is based on consensus treatment recommendations as proposed by the mSMART and the 10th IWWM Guidelines [18, 44].

In 2015, ibrutinib, the first-in-class BTKi, was approved by the United States Food and Drug Administration (FDA) and the European Medicine Agency (EMA). While the FDA label was broader for its use among TN and R/R patient populations, the EMA recommended it as a single agent for patients who have received at least one prior therapy or in first-line treatment for patients unsuitable for chemo-immunotherapy. Subsequently, a confirmatory phase 3 trial, the iNNOVATE study, led the regulatory bodies to approve ibrutinib in combination with rituximab. Since then, the second-generation, covalent BTKi, like acalabrutinib and zanubrutinib, have been evaluated in prospective clinical trials and an additional third-generation, non-covalent BTKi, pirtobrutinib, has shown promising activity as well.

While all BTKi share a common target, they differ considerably. Although both the first and second-generation BTKi bind covalently to the exposed cysteine 481 residue of BTK, thereby irreversibly inhibiting the BTK enzyme, the second-generation BTKi have higher specificity, with an improved adverse effect (AE) profile. By contrast, the emerging third generation BTKi have shown to overcome acquired covalent BTKi-induced resistance and may eventually show a superior efficacy and toxicity profile. Each BTKi was developed with the aims of improved tolerability, selectivity, and outcomes. This review outlines the different BTKi currently used or under investigation for the treatment of both TN and R/R WM.

Covalent BTKi

Ibrutinib (Formerly PCI-32765)

Ibrutinib is a first-generation BTKi that forms an irreversible covalent bond with the cysteine residue at position 481 (Cys-481) within the ATP-binding domain of the BTK enzyme [45], thereby inhibiting its kinase activity, causing prolonged target inhibition, and ultimately inducing its degradation. However, it has activity against at least nine other kinases with a cognate cysteine, including interleukin-2 inducible T-cell kinase (ITK), Tec protein tyrosine kinase (TEC), B-lymphoid tyrosine kinase (BLK), and Janus kinase 3 (JAK3), as well as epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) [45]. The IC50 against EGFR, ITK, TEC and HER2 and 4 of ibrutinib is substantially lower than that of the second-generation BTKi for the respective enzymes. It is rapidly absorbed and eliminated after oral administration, with a time to peak concentration of 1–2 h and half-life ($t_{1/2}$) of 2–3 h. The recommended dose for WM is 420 mg once daily until the disease progresses or unacceptable toxicities. Its bioavailability is doubled when taken with a meal. Ibrutinib is metabolized by hepatic cytochrome P450 (CYP) 3A enzyme and to a minor extent CYP2D6 [46]. Therefore, drug interruption or dose modifications are required when potent CYP3A inhibitors (e.g., protease inhibitors, antifungals (azoles), and macrolides) which increase the ibrutinib level or inducers (e.g., carbamazepine, phenytoin, rifampin, and St. John's wort) which decrease the ibrutinib level, are co-administered, or in the case of hepatic impairment [46]. Foods to avoid with the use of ibrutinib include Seville orange, starfruit, and grapefruit [47].

Ibrutinib has also shown efficacy in Bing–Neel syndrome (BNS), a rare central nervous system (CNS) complication of WM, as it crosses the blood–brain barrier [48]. The optimal dose for BNS has not been identified but a higher dose of 560 mg may be required for disease control [49••]. A multicenter study enrolled 28 patients with BNS who received ibrutinib. At best response, 85% of patients had improvement or resolution of their symptoms, 83% showed improvement in the radiological abnormalities, and 47% had cleared the disease in the cerebrospinal fluid [49••].

Table 1 summarizes the clinically significant data on ibrutinib in patients with WM. In a phase I study, 54% of patients with B-cell malignancies, including three of four previously treated WM patients had an objective response [56]. Subsequently, a multicenter phase II study of Ibrutinib monotherapy in symptomatic R/R WM reported an overall response rate (minor response or better) (ORR) of 90.5% and a major response rate (partial response or better) (MRR) of 73% [50]. The 2-year and 5-year progression-free survival (PFS) rates were 69% and 54%, respectively [57].

The iNNOVATE trial, a double blind phase III study evaluated the use of ibrutinib in combination with rituximab in patients with TN and R/R WM [58••]. Rituximab 375 mg/m^2 IV was given weekly during weeks 1–4 and 17–20. A total of 150 patients were randomized to rituximab-ibrutinib ($n = 75$) or rituximab-placebo ($n = 75$). Patients in the rituximab-placebo arm were allowed to cross over to receive single-agent ibrutinib upon disease progression. In the final analysis, after a median follow-up of 50 months, the 54-month PFS rate was higher with rituximab-ibrutinib

Table 1 Data from clinical trials of ibrutinib in patients with Waldenström Macroglobulinemia

Study	Phase	Treatment	Patients (*n*)	Outcomes
Advani et al. [44]	I	Ibrutinib	4 R/R	75% achieved response and continued to have response at 4 years
Treon et al. [50]	II	Ibrutinib	63 R/R	ORR – 90% MRR – 79% PFS –69% at 24 months OS – 95% at 24 months
Treon et al. [51]	II	Ibrutinib	30 TN *MYD88*^{L265P}	ORR – 100% MRR – 83% PFS – 92% at 18 months OS -100% at 18 months
Dimopoulos et al. (iNNOVATE) [52]	III	Ibrutinib	31 R/R (rituximab refractory)	ORR – 90% MRR – 71% PFS – 86% at 18 months OS – 97% at 18 months
Dimopoulos et al. [53]	III	Ibrutinib-rituximab	75 TN and R/R	ORR – 92% MRR – 72% PFS – 68% at 54 months OS – 86% at 54 months
Tam et al. (ASPEN) [54, 55••]	III	Ibrutinib	99 (18 TN; 81 R/R)	ORR – TN: 89%; R/R: 94% MRR – TN: 67%; R/R: 80% PFS – TN: 94% at 18 months; R/R: 82% at 18 months OS—93% at 18 months Updated at EHA Congress 2022: PFS at 42 months 70% OS at 42 months 85% for entire cohort

ORR Overall response rate; *MRR* Major response rate; *PFS* Progression-free survival; *OS* Overall survival; *TN* Treatment-naïve; *R/R* Relapsed/refractory; *EHA* European Haematology Association

compared to the control arm (68% vs. 25%; median not reached vs. 20.3 months) [53]. Median OS was not reached in either arm. The ORR was higher with rituximab-ibrutinib compared to the control arm (92% vs. 44%) [53]. The iNNOVATE trial demonstrated a 75% reduction and risk of disease progression or death with ibrutinib-rituximab (HR 0.25, 95% CI 0.15–0.42) and a significantly higher rate of PFS than the use of placebo-rituximab in both patients with TN and R/R WM [52, 53, 59]. There are currently no head-to-head trials comparing ibrutinib monotherapy to ibrutinib-rituximab. The lack of an ibrutinib monotherapy arm and the use of a suboptimal control (single-agent rituximab) were major criticisms of this study.

Targeted genetic testing for *MYD88* L265P mutation (by allele -specific PCR) and *CXCR4* C-terminal alterations to detect well-characterized hotspot mutations c.1013C > G/A, p.S338X (examined using bridged nucleic acids clamped Sanger sequencing with an analytic sensitivity of 1% at Mayo Clinic) and routine Sanger sequencing for other mutations (analytic sensitivity 20% at Mayo Clinic) are recommended before treatment initiation as these mutations predict response to ibrutinib, as well as other BTKi, in general. Treon et al. demonstrated a substantial difference in ORR and MRR in patients with *MYD88*^{L265P}/wild-type (WT) *CXCR4*, *MYD88*^{L265P}/*CXCR4*^{WHIM}, and *MYD88*^{WT} mutations; the MRR was 62% in patients with *MYD88*^{L265P}/*CXCR4*^{WHIM} and 92% in those with *MYD88*^{L265P}/*CXCR4*^{WT}, whereas no major response was observed in patients with *MYD88*^{WT}/*CXCR4*^{WT} genotype [71]. In a recent long-term follow-up of this study with ibrutinib monotherapy in R/R WM patients, a similar effect was persistently observed; ORR was higher among patients with *MYD88*^{L265P}/*CXCR4*^{WT} (100%) and lowest for those with *MYD88*^{WT}/*CXCR4*^{WT} (50%) [57]. The median PFS was 4.5 years for *MYD88*^{L265P}/*CXCR4*^{WHIM} compared with *MYD88*^{L265P}/*CXCR4*^{WT} which was not reached and merely 0.4 years for those with *MYD88*^{WT}/*CXCR4*^{WT} [57].

The *MYD88*^{L265P} mutation, therefore, serves as a favorable predictive marker in patients with WM treated with ibrutinib. Alternative treatment options should be considered in patients with *MYD88*^{WT}. The subclonal *CXCR4* mutation(s) is also a predictive marker and confers resistance to ibrutinib. It is therefore imperative to check for the presence of *MYD88*^{L265P} and *CXCR4* mutations before subjecting a patient to indefinite ibrutinib monotherapy [72]. Interestingly, the final analysis of the ibrutinib plus rituximab versus placebo plus rituximab study, demonstrated clinical benefit with ibrutinib-rituximab, independent of *MYD88* mutational status. Among the *CXCR4*^{WT} population, the ibrutinib-rituximab doublet showed similar PFS rates, irrespective of the *MYD88* mutation status (54-month PFS rate, 70% and 72% in *MYD88*^{WT} and *MYD88*^{mutant} sub-populations, respectively), but those with double mutations showed a numerically lower rate at 63% [53]. The next-generation sequencing panel used for genotyping in the iNNOVATE trial was, however, less sensitive, raising questions about the accuracy of its results that showed equivalent efficacy of IR irrespective of the presence of unfavorable genotypes that known to be associated with poor outcomes with ibrutinib monotherapy.

The AE of ibrutinib may be partly a result of its off-target effects. Common AE include diarrhea, rash, cytopenias, infections, arrhythmias, and bleeding [73, 74]. Long-term follow-up studies of patients on ibrutinib monotherapy in R/R WM and R/R CLL/SLL have demonstrated a similar incidence rate (12%) of atrial fibrillation (AFib) [57, 75]. A meta-analysis comparing the risk of AFib in patients treated with ibrutinib versus comparator drug showed a pooled relative risk of 3.9 (95% CI, 2.0–7.5) [76]. The rate of AFib on a pooled analysis of 20 studies was 3.3/100 person-years [76]. The underlying mechanism of AFib is potentially through inhibition of TEC, ERBB1, and ERBB2 in the heart tissue, which leads to downregulation of PI3K/AKT signaling [77]. A more recent study demonstrated with a mouse model that ibrutinib-mediated AFib is also attributable to its inhibition of C-terminal Src Kinase (CSK) [78]. Suppressing CSK leads to increased inflammation and fibrosis predisposing to AFib [78]. Treatment discontinuation due to new-onset Afib is generally not required, but patients should receive cardiology consultation and appropriate anticoagulation prophylaxis [79]. Table 2 reviews the management of select common AE of BTKi.

In clinical trials, ibrutinib is associated with approximately 50% risk of bleeding, and most of these events are grade 1–2 bleeding (petechiae and contusion). In an analysis of four randomized clinical trials, compared to the control treatments, ibrutinib was associated with an increased relative risk of 2.93 (95% CI, 1.14–7.52) of bleeding [82, 83]. For this reason, perioperative interruption of ibrutinib is advised for 3–7 days, depending on the type of surgical intervention. Another integrated analysis examined the risk of major hemorrhage with the concomitant use of anticoagulation and/or antiplatelets (AC/AP) [88]. Major hemorrhage was defined as grade > 3 bleeding, serious bleeding, or any CNS hemorrhage [88]. The exposure-adjusted relative risk for a major hemorrhage was 1.9 (95% CI, 1.2–3.0) for the total ibrutinib-treated population [88]. Ibrutinib affects the platelet function and thrombus formation by interfering with integrin signaling and von Willebrand signaling cascade [89, 90]. At the molecular level, the mechanism is likely due to the off-target inhibition of TEC or Src family kinases (SFKs) [91]. In the iNNOVATE trial, the combination of ibrutinib with rituximab did not result in a substantial variation in the AE profile [59]. Interestingly, patients in the ibrutinib-rituximab arm experienced fewer infusion-related reactions compared to the control arm [59]. This observation has been attributed to reduced cytokine release because of the simultaneous use of ibrutinib [92].

Although the rates were low in clinical trials, since ibrutinib's initial approval there have been multiple reports of opportunistic infections in patients primarily with CLL caused by *pneumocystis jirovecii*, C*ryptococcus neoformans*, ubiquitous airborne filamentous fungi (*Aspergillus*) [60, 93, 94]. There are limited data to support the use of systemic antifungal prophylaxis in all patients on ibrutinib or any BTKi currently though an increased awareness about the potential risk of an invasive fungal infection after initiating a BTKi is warranted.

A recent study from Mayo Clinic investigating ibrutinib monotherapy in patients with WM outside of the clinical trial setting reported overall outcomes that appeared to be comparable to prior clinical trials; 18% of patients required a dose reduction and 21% discontinued ibrutinib for reasons other than disease progression [95] Abrupt ibrutinib discontinuation may result in IgM rebounding, with rates between 20 and 70% [47, 95, 96]. This phenomenon should not be mistaken for disease progression. Of note, the serum IgM increase may persist for several weeks after resuming ibrutinib and does not necessarily indicate treatment failure [97]. The exact mechanism behind IgM rebounding has not been fully elucidated. However, it is known that the signal transducer and activator of transcription 5A (STAT5A) has been shown to regulate IgM secretion in WM [98, 99] and is a substrate of BTK. BTK activates STAT5 signaling, resulting in increased IgM secretion by WM cells. Inhibition of STAT5 by ibrutinib significantly decreases IgM production. Therefore, it is believed that stopping ibrutinib results in IgM rebound.

Additionally, ibrutinib suppresses inflammatory cytokines and downregulates T-cells and macrophages. In a retrospective study of 114 patients on ibrutinib in whom this drug was held for the first time for a variety of reasons, nearly 20% experienced withdrawal symptoms within a median of 2 days (range 0–5 days), characterized by fever, body aches,

Table 2 Management of the most common adverse effects

Toxicity	Management strategies
Arrhythmias including atrial fibrillation and ventricular arrhythmias [80, 81]	• Before starting a BTKi assess baseline CV risk factors, obtain an EKG. If a history of poorly controlled AFib, consider an alternative. Risk factors for AFib in cases treated with ibrutinib are as follows: • Older age (≥ 65), male sex, hypertension, pre-existing cardiac disease, history of AFib, diabetes mellitus, valvular heart disease, and p mitrale • Patients on a BTKi should be instructed to remain vigilant regarding the appearance of symptoms such as palpitations, lightheadedness/presyncope, new-onset shortness of breath, chest pressure, etc., and to seek medical care • New-onset AFib on BTKi –› obtain cardiology consultation, determine CHA2DS2-VASc score and HAS-BLED score, for risk–benefit assessment • Initiate appropriate rate or rhythm control with consideration of potential drug-drug interactions. Beta-blockers are preferred over non-dihydropyridine CCB (verapamil and diltiazem) due to their CYP3A4 inhibition or amiodarone since it is a P-glycoprotein substrate • Anticoagulation is best managed with either low-dose apixaban (given CYP3A4 interaction) or a regular dose of enoxaparin. Avoid vitamin K antagonists, fish oil, Vitamin E, and NSAIDs • Stop therapy permanently with ventricular arrhythmias
Rash	• Typically resolves with corticosteroids
Bleeding [82–84]	• If possible, attempt to complete all necessary procedures prior to therapy initiation • Consider another therapy other BTKi if dual antiplatelet therapy is indicated • If on therapy, hold BTKi for 3 days or 7 days before and after minor or major procedures, respectively • Minor bleeding –› holding BTKi should resolve bleeding tendency in 2–3 days • Severe bleeding –› initiate supportive care, hold BTKi, and transfuse platelets as appropriate even in the absence of thrombocytopenia • Decision to resume BTKi in the setting of a bleed is dependent on ongoing risk and disease status • Educate patients with bleeding to avoid OTC supplements that can increase bleeding risk like non-steroidal anti-inflammatory drugs, vitamin E, and fish oil • Bruising is commonly seen but does not relate to an increased risk of major hemorrhage and cessation of therapy is not necessary • Consider switching to LMWH or DOAC if a patient is on warfarin
Infection	• Fevers and signs of infection while on BTKi therapy should prompt consideration of an infection, including opportunistic infections like *Aspergillus* and *Pneumocystis jiroveci* pneumonia, and a complete workup should be completed • Consider holding BTKi until a definitive diagnosis is determined • Initiate appropriate antimicrobial therapy based on the isolated microorganism • Obtain infectious disease consultation if the diagnosis remains elusive despite persistent clinical suspicion for infection or in the setting of confirmed invasive fungal infections. as • Resumption of BTKi should be considered after clinical improvement from infection and when deemed appropriate by the patient's providers
Diarrhea [85••]	• Commonly occurs early in treatment (first 6-months) and is generally self-limiting • Grade 1/2–› supportive care, and antimotility agents. Consider switching ibrutinib from AM to PM or zanubrutinib from twice daily to a single dose at night • Grade ≥ 3–› consider temporary withholding of BTKi and rule-out enteric pathogens
Hypertension [85••]	• Among patients with baseline hypertension, optimize blood pressure control before BTKi initiation • Routinely monitor blood pressure and commence antihypertensive therapy for new-onset hypertension. Avoid non-dihydropyridine CCB
Cytopenias [86, 87]	• Generally, improves with time but discontinuation due to cytopenias is infrequent. Growth factors may be considered
Headache [63••]	• Typically resolves with extended use • Supportive care and acetaminophen use with or without caffeine

AFib Atrial fibrillation; *CV* Cardiovascular; *BTKi* Bruton tyrosine kinase inhibitor; *CCB* Calcium channel blocker; *LMWH* Low molecular weight heparin; *DOAC* Direct oral anticoagulants; *OTC* Over the counter

night sweats, arthralgias, chills, headache, and fatigue, with a third of patients also exhibiting features of disease progression. The symptoms resolved promptly with resumption of therapy and were associated with an improvement in IgM level to baseline (within a median of 5 months) among those that had concurrently experienced IgM rebound. Low dose prednisone (10 mg PO BID) was successfully used as a mitigation strategy among few patients. Interestingly, patients achieving deep remissions or harboring CXCR4 WT genotype were more likely to experience the withdrawal

symptoms, likely a manifestation of release of ibrutinib-mediated suppression of inflammatory cytokines, including TNFα, IL2RA and CXCL13 [100•].

To enhance and optimize the use of ibrutinib in WM, clinical trials are underway. Trials examining ibrutinib combination therapies in WM have been recently completed or are ongoing (Table 3). A recent study (NCT04273139) study shed light on the challenges associated with using ibrutinib combination therapy involving treatment-naïve patients with WM who received a fixed duration (max 2 years) combination of ibrutinib and the BCL2 inhibitor, venetoclax ($n=45$). Four cases of ventricular arrhythmias, including 2 deaths, were observed leading to early termination of the trial after a median time on therapy for approximately 10 months, and a median follow up of 24.4 months. At 24 months, PFS rate was 76% and12-month progression after the treatment was discontinued was 79% [101•].

Acalabrutinib (Formerly ACP-196)

Acalabrutinib is a potent oral second-generation BTKi. Like its predecessor, ibrutinib acalabrutinib and its active metabolite (ACP-5862) irreversibly inhibit BTK activity by covalently binding to Cys-481 within the ATP-binding domain. Acalabrutinib however demonstrates higher selectivity for BTK [102]. Unlike ibrutinib, acalabrutinib does not significantly inhibit EGFR, ITK, HCK, ERBB2, and JAK3, as indicated by kinase selectivity profiling against 395 human kinases [102, 103].

Acalabrutinib, is rapidly absorbed. The median time to peak is 0.9 h for acalabrutinib and 1.6 h for ACP-5862 [104]. The $t_{1/2}$ is 1 h for acalabrutinib and 3.5 h for ACP-5862. The bioavailability of the drug is improved when taken under fasting conditions [104]. The primary mechanism of metabolism is by CYP3A enzymes, and to a minor extent, by

Table 3 Ongoing clinical trials of BTK inhibitors in patients with Waldenström Macroglobulinemia

Intervention	Phase	Patient population	Trial ID
Zanubrutinib, Ixazomib, and Dexamethasone	II	TN WM	NCT04463953
Zanubrutinib	II	Patients with CLL/SLL, WM, MCL, or MZL intolerant to prior ibrutinib / acalabrutinib /	NCT04116437
Lenalidomide and Ibrutinib	I	Patients with B-cell NHL that has returned or not responded to treatment	NCT01955499
Ibrutinib, Bortezomib, Rituximab	II	TN WM	NCT03620903/ECWM-2
Bendamustine, Rituximab and Acalabrutinib	II	TN WM	NCT04624906
Carfilzomib + Ibrutinib vs. Ibrutinib	III	TN and R/R WM	NCT04263480/CZAR-1
APG 2575 (BCL2 inhibitor) ± (ibrutinib + Rituximab)	Ib/II	TN and R/R WM	NCT04260217/MAPLE-1
Rituximab and Ibrutinib (RI) vs. Dexamethasone, Rituximab, and Cyclophosphamide (DRC)	II/III	TN WM	NCT04061512/RAINBOW
Ibrutinib + Venetoclax	II	TN WM	NCT04273139
LOXO-338 (BCL2 inhibitor) ± Pirtobrutinib	I/II	R/R WM + other B cell malignancies	NCT05024045
Pirtobrutinib (Expanded Access)	II	R/R WM + other B cell malignancies	NCT05172700
Nemtabrutinib	I/II	R/R WM + other B cell malignancies	NCT03162536
Pevonedistat (NEDD8 inhibitor) and Ibrutinib	I	R/R WM + other B cell malignancies	NCT03479268
NX-5948 (BTK degrader/chimeric targeting molecule)	I	R/R WM + other B cell malignancies	NCT05131022
NX-2127 (dual BTK degrader/chimeric targeting molecule and immunomodulator with IMiD-like properties)	Ia	R/R WM + other B cell malignancies	NCT04830137
BGB-16673 ((BTK degrader/chimeric targeting molecule)	I	Patients with previously treated covalent binding BTK inhibitor	NCT05006716
HSK29116 (Protac; BTK inhibitor + BTK degrader)	Ia/Ib	R/R WM + other B cell malignancies	NCT04861779
Rituximab, Bendamustine and PCI-32765 (ibrutinib)	I	R/R WM + other B cell malignancies	NCT01479842
Pirtobrutinib Monotherapy, Pirtobrutinib + venetoclax Pirtobrutinib + venetoclax + rituximab	I/II	WM, other NHL or CLL intolerant to either ≥ 2 prior standard of care regimens or have received 1 prior BTKi -containing regimen	NCT03740529
Pirtobrutinib + venetoclax	II	R/R WM	NCT05734495
Acalabrutinib + Pembrolizumab (KEYNOTE145)	Ia/II	R/R WM + other B cell malignancies	NCT02362035

*Terminated early due to poor accrual

** Suspended following fatalities in another similar study of ibrutinib-venetoclax

the glutathione conjugation and amide hydrolysis, based on in vitro studies. Therefore, co-administration of acalabrutinib with CYP3A inhibitors should be avoided or dose adjustments should be considered. ACP-5862 is approximately 50% less potent than acalabrutinib for BTK inhibition [105].

In 2017, acalabrutinib received its first FDA approval for its use in R/R MCL through an accelerated approval pathway based on an open-label, phase II study [106]. Later, it has since been approved for use in CLL/SLL. Although acalabrutinib has not yet received a formal FDA approval for use in WM, a single-arm, multicenter, phase II trial has shown promising results. The study included 106 patients with either R/R who has received at least one prior therapy ($n=92$) or was TN ($n=14$). The primary endpoint of overall response was achieved in 93% of the R/R ($n=86$) and TN ($n=13$) patients. A major response was achieved in 79% and 78% in TN and R/R, respectively. The median duration of response, PFS, and OS was not reached. The 2-year PFS in the TN and R/R cohorts was 90% and 82%, respectively. The 2-year OS in the TN and R/R cohorts was 92% and 89%, respectively.

Regarding the 36 patients with the *MYD88*^{L265P} mutation, 94% ($n=34$) achieved an overall response and 78% ($n=28$) achieved a major response on acalabrutinib. Of 14 patients that were *MYD88*^{WT}, 79% ($n=11$) achieved overall response and 57% ($n=8$) achieved major response [63••]. However, this comparison is hindered by the fact that *MYD88* mutations were not determined by a validated method; hence patients classified as *MYD88*^{WT} might have carried an occult *MYD88* mutation. Based on the available studies, we cannot irrefutably determine whether acalabrutinib offers any advantage over ibrutinib in treating WM. The median follow-up of 27.4 months (IQR 26·0–29·7) is short for an indolent disease like WM and for a treatment that is not given for a fixed duration, but rather an unlimited period. Longer follow-up is needed for assessing the safety of acalabrutinib in general and in comparison, to ibrutinib. Table 4 summarizes the clinically significant data of acalabrutinib in patients with WM [107].

In theory, acalabrutinib is expected to have fewer AE due to its higher selectivity. Based on the current clinical trials of acalabrutinib in patients with WM and CLL, the most reported AE were grade 1 or 2 and resolved over time [63••, 103]. In both, the most reported were headaches followed by diarrhea (Table 5) [63••, 103]. Like zanubrutinib, and in comparison, to ibrutinib, the rate of AFib is low; only 5% developed AFib [63••].

Acalabrutinib has shown considerable activity in WM when added to the bendamustine-rituximab (BR) chemoimmunotherapy backbone in the Canadian trial, BRAWM, which utilized fixed-duration acalabrutinib, orally for 1 year at 100 mg BID (Cycle1-12) overlapping with BR for the first 6 cycles [108]. Notably, the rates of infection were high although high CR + VGPR rates were also evident; 21/35 (60%) and 17/21 (81%) among the evaluable subjects who had reached months 7 and 12, respectively. Although the median follow up is short (6 months), no patient had progressed or died. These results appear to be superior to acalabrutinib alone, or to BR, in indirect cross-trial comparisons.

A combination of rituximab and acalabrutinib is currently being assessed in patients with anti-MAG-mediated IgM peripheral neuropathy [109].

Zanubrutinib (Formerly BGB-3111)

Zanubrutinib is a highly potent second-generation BTKi. Like ibrutinib, zanubrutinib forms an irreversible covalent bond with Cys-481 in the ATP-binding domain of BTK, resulting in kinase inhibition. Unlike ibrutinib, zanubrutinib has less activity on non-BTK kinases, including EGFR and TEC [110]. Zanubrutinib is rapidly absorbed after oral administration [110]. The mean $t_{1/2}$ is approximately 2–4 h, and it is hepatically metabolized by CYP3A [110]. In healthy subjects, there was no effect on drug bioavailability when taken with food [110]. The recommended dose is 160 mg twice daily (preferred due to more frequently sustained BTK receptor occupancy in the lymphoid tissues) or 320 mg once daily for all the currently approved indications until disease progression or unacceptable toxicities. There are no required dose adjustments in mild to moderate renal impairment. However, for patients with severe hepatic impairment, 80 mg twice daily is recommended [110, 111].

Zanubrutinib received its first approval in the USA in 2019 for treating previously treated MCL. Subsequently, it was FDA-approved for WM in 2021 as primary or salvage treatment. Additionally, zanubrutinib is approved for treating patients with R/R MZL who have received at least one anti-CD20-based regimen based on the MAGNOLIA trial [112]. Table 4 summarizes the clinically significant data of zanubrutinib in patients with WM.

A multicenter phase I/II study was conducted investigating zanubrutinib in 77 patients with WM who were either TN ($n=24$) or R/R ($n=53$) and had no prior BTKi exposure. The median follow-up was 36 months in R/R patients and 24 months in TN patients. A very good partial response (VGPR) or complete response (CR) was achieved in 45.2% (95% CI 33.5–57.3) and 51% (95% CI, 15.6–55.3) in the TN and R/R cohorts, respectively. The proportion of patients achieving the best response of VGPR/CR increased with treatment duration. Major responses were seen in 82.2% of patients. In patients with *MYD88*^{L265P}/*CXCR4*^{WT} ($n=39$), ORR and MRR were 97% and 87%, respectively. In patients with *MYD88*^{L265P}/*CXCR4*^{WHIM} ($n=11$), ORR and MRR were 100% and 91%, respectively. The estimated 3-year PFS was 81%, and the OS rate was 85% [60].

Table 4 Data from clinical trials of second and third generation BTK inhibitors in patients with Waldenström Macroglobulinemia

Study	Phase	Treatment	Patients (*n*)	Outcomes
Trotman et al. [60]	I/II	Zanubrutinib	77 (24 TN; 53 R/R)	ORR – 96% MRR – 82% PFS – 81% at 24 months OS – 94% at 24 months
An et al. [61]	II	Zanubrutinib	44 R/R	ORR – 76.7% MRR – 69.8% PFS – 60.5% at 24 months OS – 87.8% at 24 months
Tam et al. (ASPEN) [54, 62••]	III	Zanubrutinib	102 (19 TN; 83 R/R)	ORR – 95% MRR – 81% PFS – 78% at 42 months OS – 88% at 42 months
Owen et al. [63••]	II	Acalabrutinib	106 (14 TN; 92 R/R)	ORR – TN: 93%; R/R: 93% MRR – TN: 79%; R/R: 78% PFS – TN: 90% at 24 months; R/R: 82% at 24 months OS – TN: 92% at 24 months; R/R: 89% at 24 months
Sekiguchi et al. [64, 65]	II	Tirabrutinib	27 (18 TN; 9 R/R)	ORR – TN: 94.4%; R/R: 100% MRR – TN: 94.4%; R/R: 88.9% PFS – 92.6% at 24 months OS – 100% at 24 months
Zhou et al. [66•] Cao et al. [67]	II	Orelabrutinib	47 R/R	ORR—92% MRR—81% PFS—89% at 12 months and 72% at 36 months OS—94% at 12 months
Dimopoulos et al. (ASPEN Sub-study) [62••, 68]	III	Zanubrutinib	28 (5 TN; 23 R/R)	ORR – TN: 80%; R/R: 81% MRR – TN: 40%; R/R: 52% PFS – TN: 60% at 18 months; R/R: 71% at 18 months OS – TN: 80% at 18 months; R/R: 90% at 18 months
Mato et al. [69••]	I/II	Pirtobrutinib	26	ORR – 68% MRR – NR PFS – NR OS – NR
Palomba et al. [70]	I/II	Pirtobrutinib	80	ORR –85% MRR – 67% ($n=63$) among pts exposed to covalent BTKi and 88% among covalent BTKi-naïve ($n=17$) PFS – NR (for entire study population); 19.4 months for covalent BTKi exposed OS – NR for entire study population; not reached for covalent BTKi exposed

ORR Overall response rate; *MRR* Major response rate; *PFS* Progression-free survival; *OS* Overall survival; *TN* Treatment-naïve; *R/R* Relapse/refractory; *BTK* Bruton tyrosine kinase; *VGPR* Very good partial response; *CR* < Complete response; *NR* Not reported; *EHA* European Haematology Association

A head-to-head phase III ASPEN trial comparing zanubrutinib to ibrutinib monotherapy was completed. Patients with $MYD88^{L265P}$ were randomly assigned to treatment with ibrutinib ($n=99$) or zanubrutinib ($n=102$) (Cohort 1).In the final analysis for the trial at 44.4-month median follow-up, the MRR and ORR, respectively in each arm remained comparable (MRR: 81% with zanubrutinib and 80% with ibrutinib group; ORR 95% with zanubrutinib and 94% with ibrutinib, but the rate of VGPR, the primary endpoint,was 36% ($n=37$) with zanubrutinib and 25% ($n=25$) with ibrutinib, $p=0.07$ [54, 55••]. Although the median time to ORR or MRR were similar between arms, the median time to attainment of VGPR was faster for patients on zanubrutinib (6.7 months) compared to ibrutinib (16.6 months); Median PFS and OS were not reached in either arm but at 42-months the PFS was 78.3% in zanubrutinib cohort and 69.7% in the Ibrutinib cohort (HR 0.63, 95% CI 0.36–1.12). The OS at 42-months was 87.5% in Zanubrutinib cohort and 85.2% in the ibrutinib cohort (HR 0.75, 95% CI (0.36–1.59). The Cohort 2 of ASPEN study analyzed a subset of 26 patients (23 R/R; 5 TN) who harbored the $MYD88^{WT}$ and received zanubrutinib on a until disease progression or unacceptable toxicity. At a median follow-up of 44.4 months, 27% achieved a

Table 5 Comparison of select adverse events between covalent BTK inhibitors in Waldenström Macroglobulinemia phase II and III trials

Adverse event	Ibrutinib				Zanubrutinib		Acalabrutinib		Tirabrutinib		Orelabrutinib	
	Treon et al. [50]		iNNOVATE [52]		ASPEN [54]		Owen et al. [63••]		Sekiguchi et al. [64]		Zhou et al. [66•]	
	Grade 2–4	Grade ≥ 3	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3	All grade	Grade ≥ 3
Arthralgia	NR	NR	16	3	13	3	20	1	NR	NR	NR	NR
Atrial fibrillation	5	2	NR	NR	2	0	5	1	NR	NR	0	0
Contusion	NR	NR	28	1	13	0	29	0	NR	NR	NR	NR
Diarrhea	3	0	42	6	21	3	33	2	7	0	6	0
Epistaxis	3	0	NR	NR	13	0	11	1	7	0	NR	NR
Fatigue	NR	NR	13	3	19	1	21	2	NR	NR	NR	NR
Headache	2	0	10	0	15	1	39	0	NR	NR	2	2
Hypertension	5	0	23	10	11	6	5	3	NR	NR	2	0
Nausea	NR	NR	19	0	15	0	23	2	11	0	NR	NR
Neutropenia	22	15	20	10	29	20	17	16	26	11	19	11
Pneumonia	8	2	19	13	2	1	9	7	NR	NR	4	4
Rash	2	0	24	1	13	0	15	0	48	6	13	0
Thrombocytopenia	14	13	16	3	10	6	5	4	14	0	28	6
Upper respiratory tract infection	NR	NR	1	0	24	0	22	0	11	0	13	0

All toxicities reported in percent (%); *NR* Not reported

VGPR ($n=7$), 4% achieved CR ($n=1$), and 65% achieved a major response [55••, 68].

A post-hoc biomarker analysis was performed using next-generation sequencing on pretreatment bone marrow samples from patients treated with zanubrutinib ($n=98$) and ibrutinib ($n=92$) with $MYD88^{Mut}$ and patients treated with zanubrutinib with $MYD88^{WT}$ ($n=20$). Patients with $CXCR4^{FS}$ or $CXCR4^{NS}$ had lower VGPR rate (17.0% vs 37.2%, $P=0.020$) and longer time to response (11.1 vs 8.4 months) than $CXCR4^{WT}$ in patients treated with BTKi. $CXCR4^{NS}$ was associated with inferior PFS (HR = 3.39, $P=0.017$) in ibrutinib, but not in zanubrutinib (HR = 0.67, $P=0.598$), but ≥ VGPR rates were similar between the treatment groups (14.3% vs 15.4%). Compared to ibrutinib, patients with $CXCR4^{NS}$ who were treated with zanubrutinib had a favorable MRR (85.7% vs 53.8%, $P=0.09$) and PFS (HR = 0.30, $P=0.093$). In patients with mutated *TP53*, significantly lower MRR was observed with ibrutinib (63.6% vs 85.7%, $P=0.04$) in comparison to patients who did not have this mutation, but not with zanubrutinib (80.8% vs 81.9%, $P=0.978$). In mutated *TP53*, compared to ibrutinib, zanubrutinib had higher ≥ VGPR (34.6% vs 13.6%, $P<0.05$), numerically improved MRR (80.8% vs 63.6%, $P=0.11$), and longer PFS (not reached vs 44.2 months, HR = 0.66, $P=0.37$). The study showed that WM patients with mutated *CXCR4* or *TP53* in general had had poorer prognosis when treated with BTKi. The outcomes in these subpopulations, however appeared to be more favorable with zanubrutinib versus ibrutinib [113].

The most common AE reported with zanubrutinib are upper respiratory infection, contusion, and cough (Table 5) [60]. The rate of AFib and major bleeding was low with the use of zanubrutinib [60]. In the ASPEN trial, exposure-adjusted grade 1–2 bleeding incidence was higher among ibrutinib patients [54]. Ibrutinib patients experienced a tenfold higher incidence of AFib/flutter and a two-fold increased frequency of hypertension on an exposure-adjusted basis [54]. Lower-grade bleeding with zanubrutinib is most likely due to the on-target effect of BTK inhibition on platelet function [112]. The relative sparing of other kinases implicated in hemostasis, like TEC, likely impacts the reduced incidence and severity of bleeding in comparison to ibrutinib [114]. In comparison to ibrutinib, patients who took zanubrutinib experienced more than a twofold incidence of any grade (25% vs. 12%) and grade ≥ 3 (20% vs. 8%) neutropenia [54]. Despite a higher rate of neutropenia, the risk of infections was comparable between ibrutinib and zanubrutinib [54]. With a longer follow up, the safety of zanubrutinib has become more evident. Atrial fibrillation/flutter rates were 8% with zanubrutinib versus 24% with ibrutinib, although neutropenia rates were higher with zanubrutinib (35% versus 20%) [55••]. There were 3% and 5% AEs leading to death in the zanubrutinib and ibrutinib arms, respectively, while 9% of patients on zanubrutinib versus 20% patients discontinued therapy due to AEs [55••, 62••].

Tirabrutinib (ONO/GS-4059)

Tirabrutinib is a potent and selective second-generation BTKi that is currently only registered in Japan. Like the aforementioned BTKi, tirabrutinib irreversibly and covalently binds to the Cys-481. Compared with ibrutinib, tirabrutinib has greater selectivity against potential off-target enzymes, including EGFR, IRK, and BMX, and lower selectivity for TEC [115]. The combination of tirabrutinib with idelalisib, rituximab, and GS-5829 (a BET inhibitor) has demonstrated synergistic or additive anti-tumor effects in diffuse large B-cell lymphoma (DLBCL) in vitro and/or in xenograft models [116–119].

Tirabrutinib is administered orally and in a fasting state [120]. The mean $t_{1/2}$ is about 6.5–8 h [121]. The primary mechanism of metabolism is hepatic by CYP3A4. The dose administered for WM is 480 mg once daily [64]. There are no studies to support dosing adjustments for renal or hepatic impairment.

In 2020, tirabrutinib received approval in Japan for use in the treatment of R/R primary central nervous system lymphoma (PCNLS) and in TN or R/R WM. The initial results of the phase II trial conducted in Japan included 27 patients with WM (18 TN; 9 R/R). The ORR was 94% and 100% in the TN and R/R cohorts with a median follow-up of 6.5 and 8.3 months, respectively [122]. The MRR for all the patients was 88.9%. In a subsequent update, PFS and OS were not reached at a median follow up of 24.8 months. The 2-year outcomes from the phase II study were recently published. The 24-month PFS and OS were 92.6% and 100%, respectively [65]. The MRR in all the patients increased to 92.6% [65]. Of 27 patients, 25 patients (96.2%) carried the $MYD88^{L265P}$ mutation, 4 patients (15.4%) had $CXCR4^{WHIM}$, and 3 patients (11.5%) had both $CXCR4^{WHIM}$ and $MYD88^{L265P}$ mutations [64].

Tirabrutinib is overall well-tolerated, and the toxicity profile is manageable. The most common any grade AE were rash, neutropenia, and leukopenia (Table 5) [65, 121, 122]. Treatment-related hypertriglyceridemia was also observed. In the phase II trial, six of the 27 patients experienced an increase in the serum IgM (IgM rebound phenomenon) due to therapy interruption. The bleeding events were similar in frequency and severity as seen with ibrutinib [65].

Orelabrutinib

In the US orelabrutinib, another novel small molecule BTKi has been granted a Breakthrough Therapy Designation for the treatment of R/R MCL by the Food and

Drug Administration FDA. Its activity is currently being explored in B cell malignancies and autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus and primary immune thrombocytopenia.

A phase 2 trial of orelabrutinib involved patients with R/R WM and demonstrated high efficacy (Table 5) [66•]. The results were updated after a longer follow up (median 31.9 months). AEs were similar to those observed with other covalent BTKi, and include cytopenias, upper respiratory tract infection, weight gain and rash. Hepatitis B reactivation associated death was noted in a patient. Orelabrutinib is approved by the China National Medical Products Administration for the treatment of patients with R/R CLL, SLL and MCL [123].

Acquired Resistance to Covalent BTKi

Patients with WM can relapse while on ibrutinib therapy. Acquired subclonal mutations in BTK at the binding site of ibrutinib (BTK^{Cys481}) that are absent before the treatment with ibrutinib, or mutation in the downstream mediator, phospholipase C gamma 2 (PLCG2), allowing for the circumvention of BTK signaling, have been identified to account for some of the progression events in WM patients on ibrutinib [124]. The mutation leads to enhanced growth and survival through the re-activation of the extracellular signal-regulated kinase (ERK)1/2 mitogen-activated protein (MAP) kinase pathway [125]. ERK1/2 has been demonstrated to reactivate in subclones harboring $BTK^{Cys481Ser}$ mutation and leads to ibrutinib resistance. [125]. Interestingly, it also confers a protective effect against ibrutinib on the neighboring BTK wild-type expressing cells, mediated via the release of several prosurvival and inflammatory cytokines, including interleukin-6 (IL-6) and IL-10 [125]. Alternative drivers for ibrutinib resistance have been identified and include deletions on chromosome 6q, including homozygous deletions, and 8q, mutations in ubiquitin ligases, innate immune signaling, toll-like receptor (TLR)/MYD88 pathway regulators, AKT and Bcl-2 associated pathways [126]. Ibrutinib resistance with associated disease progression or Richter transformation has also been demonstrated in patients with CLL and MZL on ibrutinib [127–129].

Disease progression due to drug resistance is not unique to ibrutinib as this has been identified to be a therapeutic downfall in other covalent BTKi although there are currently no studies specifically demonstrating resistance to acalabrutinib or zanubrutinib in WM patients [130–132].

Non-covalent BTKi

Pirtobrutinib (LOXO-305)

Pirtobrutinib is a novel, investigational, highly selective, reversible BTKi with nanomolar potency against both WT and C481-mutated BTK [133]. In preclinical models, pirtobrutinib demonstrated minimal off-target kinase and non-kinase inhibitory activity [133]. The BRUIN study is a first-in-human, multicenter, phase I/II study of pirtobrutinib monotherapy in patients with advanced B-cell malignancies who had received at least two prior lines of therapy, or one prior line of therapy if a covalent BTKi was received as first-line therapy (Table 4). Patients were included regardless of BTKi exposure status and C481-mutation status. All patients received pirtobrutinib orally once daily in 28-day cycles until unacceptable toxicity or disease progression [69••, 70].

The maximum tolerated dose was not reached during phase I since no dose-limiting toxicities were observed. The recommended phase II dose was 200 mg once daily. The study included a total of 323 patients of which 26 had WM [69% ($n=18$ patients previously exposed to a BTKi; 12 discontinued due to progressive disease on BTKi and 6 due to toxicity/other reasons), 89% to chemotherapy, 92% to anti-CD 20 antibody and 12% to a BCL2 inhibitor]. Of 19 patients with WM that were efficacy evaluable, the ORR was 68% (95% CI 44–87) and the response was similar among 13 efficacy evaluable patients with WM who had received a covalent BTKi previously (69%, $n=9$ responded). Ten (77%) of 13 responding patients with WM remained on treatment with a median follow-up of 5 months [69••, 70].

The most frequently observed AE were fatigue, diarrhea, contusion, rash and neutropenia. Most AE were grade 1–2 except for neutropenia with a 6% and 4% of grade 3 and 4, respectively. The AE frequently seen with covalent BTKi were less frequent with pirtobrutinib and almost exclusively grade 1–2. Notably, low rates of BTK-inhibition related toxicities, including atrial arrhythmias (1%) and major bleeding, were observed, although patients with controlled AFib and those on concurrent anticoagulation (barring warfarin) and antiplatelet agents were allowed to enroll.

Updated data were recently published and presented at the American Society of Hematology 2022 Annual Conference. The cohort increased to include 80 patients with WM, of whom 63 (79%) patients had received prior covalent BTKi. Of these 63 patients, 41 (65%) were covalent BTKi refractory having discontinued it due to disease progression. The results are outlined in Table 4 [70].

Nemtabrutinib (ARQ 531/MK-1026)

Nemtabrutinib is another potent, reversible, orally administered BTKi which binds non-covalently to and inhibits the activity of both the C481S WT and C481S-mutated BTK. It is less selective and has significant activity on other kinases including Src, ERK, and AKT [134]. In addition to inhibiting BTK, nemtabrutinib inhibits signaling downstream of PLCG2 which is an alternative pathway to exert therapeutic action in B-cell malignancies [134].

A phase I dose-escalation study of nemtabrutinib has been completed in 40 patients with R/R B-cell malignancies (CLL/SLL $n=26$, RT $n=6$, DLBCL $n=3$, FL $n=4$, MCL $n=1$) (Table 5). The patients received a median of four prior treatments and were all previously treated with an irreversible BTKi. Eighty-five percent of patients with CLL had C481S-mutated BTK. The study determined that 65 mg daily was the recommended phase 2 dose in patients with evidence of efficacy for patients with R/R B-cell malignancies, including BTK C481S mutated CLL resistant to covalent BTKi [135]. Large studies (NCT04728893, NCT03162536) investigating BTKi are currently ongoing and include patients with WM. The cohort H of NCT04728893 is exclusively enrolling patients who are relapsed or refractory to standard therapies for WM including chemoimmunotherapy and a covalent irreversible BTKi.

While non-covalent BTKi offer an effective alternative to the patients whose WM cells are resistant to covalent BTKi, recent data suggesting resistance to the non-covalent BTKi have emerged from the genomic analyses comparing pretreatment specimens with those obtained at disease progression [136]. The BRUIN trial investigators identified nine patients among 55 with R/R CLL who were treated with pirtobrutinib monotherapy. Seven of these nine patients had one or more mutations identified in the kinase domain of BTK in regions other than the Cys481 (non-C481 BTK mutation) [136]. In the other two patients, mutations in the downstream BTK substrate, PLC gamma 2, that permitted escape from BTK inhibition, were identified both in pre and post-treatment specimens [136].

Conclusion

The treatment landscape of WM has drastically changed since the introduction of BTKi. Although BTKi are not curative, clinical trials have demonstrated significant activity in both TN and R/R WM. Ibrutinib's toxicity profile is poorer than the next-generation BTKi and the AE profile and acquired resistance have catapulted the emergence of more selective agents, with fewer off-target effects, and therapeutic approaches to overcome resistance. The covalent, second-generation BTKi have demonstrated meaningful outcomes and a superior safety profile. However, despite improved selectivity, they carry the risk of treatment-emergent AE, particularly when given on a continuous basis. In clinical practice, selection of the appropriate BTKi should be based on the differential toxicity profile and access to the different agents of from this class. For example, acalabrutinib is generally avoided in patients with headaches. Ibrutinib is especially not recommended for patients who have a high risk of cardiovascular and cerebrovascular diseases. Although studies identifying acquired resistance patterns for the second-generation inhibitors are lacking, particularly in WM, one would expect BTK mutations to occur with any covalent inhibitor that shares the mechanism of action. More research is needed in this area. Still, the risk of covalent BTKi acquired resistance is a potential drawback that shines a light on the value of emerging, novel, non-covalent BTKi.

A proof-of-principal study demonstrated that delayed responses with ibrutinib monotherapy in patients with mutated *CXCR4* may be tackled with the use of ulocuplumab, a CXCR4 antagonist, in combination with ibrutinib. The combination rapidly led to a major response among patients with $MYD88^{Mut}$ and $CXCR4^{Mut}$ WM who were BTKi-naïve. Unfortunately, further development of ulocuplumab has been halted by its manufacturer. Another ongoing phase 1b, open-label, multicenter, single-arm study is examining the role of mavorixafor, an oral, small-molecule antagonist of CXCR4, in patients with WM harboring *MYD88* and *CXCR4* mutations, with preliminary data showing promising activity [137].

Table 3 outlines additional ongoing clinical trials investigating the use of BTKi in patients with WM. There are many non-covalent BTKi currently under investigation. Besides novel BTK inhibitors, small-molecule–induced BTK degraders are being developed to overcome the limitations posed by the traditional BTK inhibitors that are not specific for the BTK enzymes.

Currently, with the availability of both ibrutinib and zanubrutinib in the US, we prefer the use of the latter, given its improved safety profile among patients with WM. However, in the absence of a randomized controlled trial against bendamustine-rituximab (BR), the option to use one approach over the other in the previously untreated patients with active WM largely depends on patient and clinician preference. A recent multicenter international collaborative study evaluating the two approaches (ibrutinib vs BR) in an age matched treatment-naïve population showed that significantly deeper responses were achieved with BR, although 4-year PFS and OS rates were similar between the two approaches [138•]. Although limited data regarding optimal sequencing of therapies exist in WM, our approach outside of clinical trials is to use BR as primary therapy and continuous zanubrutinib therapy in the R/R setting, especially in light of data showing comparable efficacy of this agent in both the TN and R/R

patient populations [139]. We anticipate that the future of BTKi use in WM will continue to expand as ongoing clinical trials are completed and clinicians become more familiar with this class of drugs and the management of the toxicities. Complete response is elusive with both covalent and non-covalent BTKi, and combination regimens to improve upon the efficacy and limit the treatment duration are under development in WM.

Author Contributions RKT, JPA and PK collected the data. RKT wrote the initial draft and prepared the tables. JPA edited the manuscript. PK revised the manuscript and the tables. All authors reviewed and approved the final manuscript.

Data Availability No datasets were generated or analysed during the current study. P.K is the principal investigator of trials for which Mayo Clinic has received research funding from Amgen, Regeneron, Bristol Myers Squibb, Loxo Pharmaceuticals, Ichnos, Karyopharm, Sanofi, AbbVie and GlaxoSmithKline. Prashant Kapoor has served on the Advisory Boards of BeiGene, Mustang Bio, Pharmacyclics, X4 Pharmaceuticals, AstraZeneca, Kite, Oncopeptides, Angitia Bio, GlaxoSmithKline, AbbVie and Sanofi.

Declarations

Conflict of Interest RKT and JPA declare no competing interests. P.K is the principal investigator of trials for which Mayo Clinic has received research funding from Amgen, Regeneron, Bristol Myers Squibb, Loxo Pharmaceuticals, Ichnos, Karyopharm, Sanofi, AbbVie and GlaxoSmithKline. Prashant Kapoor has served on the Advisory Boards of BeiGene, Mustang Bio, Pharmacyclics, X4 Pharmaceuticals, AstraZeneca, Kite, Oncopeptides, Angitia Bio, GlaxoSmithKline, AbbVie and Sanofi.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Ghobrial IM, Gertz MA, Fonseca R. Waldenström macroglobulinaemia. Lancet Oncol. 2003;4(11):679–85.
2. Fonseca R, Hayman S. Waldenström macroglobulinaemia. Br J Haematol. 2007;138(6):700–20.
3. Kyle RA, et al. Fifty-year incidence of Waldenström Macroglobulinemia in Olmsted County, Minnesota, from 1961 through 2010: a population-based study with complete case capture and hematopathologic review. Mayo Clin Proc. 2018;93(6):739–46.
4. Yin X, et al. Trends in incidence and mortality of Waldenström Macroglobulinemia: a population-based study. Front Oncol. 2020;10:1712.
5. Castillo JJ, Ghobrial IM, Treon SP. Biology, prognosis, and therapy of waldenström macroglobulinemia. Cancer Treat Res 2015;165:177–195.
6. Treon SP, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. N Engl J Med. 2012;367(9):826–33.
7. Lin SC, Lo YC, Wu H. Helical assembly in the MyD88-IRAK4-IRAK2 complex in TLR/IL-1R signalling. Nature. 2010;465(7300):885–90.
8. Varettoni M, et al. Prevalence and clinical significance of the MYD88 (L265P) somatic mutation in Waldenstrom's macroglobulinemia and related lymphoid neoplasms. Blood. 2013;121(13):2522–8.
9. Yang G, et al. A mutation in MYD88 (L265P) supports the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase in Waldenström macroglobulinemia. Blood. 2013;122(7):1222–32.
10. Hunter ZR, et al. The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. Blood. 2014;123(11):1637–46.
11. Kaiser LM, et al. CXCR4 in Waldenström's Macroglobulinema: chances and challenges. Leukemia. 2021;35(2):333–45.
12. Gustine JN, et al. CXCR4 (S338X) clonality is an important determinant of ibrutinib outcomes in patients with Waldenstrom macroglobulinemia. Blood Adv. 2019;3(19):2800–3.
13. Treon SP, et al. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. Blood. 2014;123(18):2791–6.
14. Varettoni M, et al. Pattern of somatic mutations in patients with Waldenström macroglobulinemia or IgM monoclonal gammopathy of undetermined significance. Haematologica. 2017;102(12):2077–85.
15. Castillo JJ, et al. Recommendations for the diagnosis and initial evaluation of patients with Waldenström Macroglobulinaemia: a Task Force from the 8th International Workshop on Waldenström Macroglobulinaemia. Br J Haematol. 2016;175(1):77–86.
16. Kastritis E, et al. Waldenström's macroglobulinaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; 29(Suppl 4): iv41-iv50.
17. Kyle RA, et al. Prognostic markers and criteria to initiate therapy in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol. 2003;30(2):116–20.
18. Kapoor P, et al. Diagnosis and Management of Waldenström Macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines 2016. JAMA Oncol. 2017;3(9):1257–65.
19. Owen RG, et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol. 2003;30(2):110–5.
20. Pophali PA, et al. Prevalence and survival of smouldering Waldenström macroglobulinaemia in the United States. Br J Haematol. 2019;184(6):1014–7.
21. Kyle RA, et al. Progression in smoldering Waldenstrom macroglobulinemia: long-term results. Blood. 2012;119(19):4462–6.
22. Bustoros M, et al. Progression risk stratification of asymptomatic Waldenström macroglobulinemia. J Clin Oncol. 2019;37(16):1403–11.
23. Alexanian R, et al. Asymptomatic Waldenstrom's macroglobulinemia. Semin Oncol. 2003;30(2):206–10.
24. Baldini L, et al. Immunoglobulin M monoclonal gammopathies of undetermined significance and indolent Waldenstrom's macroglobulinemia recognize the same determinants of evolution into symptomatic lymphoid disorders: proposal for a common prognostic scoring system. J Clin Oncol. 2005;23(21):4662–8.
25.• Zanwar S, et al. Disease outcomes and biomarkers of progression in smouldering Waldenström macroglobulinaemia. Br

J Haematol. 2021;195(2): 210–216. **A retrospective study that identified biomarkers (hemoglobin ≤123 g/L and β2-microglobulin ≥2.7 μg/mL) in patients with smouldering Waldenström macroglobulinaemia (SWM) that predict a shorter time to progression to active WM. The study also revealed comparable survival of SWM and a matched USA population.**

26. Morel P, et al. International prognostic scoring system for Waldenstrom macroglobulinemia. Blood. 2009;113(18):4163–70.
27. Zanwar S, et al. Modified staging system for Waldenström Macroglobulinemia (MSS-WM): a multi-institutional externally validated prognostic model for active/symptomatic Waldenström Macroglobulinemia. Blood. 2023;142(Supplement 1):3030–3030.
28. Kastritis E, et al. A revised international prognostic score system for Waldenström's macroglobulinemia. Leukemia. 2019;33(11):2654–61.
29. Gertz MA. Waldenström macroglobulinemia: 2021 update on diagnosis, risk stratification, and management. Am J Hematol. 2021;96(2):258–69.
30. Rummel MJ, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381(9873):1203–10.
31. Dimopoulos MA, et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. J Clin Oncol. 2007;25(22):3344–9.
32. Paludo J, et al. Dexamethasone, rituximab and cyclophosphamide for relapsed and/or refractory and treatment-naïve patients with Waldenstrom macroglobulinemia. Br J Haematol. 2017;179(1):98–105.
33. Paludo J, et al. Bendamustine and rituximab (BR) versus dexamethasone, rituximab, and cyclophosphamide (DRC) in patients with Waldenström macroglobulinemia. Ann Hematol. 2018;97(8):1417–25.
34. Treon SP, et al. Primary therapy of Waldenström macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05–180. J Clin Oncol. 2009;27(23):3830–5.
35. Ghobrial IM, et al. Phase II trial of weekly bortezomib in combination with rituximab in relapsed or relapsed and refractory Waldenstrom macroglobulinemia. J Clin Oncol. 2010;28(8):1422–8.
36. Dimopoulos MA, et al. Primary therapy of Waldenström macroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). Blood. 2013;122(19):3276–82.
37. Treon SP, et al. Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenström's macroglobulinemia. Blood. 2014;124(4):503–10.
38. Castillo JJ, et al. Prospective clinical trial of ixazomib, dexamethasone, and rituximab as primary therapy in Waldenström macroglobulinemia. Clin Cancer Res. 2018;24(14):3247–52.
39. Castillo JJ, et al. Ixazomib, dexamethasone, and rituximab in treatment-naive patients with Waldenström macroglobulinemia: long-term follow-up. Blood Adv. 2020;4(16):3952–9.
40. Burger JA. Bruton tyrosine kinase inhibitors: present and future. Cancer J. 2019;25(6):386–93.
41. Stevenson FK, et al. B-cell receptor signaling in chronic lymphocytic leukemia. Blood. 2011;118(16):4313–20.
42. Satterthwaite AB, Witte ON. The role of Bruton's tyrosine kinase in B-cell development and function: a genetic perspective. Immunol Rev. 2000;175:120–7.
43. Pals ST, Kersten MJ, Spaargaren M. Targeting cell adhesion and homing as strategy to cure Waldenstrom's macroglobulinemia. Best Pract Res Clin Haematol. 2016;29(2):161–8.
44. Castillo JJ, et al. Consensus treatment recommendations from the tenth International Workshop for Waldenström Macroglobulinaemia. Lancet Haematol. 2020;7(11):e827–37.
45. Davids MS, Brown JR. Ibrutinib: a first in class covalent inhibitor of Bruton's tyrosine kinase. Future Oncol (Lond, Engl). 2014;10(6):957–67.
46. Pharmacyclics, I. ImbruvicaTM (ibrutinib) capsules for oral use; US prescribing information. 2013.
47. Abeykoon JP, Yanamandra U, Kapoor P. New developments in the management of Waldenström macroglobulinemia. Cancer Manag Res. 2017;9:73–83.
48. Mason C, et al. Ibrutinib penetrates the blood brain barrier and shows efficacy in the therapy of Bing Neel syndrome. Br J Haematol. 2017;179(2):339–41.
49.•• Castillo JJ, et al. Ibrutinib for the treatment of Bing-Neel syndrome: a multicenter study. Blood. 2019;133(4):299-305. **A retrospective, multicenter study that demonstrated a favorable response with ibrutinib therapy in patients with Bing-Neal syndrome.**
50. Treon SP, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med. 2015;372(15):1430–40.
51. Treon SP, et al. Ibrutinib monotherapy in symptomatic, treatment-naïve patients with Waldenström macroglobulinemia. J Clin Oncol. 2018;36(27):2755–61.
52. Dimopoulos MA, et al. Ibrutinib for patients with rituximab-refractory Waldenström's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial. Lancet Oncol. 2017;18(2):241–50.
53. Buske C, et al. Ibrutinib plus rituximab versus placebo plus rituximab for waldenström's macroglobulinemia: final analysis from the randomized phase III iNNOVATE study. J Clin Oncol. 2022;40(1):52–62.
54. Tam CS, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenstrom macroglobulinemia: the ASPEN study. Blood. 2020;136(18):2038–50.
55. •• Dimopoulos MA, et al. Zanubrutinib versus ibrutinib in symptomatic Waldenström macroglobulinemia: final analysis from the randomized phase III ASPEN study. J Clin Oncol. 2023; 41(33):5099–5106. **The phase III ASPEN study demonstrated the comparable efficacy and improved safety of zanubrutinib versus ibrutinib in patients with WM. The final analysis published reported the long term outcomes from ASPEN.**
56. Advani RH, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol. 2013;31(1):88–94.
57. Treon SP, et al. Long-term follow-up of ibrutinib monotherapy in symptomatic, previously treated patients with Waldenström macroglobulinemia. J Clin Oncol. 2021;39(6):565–75.
58.•• Dimopoulos MA, et al. A phase 3 clinical trial that evaluated the effect of adding ibrutinib to rituximab in patients with relapse/refractory and treatment naive WM. N Engl J Med. 2018;378(25):2399–2410. **A phase 3 clinical trial that evaluated the effect of adding ibrutinib to rituximab in patients with relapse/refractory and treatment naive WM.**
59. Buske C, et al. Ibrutinib treatment in Waldenström's macroglobulinemia: follow-up efficacy and safety from the iNNOVATETM study. Blood. 2018;132:149.
60. Trotman J, et al. Zanubrutinib for the treatment of patients with Waldenstrom macroglobulinemia: 3 years of follow-up. Blood. 2020;136(18):2027–37.
61. An G, et al. A Phase II Trial of the Bruton Tyrosine-Kinase Inhibitor Zanubrutinib (BGB-3111) in Patients with Relapsed/

Refractory Waldenström Macroglobulinemia. Clin Cancer Res. 2021;27(20):5492–5501.

62.•• Dimopoulos M, et al. Long-term follow-up results of a phase 3 randomized trial of zanubrutinib (Zanu) vs ibrutinib (Ibr) in patients (Pts) with Waldenstrom macroglobulinemia [abstract], in European Hematology Association Annual Meeting. 2022. **ASPEN is the largest phase 3, head-to-head trial of zanubrutinib versus ibrutinib comparison in WM.**

63.•• Owen RG, et al. Acalabrutinib monotherapy in patients with Waldenström macroglobulinemia: a single-arm, multicentre, phase 2 study. Lancet Haematol. 2020;7(2):e112–e121. **A single-arm, multicentre, phase 2 trial with the aim to evaluate the activity and safety of acalabrutinib in patients with WM.**

64. Sekiguchi N, et al. A multicenter, open-label, phase II study of tirabrutinib (ONO/GS-4059) in patients with Waldenstrom's macroglobulinemia. Cancer Sci. 2020;111(9):3327–37.

65. Sekiguchi N, et al. Two-year outcomes of tirabrutinib monotherapy in Waldenström's macroglobulinemia. Cancer Science, 2022;113(6):2085–2096.

66. • Cao X-x, et al. Evaluation of orelabrutinib monotherapy in patients with relapsed or refractory Waldenstrom's macroglobulinemia in a single-arm, multicenter, open-label, phase 2 study. eClinicalMedicine. 2022;52:101682. **A prospective, multicenter study of orelabrutinib in patients with WM who had at least one prior line of treatment. The purpose of this study was to evaluate the efficacy and safety of orelabrutinib in patients with relapsed or refractory WM.**

67. Cao X, et al. Orelabrutinib monotherapy in patients with relapsed or refractory Waldenström's macroglobulinemia in a single-arm, multicenter, open-label, phase 2 study: long term follow-up results. Blood. 2023;142(Supplement 1):3039–3039.

68. Dimopoulos M, et al. Zanubrutinib for the treatment of MYD88 wild-type Waldenström macroglobulinemia: a substudy of the phase 3 ASPEN trial. Blood Adv. 2020;4(23):6009–18.

69.•• Mato AR, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet. 2021; 397(10277): 892-901. A prospective, multicenter study of orelabrutinib in patients with WM who had at least one prior line of treatment. The purpose of this study was to evaluate the efficacy and safety of orelabrutinib in patients with relapsed or refractory WM. **A first-in-human, multicentre, open-label, phase 1/2 trial of pirtobrutinib with the goal to evaluate the safety and efficacy pirtobrutinib, a highly selective, reversible BTK inhibitor, in relapsed/refractory B-cell malignancies.**

70. Palomba ML, et al. Efficacy of pirtobrutinib, a highly selective, non-covalent (Reversible) BTK inhibitor in relapsed / refractory Waldenström macroglobulinemia: results from the Phase 1/2 BRUIN study. Blood. 2022;140(Supplement 1):557–60.

71. Treon SP, Xu L, Hunter Z. MYD88 mutations and response to ibrutinib in Waldenström's macroglobulinemia. N Engl J Med. 2015;373(6):584–6.

72. Zanwar S, Abeykoon JP, Kapoor P. Novel treatment strategies in the management of Waldenstrom Macroglobulinemia. Curr Hematol Malig Rep. 2020;15(1):31–43.

73. Paydas S. Management of adverse effects/toxicity of ibrutinib. Crit Rev Oncol Hematol. 2019;136:56–63.

74. Paulus A, et al. Waldenstrom macroglobulinemia cells devoid of BTK(C481S) or CXCR4(WHIM-like) mutations acquire resistance to ibrutinib through upregulation of Bcl-2 and AKT resulting in vulnerability towards venetoclax or MK2206 treatment. Blood Cancer J. 2017;7(5):e565.

75. Munir T, et al. Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. Am J Hematol. 2019;94(12):1353–63.

76. Leong DP, et al. The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis. Blood. 2016;128(1):138–40.

77. McMullen JR, et al. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. Blood. 2014;124(25):3829–30.

78. Xiao L, et al. Ibrutinib-mediated atrial fibrillation attributable to inhibition of C-Terminal Src kinase. Circulation. 2020;142(25):2443–55.

79. Gustine JN, et al. Atrial fibrillation associated with ibrutinib in Waldenström macroglobulinemia. Am J Hematol. 2016;91(6):E312–3.

80. Vrontikis A, et al. Proposed algorithm for managing ibrutinib-related atrial fibrillation. Oncology (Williston Park). 2016;30(11):970–4 (980-1, c3).

81. Shanafelt TD, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL). Leuk Lymphoma. 2017;58(7):1630–9.

82. Mock J, et al. Risk of major bleeding with ibrutinib. Clin Lymphoma Myeloma Leuk. 2018;18(11):755–61.

83. Yun S, et al. Risk of atrial fibrillation and bleeding diathesis associated with ibrutinib treatment: a systematic review and pooled analysis of four randomized controlled trials. Clin Lymphoma Myeloma Leuk. 2017;17(1):31-37.e13.

84. Shatzel JJ, et al. Ibrutinib-associated bleeding: pathogenesis, management and risk reduction strategies. J Thromb Haemost. 2017;15(5):835–47.

85.•• Tam CS, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood. 2020;136(18):2038–2050. **A novel phase 3 trial comparing the efficacy and safety of ibrutinib with zanubrutinib in patients with WM. The results demonstrate that zanubrutinib treatment was associated with a trend toward better response quality and less toxicity.**

86. Rogers KA, et al. Incidence and description of autoimmune cytopenias during treatment with ibrutinib for chronic lymphocytic leukemia. Leukemia. 2016;30(2):346–50.

87. de Weerdt I, et al. Incidence and management of toxicity associated with ibrutinib and idelalisib: a practical approach. Haematologica. 2017;102(10):1629–39.

88. Brown JR, et al. Incidence of and risk factors for major haemorrhage in patients treated with ibrutinib: an integrated analysis. Br J Haematol. 2019;184(4):558–69.

89. Bye AP, et al. Ibrutinib inhibits platelet integrin alphaIIbbeta3 Outside-in signaling and thrombus stability but not adhesion to collagen. Arterioscler Thromb Vasc Biol. 2015;35(11):2326–35.

90. Levade M, et al. Ibrutinib treatment affects collagen and von Willebrand factor-dependent platelet functions. Blood. 2014;124(26):3991–5.

91. Bye AP, et al. Severe platelet dysfunction in NHL patients receiving ibrutinib is absent in patients receiving acalabrutinib. Blood Adv. 2017;1(26):2610–23.

92. Greil R, et al. Pretreatment with ibrutinib reduces cytokine secretion and limits the risk of obinutuzumab-induced infusion-related reactions in patients with CLL: analysis from the iLLUMINATE study. Ann Hematol. 2021;100(7):1733–42.

93. Bercusson A, et al. Ibrutinib blocks Btk-dependent NF-κB and NFAT responses in human macrophages during Aspergillus fumigatus phagocytosis. Blood. 2018;132(18):1985–8.

94. Varughese T, et al. Serious infections in patients receiving ibrutinib for treatment of lymphoid cancer. Clin Infect Dis. 2018;67(5):687–92.

95. Abeykoon JP, et al. Ibrutinib monotherapy outside of clinical trial setting in Waldenstrom macroglobulinaemia: practice patterns, toxicities and outcomes. Br J Haematol. 2020;188(3):394–403.

96. Gustine JN, et al. Ibrutinib discontinuation in Waldenström macroglobulinemia: etiologies, outcomes, and IgM rebound. Am J Hematol. 2018;93(4):511–7.
97. Castillo JJ, et al. Impact of ibrutinib dose intensity on patient outcomes in previously treated Waldenström macroglobulinemia. Haematologica. 2018;103(10):e466–8.
98. Hodge LS, et al. Constitutive activation of STAT5A and STAT5B regulates IgM secretion in Waldenstrom's macroglobulinemia. Blood. 2014;123(7):1055–8.
99. Mahajan S, et al. Transcription factor STAT5A is a substrate of Bruton's tyrosine kinase in B cells. J Biol Chem. 2001;276(33):31216–28.
100.• Castillo JJ, et al. Ibrutinib withdrawal symptoms in patients with Waldenström macroglobulinemia. Haematologica. 2018;103(7):e307–e310. **A retrospective study the describes the symptoms of withdrawal and the rate of withdrawal symptoms in WM patients who hold ibrutinib therapy.**
101.• Castillo JJ, et al. Ibrutinib and venetoclax in symptomatic, treatment-naive patients with Waldenström macroglobulinemia. Blood. 2023; 142(Supplement 1): 1661-1661. **A prospective study evaluating ibrutinib and venetoclax in treatment-naive WM. This study presents the follow-up data after stopping therapy to assess ongoing safety and response durability in WM.**
102. Barf T, et al. Acalabrutinib (ACP-196): a covalent bruton tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. J Pharmacol Exp Ther. 2017;363(2):240–52.
103. Byrd JC, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374(4):323–32.
104. LP, A.P., CALQUENCE (acalabrutinib) capsules, for oral use Initial U.S. Approval: 2017.
105. Wu J, Zhang M, Liu D. Acalabrutinib (ACP-196): a selective second-generation BTK inhibitor. J Hematol Oncol. 2016;9:21.
106. Wang M, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet. 2018;391(10121):659–67.
107. NCCN Clinical Practice Guidelines in Oncology Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma. 2022 12/7/2021; Available from: https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf.
108. Berinstein N, et al. Indolent lymphoma: high CR and VGPR rate with fixed duration Bendamustine, Rituximab and Acalabrutinib in Waldenstroms Macroglobulinaemia (BRAWM). Blood. 2023;142(Supplement 1):3037–3037.
109. Sarosiek SR, et al. Prospective study of acalabrutinib with rituximab in patients with symptomatic anti-MAG mediated IgM peripheral neuropathy. Blood. 2023;142(Supplement 1):213–213.
110. Tam CS, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. Blood. 2019;134(11):851–9.
111. Ou YC, et al. A phase 1, open-label, single-dose study of the pharmacokinetics of zanubrutinib in subjects with varying degrees of hepatic impairment. Leuk Lymphoma. 2020;61(6):1355–63.
112. Opat S, et al. The MAGNOLIA trial: zanubrutinib, a next-generation bruton tyrosine kinase inhibitor, demonstrates safety and efficacy in relapsed/refractory marginal zone lymphoma. Clin Cancer Res. 2021;27(23):6323–32.
113. Tam CS, et al. Biomarker analysis of the ASPEN study comparing zanubrutinib to ibrutinib in patients with Waldenström Macroglobulinemia. Blood Adv 2024.
114. Chen J, et al. The effect of Bruton's tyrosine kinase (BTK) inhibitors on collagen-induced platelet aggregation, BTK, and tyrosine kinase expressed in hepatocellular carcinoma (TEC). Eur J Haematol 2018;101(5):604–612.
115. Liclican A, et al. Biochemical characterization of tirabrutinib and other irreversible inhibitors of Bruton's tyrosine kinase reveals differences in on - and off - target inhibition. Biochim Biophys Acta Gen Subj. 2020;1864(4): 129531.
116. Kozaki R, et al. Responses to the selective Bruton's Tyrosine Kinase (BTK) inhibitor tirabrutinib (ONO/GS-4059) in diffuse large b-cell lymphoma cell lines. Cancers. 2018;10(4):127.
117. Yahiaoui A, et al. PI3Kδ inhibitor idelalisib in combination with BTK inhibitor ONO/GS-4059 in diffuse large B cell lymphoma with acquired resistance to PI3Kδ and BTK inhibitors. PLoS ONE. 2017;12(2):e0171221.
118. Yasuhiro T, et al. Anti-tumor efficacy study of the Bruton's tyrosine kinase (BTK) inhibitor, ONO/GS-4059, in combination with the glycoengineered type II anti-CD20 monoclonal antibody obinutuzumab (GA101) demonstrates superior in vivo efficacy compared to ONO/GS-4059 in combination with rituximab. Leuk Lymphoma. 2017;58(3):699–707.
119. Bates J, et al. The combination of a BET inhibitor (GS-5829) and a BTK inhibitor (GS-4059) potentiates DLBCL cell line cell death and reduces expression of MYC, IL-10, and IL-6 in vitro. Blood. 2016;128(22):5116–5116.
120. Dhillon S. Tirabrutinib: first approval. Drugs. 2020;80(8):835–40.
121. Walter HS, et al. A phase 1 clinical trial of the selective BTK inhibitor ONO/GS-4059 in relapsed and refractory mature B-cell malignancies. Blood. 2016;127(4):411–9.
122. Yamagami J, et al. A multicenter, open-label, uncontrolled, single-arm phase 2 study of tirabrutinib, an oral Bruton's tyrosine kinase inhibitor, in pemphigus. J Dermatol Sci. 2021;103(3):135–42.
123. Dhillon S. Orelabrutinib: first approval. Drugs. 2021;81(4):503–7.
124. Xu L, et al. Acquired mutations associated with ibrutinib resistance in Waldenström macroglobulinemia. Blood. 2017;129(18):2519–25.
125. Chen JG, et al. BTK(Cys481Ser) drives ibrutinib resistance via ERK1/2 and protects BTK(wild-type) MYD88-mutated cells by a paracrine mechanism. Blood. 2018;131(18):2047–59.
126. Jimenez C, et al. Genomic evolution of ibrutinib-resistant clones in Waldenstrom macroglobulinaemia. Br J Haematol. 2020;189(6):1165–70.
127. Hershkovitz-Rokah O, et al. Ibrutinib resistance in mantle cell lymphoma: clinical, molecular and treatment aspects. Br J Haematol. 2018;181(3):306–19.
128. Zhang SQ, et al. Mechanisms of ibrutinib resistance in chronic lymphocytic leukaemia and non-Hodgkin lymphoma. Br J Haematol. 2015;170(4):445–56.
129. Paulus A. et al. Waldenstrom macroglobulinemia cells devoid of BTK(C481S) or CXCR4(WHIM-like) mutations acquire resistance to ibrutinib through upregulation of Bcl-2 and AKT resulting in vulnerability towards venetoclax or MK2206 treatment. Blood Cancer J. 2017;7(5):e565.
130. Woyach J, et al. Resistance to acalabrutinib in CLL is mediated primarily by BTK mutations. Blood. 2019;134(Supplement_1):504–504.
131. Estupiñán HY, et al. BTK gatekeeper residue variation combined with cysteine 481 substitution causes super-resistance to irreversible inhibitors acalabrutinib, ibrutinib and zanubrutinib. Leukemia. 2021;35(5):1317–29.
132. Handunnetti SM, et al. BTK Leu528Trp - a potential secondary resistance mechanism specific for patients with chronic lymphocytic leukemia treated with the next generation BTK inhibitor zanubrutinib. Blood. 2019;134(Supplement_1):170–170.
133. Brandhuber B, et al. LOXO-305, a next generation reversible BTK inhibitor, for overcoming acquired resistance to irreversible BTK inhibitors. Clin Lymphoma Myeloma Leuk. 2018;18:S216.

134. Reiff SD, et al. The Bruton's Tyrosine Kinase (BTK) inhibitor ARQ 531 effectively inhibits wild type and C481S mutant BTK and is superior to ibrutinib in a mouse model of chronic lymphocytic leukemia. Blood. 2016;128(22):3232–3232.
135. Woyach J, et al. Final results of phase 1, dose escalation study evaluating ARQ 531 in patients with relapsed or refractory B-cell lymphoid malignancies. Blood. 2019;134(Supplement_1):4298–4298.
136. Wang E, et al. Mechanisms of resistance to noncovalent Bruton's tyrosine kinase inhibitors. N Engl J Med. 2022;386(8):735–43.
137. Dale DC, et al. Oral administration of Mavorixafor, a CXCR4 antagonist, increases peripheral white blood cell counts across different disease states [abstract], in American Society of Hematology Annual Meeting 2021: Atlanta, Georgia.
138.• Abeykoon JP. et al. Bendamustine rituximab (BR) versus ibrutinib (Ibr) as primary therapy for Waldenström macroglobulinemia (WM): An international collaborative study. J Clin Onco 2022;40(16):7566–47566. **A multi-institutional, international, collaborative study to compare BR and single-agent ibrutinib in patients with treatment naïve WM.**
139. Tawfiq R, et al. Outcomes in treatment patterns after first relapse in patients with Waldenstrom macroglobulinemia [abstract], in European Hematology Association Annual Meeting. 2022.