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Zanubrutinib in the treatment of Waldenström Macroglobulinemia

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ABSTRACT
Waldenström Macroglobulinemia (WM) is an uncommon malignancy of IgM-secreting lymphoplasmacytic cells. The spectrum of acquired somatic mutations is heterogeneous, with MYD88 mutations occurring in more than 90%. Recurrent mutations in CXCR4, KMT2D, ARID1A, TERT, and TP53 are also detected, with some of these impacting prognosis or treatment response. The recognition of B-cell receptor (BCR) signalling in B-cell neoplasm pathophysiology led to the clinical development of the first-in-class Bruton tyrosine kinase inhibitor (BTKi) ibrutinib. Despite efficacy, off-target inhibition of TEC, EGFR, CSK and other kinases impact its safety and tolerability. The second-generation BTKi, zanubrutinib and acalabrutinib, are better tolerated with lower rates of discontinuation. Zanubrutinib is more selective for BTK than other structurally related kinases. While there have not been any studies directly comparing acalabrutinib to zanubrutinib, the efficacy of zanubrutinib was superior to ibrutinib in WM patients with MYD88 wild type, CXCR4 or TP53 mutations. However, patients with CXCR4 and TP53 mutations receiving BTKi still fare worse than those without, highlighting the need for other therapeutic strategies. Herein, we review the clinical development of zanubrutinib in WM including the impact of genetic subtypes and advise on the management of adverse events and drug resistance.

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Zanubrutinib; waldenstrom macroglobulinemia; Bruton tyrosine kinase inhibitor; B-cell malignancy; lymphoplasmacytic lymphoma

1. Introduction

Since Swedish hematologist Jan Waldenström first described the eponymous condition in three patients in 1944, the definition has evolved from a clinical syndrome to a clinicopathological diagnosis with an incidence of 0.3/100,000 cases per year [1,2]. WM is a heterogenous indolent B-cell lymphoma of clonal IgM-secreting lymphoplasmacytic cells with classical features of hyperviscosity, autoimmune phenomena, cryoglobulinaemia, and peripheral neuropathy [3].

There is a growing appreciation of how the mutation spectrum in WM is relevant to prognosis and response to available therapies. Acquired genetic mutations associated with WM are common and diverse, with mutations in the MYD88^{L265P} gene seen in >90% of cases [4]. Mutations in CXCR4 are present in up to 30% of cases, and KMT2D, ARID1A, TERT, and TP53 are also recurrent [5].

In patients who require treatment, therapies have until recently been limited to plasma exchange for rapid control of paraprotein-related manifestations, and chemoimmunotherapy with inherent toxicities and risks of inducing refractory disease and future development of clonal myeloid disorders such as myelodysplastic syndrome or acute myeloid leukemia.

Ibrutinib, the first-generation BTKi, offered an effective non-chemoimmunotherapy option for WM. However, it was associated with off-target activity against other kinases and significant adverse events (AEs) including cardiac, gastrointestinal, and skin toxicities which have driven the development of the second-generation BTKis zanubrutinib and acalabrutinib [6,7].

2. History of zanubrutinib

The recognition of aberrant BCR signaling in the improved survival of malignant B cells guided the development of several agents able to target kinases in the BCR pathway including spleen tyrosine kinase (SYK), BTK and phosphoinositol-3-kinase (PI3K) [8–10]. A common feature of these early agents was their lack of specificity, with off-target effects contributing to toxicity [8]. The first-in-class BTKi PCI-32765 (ibrutinib) was empirically tested in a range of B-cell malignancies with best responses seen in mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and WM [11–13].

Ibrutinib was approved by the Federal Drug Association (FDA) for relapsed CLL in 2013 and subsequently for WM in 2015 using data from a pivotal phase II study which reported an overall response rate (ORR) of 90.5% and two-year progression free survival (PFS) of 69% from a total of 63 patients with relapsed WM [14]. While highly efficacious, it was soon appreciated that patients receiving ibrutinib were experiencing AEs including hypertension (HTN) and atrial fibrillation (AF) attributable to inhibition of terminal SRC kinase (CSK), platelet-type bleeding due to inhibition of TEC kinase which mediates platelet GpVI-mediated activation and diarrhea and skin rash due to off-target inhibition of EGFR [6,7,15,16].

This appreciation led to the development of zanubrutinib which was designed to enhance specificity for BTK, minimize off-target binding and associated toxicities, and improve pharmacokinetic properties including bioavailability and drug-drug interactions [17]. Studies of kinase selectivity have confirmed

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Article highlights

- Waldenstrom Macroglobulinemia (WM) is an uncommon, incurable indolent B-cell lymphoma with a heterogeneous spectrum of somatic mutations, of which MYD88 is most common. The clinical significance of the mutation spectrum on prognosis and response to treatment is increasingly becoming appreciated.
- The first-in-class Bruton tyrosine kinase inhibitor (BTKi) ibrutinib transformed the therapeutic landscape, but this class of medications has off-target activity against other kinases and lead to adverse events such as hypertension, cardiac arrhythmias and gastrointestinal effects. The second generation BTKi acalabrutinib and zanubrutinib are better tolerated due to improved selectivity for the binding pocket of BTK and have lower rates of discontinuation and side effects.
- The landmark ASPEN trial, a multicenter phase III study compared ibrutinib with zanubrutinib in patients with WM. Zanubrutinib was shown to be superior to ibrutinib with improved response rates, more durable responses, and fewer adverse events.
- Zanubrutinib is a well-tolerated BTKi with proven efficacy in WM, including in those harboring the MYD88 wild type, CXCR4 or TP53 mutations.

the greater selectivity of zanubrutinib for BTK versus other kinases, underpinning the improved safety profile [18].

3. Mechanism of action of BTKi in WM

BTK plays a key role in signaling pathways required for the survival of the malignant clone in WM. Constitutive activation of BTK is induced through the somatic mutation of myeloid differentiation factor MYD88, an adaptor protein that facilitates cross-talk between the toll like receptor (TLR) and BCR [19]. The MYD88^{L265P} mutation affects the TLR/interleukin-1 receptor domain of the MYD88 protein and leads to its constitutive activation by forming a myddosome, a large intracellular oligomeric complex leading to downstream activation of NFκB and pro-survival signaling [19].

Mutated MYD88 also upregulates the HCK transcription factor which mediates pro-survival signaling through BTK, PI3K/AKT, and MAPK1/3. HCK is also a target of ibrutinib, but less so zanubrutinib [18,20,21]. Deletions in chromosome 6q are observed frequently in patients with WM, resulting in the loss of regulators of MYD88 signaling, including the important inhibitor of BTK (IBTK) and the NFκB regulators HIVEP2 and TNFAIP3 [20,22].

BTK has been suggested to play a role in the signaling of G-coupled chemokine receptors (including CXCR4), cytokine receptors (CD19, CD38, CD40), TNF family receptors, integrins, and TLRs. However, CXCR4 mutated WM is relatively resistant to BTKi, particularly ibrutinib, with alternative pro-survival signals mediated through PI3K/AKT and MAPK/ERK1/2 signaling [22,23].

4. Pharmacology of zanubrutinib

Zanubrutinib is an oral, irreversible BTKi which forms a covalent bond at Cys481 within the adenosine triphosphate-binding pocket of BTK and is more selective for this site than other structurally related kinases as previously discussed [18,24]. Whilst a dose of 40 mg daily achieved 100% BTK occupancy in peripheral blood, the clinical dose was selected to achieve 100% occupancy in lymph nodes, achieved with 160 mg twice daily. Similarly, 320 mg once daily dose achieved 94% BTK lymph node occupancy and either of these dosing schedules is permissible in clinical practice [24].

The bioavailability of zanubrutinib is 4–8 times higher than that of ibrutinib permitting sustained therapeutic exposure, above the half-maximal inhibitory concentration (IC50) during entire dose interval for both daily and twice daily dosing schedules, unlike ibrutinib where drug levels fall below IC50 after 6 hours [24,25]. Due to higher selectivity, zanubrutinib can achieve high plasma exposure without accompanying toxicity. This was supported by the lack of dose limiting toxicities (DLT) in the phase 1 safety and efficacy evaluation study in 144 patients with CLL [26].

Dosing with food did not result in significant changes to the area under the curve (AUC) of zanubrutinib, permitting it to be taken with or without food [24]. Although zanubrutinib has pH-dependent solubility, gastric acid reducing agents such as proton pump inhibitors do not appear to affect absorption, and no dose reduction is required with concomitant administration of mild CYP3A inhibitors; a dose reduction is however required if taken in combination with moderate or strong CYP3A inhibitors [24].

Dose reductions are also recommended for zanubrutinib in severe Child-Pugh C hepatic impairment (to 80 mg twice daily), and to use caution in severe renal impairment or dialysis patients due to lack of data. No dose adjustments are required for mild liver disease or mild-moderate renal impairment [27].

Data is emerging on the central nervous system (CNS) penetration of zanubrutinib. A study of 13 diffuse large B-cell lymphoma (DLBCL) patients showed a CSF/plasma drug concentration ratio of 42.7% ± 27.7% (range, 8.6%-106.3%) [28]. The clinical efficacy of zanubrutinib in CNS disease was demonstrated in this study, in addition to a case report in Bing Neel syndrome, a rare CNS manifestation of WM [28,29].

5. BTKi treatment data in WM

The role of chemoimmunotherapy (CIT) in WM is established, with evidence largely gained from retrospective case series and phase 2 clinical trials [30–33]. There are no prospective trials comparing the two most common frontline CIT regimens, namely bendamustine/rituximab (BR) and dexamethasone/rituximab/cyclophosphamide (DRC), with a retrospective analysis suggesting longer PFS with BR compared with DRC (5.2 years to 4.3 years) [34]. Frontline studies comparing chemoimmunotherapy with BTKi are also lacking.

The phase III iNNOVATE study compared WM patients treated with rituximab + placebo vs. rituximab + ibrutinib 420 mg daily, with PFS the primary end point. With a median follow up of 50 months, median PFS was not reached (57.7 months to not evaluable) vs. 20.3 months with rituximab alone. Higher response rates (partial response or better) were achieved with rituximab + ibrutinib (76% vs. 32% with rituximab + placebo; $p < 0.0001$). The PFS benefit was regardless of MYD88 or CXCR4 mutation status [35].

Acalabrutinib, a second-generation BTKi has also demonstrated efficacy in R/R WM however it is not currently approved by the FDA for this indication nor is it approved in several jurisdictions [36]. There is no head-to-head trial comparing acalabrutinib to other BTKis.

In the phase II ACE-WM-001 study, a single-arm multicentre trial published in 2020, 106 patients were treated with acalabrutinib 100 mg twice daily. At a median follow up of 27.4 months 13 of 14 (95%) treatment naïve (TN) and 86 of 92 (93%) RR WM patients achieved an overall response (OR). AEs leading to dose withholding occurred in 57 (54%) of 106 patients. AF occurred in five patients (5%), HTN in 5 (5%), with three events being grade 3. Bleeding occurred in 61 (58%), with grade ≥3 bleeding in 3 patients. There was one death from intracranial hemorrhage [37]. A recent study, the BRAWM trial, combined BR with acalabrutinib in a one-year fixed duration treatment course of six cycles BR and 365 days acalabrutinib. Preliminary minimal residual disease (MRD) analysis has shown most evaluable participants have become MRD-negative over time [38]. This trial is ongoing.

The phase II zanubrutinib trial BGB-3111–210 is a single arm open label multicentre study conducted in China. Forty-four patients with relapsed or refractory (R/R) to at least one prior therapy were treated with 160 mg zanubrutinib twice daily. After a median follow up of 33 months major response rate (MRR) was 69.8% with VGPR or better in 32.6% of patients. Median PFS was not reached. The most frequently reported grade ≥3 AE was neutropenia (31.8%), thrombocytopenia (20.5%), and pneumonia (20.5%). No episodes of atrial arrythmias occurred [39].

The landmark ASPEN trial published in 2020 is a multicentre phase III study that compared ibrutinib with zanubrutinib for patients with MYD88^{L265P} WM, including 167 patients with R/R disease after ≥ 1 prior line of therapy and 37 TN patients deemed unsuitable for chemoimmunotherapy. Patients were assigned 1:1 to receive ibrutinib 420 mg daily or zanubrutinib 160 mg twice daily until disease progression or intolerance. Patients with MYD88^{WT} were given zanubrutinib on a non-randomized arm. The primary endpoint were those patients who achieved a very good partial response (VGPR) or complete response (CR). Of all MYD88^{L265P} patients, 29 (28%) zanubrutinib patients and 19 (19%) ibrutinib patients achieved a VGPR ($p = 0.09$) and no patients achieved a CR. AF, bruising, diarrhea, and hemorrhage, and early discontinuation were ≥10% more common in ibrutinib patients, and whilst neutropenia was ≥10% higher in zanubrutinib patients this did not translate to more frequent incidence of infection [40].

The final analysis of the ASPEN study, published in 2023, used a primary end point combining the VGPR and CR rates. At 44.4 months median follow up, VGPR + CR rates were 36.3% with zanubrutinib compared to 25.3% with ibrutinib. MRR for CXCR4^{MUT} disease were numerically lower compared with the CXCR4^{WT} (64% vs. 63% and 79% vs. 80% for zanubrutinib vs. ibrutinib respectively) but were comparable across treatment arms. Zanubrutinib treated patients exhibited fewer side effects associated with off-target binding, especially cardiovascular toxicity, and the study concluded overall that there is improved long-term safety and tolerability of zanubrutinib compared with ibrutinib, and zanubrutinib provides deeper and more durable responses in patients with WM [41]. Table 1 lists landmark studies using BTKi in WM.

WM patients with CXCR4 mutations have also been associated with lower response rates and shorter median PFS in patients treated with ibrutinib in other studies [14,46]. Currently, it is recommended to prefer chemoimmunotherapy for those patients with CXCR4 mutations, and BTKi for those with MYD88^{L265P} and CXCR4^{WT} whilst still taking patient factors such as age, comorbidities, and personal choice into treatment decisions [47].

While cross-trial comparisons are fraught, the VGPR rates for acalabrutinib in the phase II trial (TN: 0%, R/R

Table 1. Landmark studies using BTKi in WM.

Studies	Patient group	IP	Phase	Number of patients	Median lines of prior therapy	Median follow up (months)	ORR (%)	MRR (%)	VGPR/ CR (%)	PFS	OS
Treon et al., [14]	R/R	Ibrutinib	II	63	2	N/A	90.5	73	N/A	54% at 60m	87% at 60m
Dimopoulos et al., [42]	R/R	Ibrutinib	II	31	4	18.1	9	71	13	86% at 18m	97% at 18m
Treon et al., [43]	TN	Ibrutinib	II	30	0	14.6	100	83	20	92% at 18m	100% at 18m
Dimopoulos et al., [44]	TN and R/R	Ibrutinib + Rituximab	III	75	2	26.5	92	72	NA	82% at 30m	94% at 30m
Owen et al., [37]	TN	Acalabrutinib	II	14	0	27.4	93	79	7	90% at 24m	92% at 24m
	R/R	Acalabrutinib		92	2	27.4	93	78	33	82% at 24m	89% at 24m
Trotman et al., [45]	TN and R/R	Zanubrutinib	I/II	77	2	36	95.9	82	45.2	80.5% at 36m	84.8% at 36m
Dimopoulos et al., (ASPEN) [41]	TN and R/R	Ibrutinib	III	99	1	42.2	93.9	79.8	25.3	NR at 44m	NR at 44m
		Zanubrutinib		102	1	44.4	95.1	81.4	36.3	NR at 44m	NR at 44m

Abbreviations: IP = investigational product, R/R = relapsed/refractory, TN = treatment naïve, m = months, NR = not reached.

Table 2. Comparison of adverse event rates (all grades) across ASPEN and ACE-WM-001 [48,49].

	ASPEN		ACE-WM-001
	Zanubrutinib	Ibrutinib	Acalabrutinib
Atrial arrhythmia	2%	15%	10%
Hypertension	11%	17%	7%
Bleeding	49%	58%	62%
Infection	67%	66%	76%
Neutropenia	30%	13%	21%
Diarrhoea	21%	31%	39%
Secondary malignancy	12%	11%	11%

9%) were lower than the rates reported in the ASPEN trial for ibrutinib (TN: 17%, R/R 20%) or zanubrutinib (TN: 26%, R/R 29%) [37,40].

6. Adverse events

Despite recent rapid drug development WM remains an incurable disease. Whilst BTKis are an attractive treatment option given efficacy, ease of delivery, and safety, they all have known side effects, and these must be monitored and managed after discussing risks with the patient.

Table 2 compares the most common all-grade AEs in the ASPEN study and the phase II acalabrutinib trial, using 5 year follow-up data [48,49]. The ASPEN trial showed rates of AEs leading to death, discontinuation, or withholding of treatment or dose reduction were lower in the zanubrutinib arm [49].

The incidence of disseminated or invasive fungal infections (IFI) has been described in patients treated with ibrutinib, with aspergillus being the most common fungal pathogen [50]. It has been suggested that both on and off-target effects of BTKis contribute to dysfunction of immune effector cells which may mediate impaired immune responses to opportunistic infectious agents [50]. Whilst the second-generation BTKis have less off-target effects compared with ibrutinib, cases of invasive aspergillosis involving the CNS have now been reported with both acalabrutinib and zanubrutinib, raising concerns about the risk of immunosuppression and the requirement to monitor patients carefully for both common and opportunistic infections [51–53].

7. Zanubrutinib in clinical variants of WM

Bing-Neel syndrome (BNS) is a rare but disabling extramedullary manifestation of WM characterized by CNS involvement by lymphoplasmacytic cells. Therapy is restricted to agents with good CNS penetration, however, traditional cytotoxic agents such as high-dose methotrexate and cytarabine are typically poorly tolerated in older patients with BNS. Ibrutinib crosses the blood-brain barrier and has been examined in a case series of 28 patients, with 85% reporting neurological improvement, and 83% showing improvement or resolution of symptoms, or improvement in radiological abnormalities [54]. A case series of 30 patients with BNS receiving zanubrutinib similarly reported neurological improvement/resolution, 38% of patients demonstrated a CR, and radiological abnormalities improved in 92% of patients [55].

Peripheral neuropathy (PN) is a cause of morbidity in patients with WM, occurring in up to 20% of patients [56]. An ad hoc analysis of the ASPEN trial identified 49 patients with PN symptoms, including 27 treated with zanubrutinib and 22 treated with ibrutinib. Thirty-five (71.4%) experienced resolution of PN, with a median time to resolution of 4.6 months (range 1.1–46.8), with zanubrutinib and 14.1 months (range 1–44) with ibrutinib. PN resolution correlated with attainment of a major response and lower baseline anti-MAG antibody levels [56].

CANOMAD syndrome (chronic ataxic neuropathy, ophthalmoplegia, monoclonal IgM paraprotein, cold agglutinins, and anti-disialosyl antibodies) is a rare syndrome characterized by chronic neuropathy with sensory ataxia, ocular and/or bulbar motor weakness and an IgM antibody directed against gangliosides containing disialosyl epitopes. Approximately half of such patients will have an underlying diagnosis of WM. Clinical experience with BTKi is limited to two cases treated with ibrutinib who both experienced stabilization of disease [57]. The efficacy of zanubrutinib in this syndrome has not yet been established.

8. Amyloidosis in WM

Amyloidosis is a complex disorder characterized by pathogenic protein misfolding and accumulation which can lead to life-threatening organ dysfunction unless effective therapy is rapidly instituted. WM-associated immunoglobulin IgM light chain (AL) amyloidosis is seen in approximately 7.5% of patients with WM, and most commonly affects the heart, nerves, lymph nodes, lung, and kidneys [58]. The 2023 International Workshop on Waldenström Macroglobulinemia (IWWM) consensus panel 6 provides key recommendations, including aiming to rapidly reduce the amyloid protein concentration and to achieve VGPR/CR as quickly as possible; autologous stem cell transplant (ASCT) should be considered in eligible patients [59,60].

There are no large clinical trial data available to guide treatment decisions in this disease. Ibrutinib has been reviewed in a small series of eight patients with AL-associated with WM or marginal zone lymphoma following at least one prior line of therapy. Unfortunately ibrutinib was tolerated poorly and provided unsatisfactory disease control [61]. Assessment of second-generation BTKi such as zanubrutinib with enhanced specificity for BTK receptors is warranted. Patient enrollment in clinical trials for this condition should be encouraged.

9. Molecular subsets biomarkers

Earlier studies using ibrutinib in WM identified inferior response rates of patients with $MYD88^{WT}$ or $CXCR4^{MUT}$ than patients with $MYD88^{L265P}$ [14]. Additionally, patients with $MYD88^{WT}$ had shorter overall survival, and those with $CXCR4^{MUT}$ shorter PFS [14,62].

The poor response of MYD88^{WT} patients receiving ibrutinib in the pivotal study was the driver behind the design of the non-randomized MYD88^{WT} cohort in the ASPEN trial who received only zanubrutinib. Whilst only seven patients with MYD88^{WT} were included in the original ibrutinib trial, there were no major responses seen, and a median PFS of only 21 months [14]. In contrast, patients with MYD88^{WT} receiving zanubrutinib on the ASPEN trial achieved an 81% ORR with a 65% major response and a 42-month event free survival (EFS) of 53.8% [40,63].

TP53 mutations, while uncommon (2.6%) were previously reported to be associated with both aggressive and treatment refractory disease in the patients receiving chemoimmunotherapy, however less was known in patients receiving BTKi [64]. ARID1A is thought to act as a tumor suppressor via modulation of TP53. ARID1A mutations occur in 17% of cases and has been previously associated with higher bone marrow disease burden and lower hemoglobin and platelets but its impact on response to BTKi was not known [65].

The impact of these mutations in patients receiving zanubrutinib was further examined in a post hoc biomarker study of the ASPEN trial which evaluated bone marrow samples from 210 patients from both mutated and unmutated cohorts receiving zanubrutinib or ibrutinib. CXCR4 (25.7%), TP53 (24.8%), ARID1A (15.7%), and TERT2 (9%) mutations were the most commonly seen [66]. Overall, patients with CXCR4^{MUT} receiving either drug had lower rates of deep response compared with CXCR4^{WT} (VGPR; 17% vs. 37.2%, $P = 0.020$) and longer time to response (11.1 vs. 8.4 months). CXCR4^{MUT} were associated with inferior PFS in patients receiving ibrutinib but not in those receiving zanubrutinib (hazard ratio (HR) 3.39; $P = 0.017$, and HR 0.67; $P = 0.598$ respectively).

Similar observations were seen in patients with TP53^{MUT}. In patients treated with ibrutinib, these mutations were significantly associated with lower major response rate (MRR) ($P = 0.04$) and a trend toward a lower VGPR and CR rate ($P = 0.20$) than TP53^{WT}. In patients treated with zanubrutinib however, MRR ($P = 0.98$) and VGPR + CR rates ($P = 0.64$) were similar between TP53^{WT} and TP53^{MUT} WM. Overall, patients with TP53^{MUT} had a longer time to response and worse PFS compared with TP53^{WT} [66].

Collectively, patients with WM harboring CXCR4^{MUT} or TP53^{MUT} had a worse prognosis compared with patients with WT alleles, however, treatment with zanubrutinib led to better clinical outcomes [66].

10. Resistance mutations and management

The causes for covalent BTKi failure in WM have not been defined to the same extent as in CLL but are likely to include acquisition of BTKi resistance and other mutations that circumvent the BCR signaling pathway. As patients are continuously exposed to BTKis, spontaneous mutations leading to resistance to treatment are selected and the tumor population becomes enriched with these cells, ultimately leading to drug resistance [67].

Studies of ibrutinib resistance in WM have identified point mutations in BTK at the covalent binding site BTK^{C481} or its downstream mediator, PLCG2, where such mutations at the binding site reduces the affinity of BTKi to the protein and lead to reduced efficacy of BTKi [68,69]. In patients treated with zanubrutinib, C481S/R or L528W mutations in BTK have been reported as potentially being response for resistance, also by impairing binding affinity [70].

A small sub study of five patients with disease progression whilst taking zanubrutinib on the ASPEN trial included those with MYD88^{WT} and MYD88^{L265P}. Paired baseline and progression samples were available for four patients. BTK^{C481} mutation was identified in one patient (though mutation status was not known at baseline). Interestingly, 4 out of 5 (80%) had TP53 mutations, and 2 of 5 (40%) had mutations within the TERT promoter [66].

Other alterations associated with BTK resistance include deletions on chromosomes 6q and 8p, which disrupt BTK, MYD88/NFκB, and apoptotic signaling [71]. Recurrent mutations in ubiquitin ligases and other TLR/MYD88 pathway regulators have also been associated with resistance mechanisms [71].

The non-covalent BTKi pirtobrutinib has been studied in 80 patients with WM, of which 63 had previously been exposed to a BTKi, with 41 discontinuing due to progressive disease. The ORR was 85% with a MRR of 63%. The median PFS was 19.4 months for covalent BTKi exposed [19].

Other strategies being studied in BTKi refractory patients include combination therapy with PI3K inhibitors or use of BCL2 inhibitors (BCL2i), proteasome inhibitors, BTK degraders such as NX-5948 and BGB-16673, CXCR4-targeting agents such as ulocuplumab, MALT-1 inhibitors (JNJ-67856633, ABBV-525), antibody-drug-conjugates such as loncastuximab tesirine, bispecific antibodies (mosunetuzumab, epcoritamab, and odronextamab) and chimeric antigen receptor T-cells (CART) targeted against CD19 [72].

11. Practical management and supportive care

Despite WM following an indolent course in many patients, the diagnosis of an incurable malignancy can be distressing; managing the psychological wellbeing of each patient in addition to their physical health is vital. Additionally, given many do not require immediate treatment following diagnosis, this provides a window of opportunity to ensure patients are up to date with age-appropriate malignancy screening such as breast and bowel cancer programs, and a chance to improve or manage cardiovascular risk factors [73].

Patients with B-cell malignancies and/or associated hypogammaglobulinaemia can have blunted humoral responses to vaccinations, exacerbated by exposure to anti-CD20 therapy such as rituximab [74]. Ensuring patients are vaccinated, including for COVID-19, pneumococcal, influenza, and herpes zoster virus, preferably prior to initiation of therapy, is very important.

12. Future directions

While most patients with WM receiving continuously administered BTKi such as zanubrutinib can anticipate a near-normal life expectancy, there is inherent risk of immune deficiency, acquisition of resistance mutations and cumulative toxicities. Patients with mutations such as TP53 still fare worse, with continuous disease progression necessitating better treatments. Other patients with adverse clinical features such as amyloidosis and peripheral neuropathy also need better therapy.

These observations have led investigators to pursue combinations of highly potent novel agents including BTKi, BCL2i and various antibodies, with the aim of achieving deep remissions, long treatment-free periods, and immune restoration. Whether such novel strategies should be employed in the frontline with the aim of achieving MRD-negative CR, or in previously treated multi-refractory patients is a complex question involving considerations of efficacy, toxicity, and competing causes of morbidity and mortality.

13. Conclusion

Significant advances in understanding the pathophysiology of WM has been instrumental to the development of novel therapies such as the BTKis. However, WM remains an incurable disease where the goal of treatment is to not only prolong survival but to improve quality of life and reduce disease and treatment side effects.

The choice of upfront and R/R treatments depends on both disease and patient factors and must be discussed with each patient individually. The impressive array of new and alternative agents currently in clinical trials makes it an exciting time to manage this subtype of lymphoma. The aim is to find a treatment that achieves a deep remission whilst minimizing treatment-related AEs, to allow limited duration therapy without the use of chemotherapy containing regimens. Zanubrutinib is a well-tolerated BTKi with proven efficacy in the difficult to treat WM patients, including in those whose disease harbors MYD88^{WT}, CXCR4 mutation or TP53 mutations, and its efficacy and tolerability make it an excellent candidate for combination therapy.

Disclosure statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Author contribution

Elizabeth Goodall – conceptualization, investigation, project administration, visualization, writing – original draft, writing – review and editing
Stephen Opat – conceptualization, investigation, supervision, validation, writing -original draft, writing – review and editing

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval () and/or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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