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Lymphoma (JL Muñoz, Section Editor)

How to Sequence Therapies in Waldenström Macroglobulinemia

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Opinion statement

There are multiple treatment options in patients with Waldenström macroglobulinemia, including chemotherapy, monoclonal antibodies, proteasome inhibitors, and covalent Bruton tyrosine kinase (BTK) inhibitors. The choice of therapy should take into account the patient's clinical presentation, comorbidities, and preferences. A thorough discussion should take place to outline the administration, safety, and efficacy of the regimens under consideration. The patient's genomic profile can provide insightful information for the treatment selection. In the frontline and relapsed settings, we favor ibrutinib monotherapy over chemoimmunotherapy or proteasome inhibitor-based regimens in patients with *MYD88* and without *CXCR4* mutations. For patients with *MYD88* and *CXCR4* mutations or without *MYD88* or *CXCR4* mutations, chemoimmunotherapy or proteasome inhibitor-based regimens are favored, but efficacy data with ibrutinib in combination with rituximab and with novel covalent BTK inhibitors are emerging. Autologous stem cell transplant should be considered in special cases in the relapsed setting. Participation in clinical trials is positively encouraged in WM patients in frontline and relapsed settings. Agents of interest include the BCL2 antagonist venetoclax, the CXCR4 inhibitor mavorixafor, and the non-covalent BTK inhibitors pirtobrutinib and ARQ-531.

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Introduction

Lymphoplasmacytic lymphoma (LPL) is a rare neoplasm characterized by the presence of clonal B lymphocytes, lymphoplasmacytic cells, and plasma cells generally found in the bone marrow, spleen, and lymph nodes [1]. LPL is characterized by a monoclonal IgM paraprotein in ~95% of cases and, in this setting, is referred to as Waldenström macroglobulinemia (WM). The remaining cases of LPL that do not associate with an IgM paraproteinemia are not considered WM but have similar outcomes and should be managed following WM guidelines [2, 3].

Patients with WM may present with signs or symptoms related to an elevated paraprotein, bone marrow infiltration, or extramedullary involvement. Constitutional symptoms are common and include fatigue, night sweats, fevers, and weight loss. WM-related neuropathy is typically slowly progressive, length-dependent, sensory, bilateral, and symmetrical. Hyperviscosity symptoms such as oronasal bleeding, headaches, shortness of breath, or visual changes may also occur. Other rarer clinical features include cryoglobulinemia, cold agglutinin anemia, light chain amyloidosis, and central nervous system involvement (aka Bing-Neel syndrome). Many patients with WM do not require treatment at the time of diagnosis, but even in the absence of treatment patients should be monitored closely to determine the appropriate time to initiate therapy based on laboratory values and clinical symptoms [4].

The rarity of WM has limited the ability to perform large, randomized trials comparing the available regimens, but smaller, high-quality prospective single-arm studies have led to the development of many safe and effective therapies. Considering the scarcity of randomized controlled trials providing a direct comparison of treatment options or guidance regarding therapy sequencing, the choice of treatment should consider patient-specific characteristics and anticipated toxicities, as well as patient and provider preference. Additionally, the mutational status of *MYD88* and *CXCR4* is known to affect treatment response and progression-free survival. For this reason, determination of the genomic profile of the disease should be considered of utmost importance and this information utilized when making treatment decisions.

The importance of genomic profiling

In recent years, the discovery of two highly prevalent, recurrent mutations in *MYD88* and *CXCR4* has changed the diagnostic and therapeutic landscape of WM.

Somatic mutations in *MYD88*, including the most common *L265P* and the less common non-*L265P* variants, are detected in more than 90% of WM and in 50 to 70% of patients with non-IgM LPL [5–11]. The *MYD88 L265P* mutation ($MYD88^{L265P}$), however, is not specific to WM and can be detected in other hematologic disorders, such as marginal zone lymphoma and IgM monoclonal gammopathy of undetermined significance, although it has not been detected in IgM multiple myeloma [9, 12–15]. WM patients who do not harbor MYD88 mutations (*MYD88* wild type or $MYD88^{WT}$) appear to need therapy at an earlier time, have a higher risk of transforming into an aggressive lymphoma, have lower response rates to ibrutinib, and have shorter overall survival [4, 16–18].

Acquired somatic mutations in the N-terminal of *CXCR4* are also characteristic of WM and have been detected in 30 to 40% of WM patients and in 20 to 25% of non-IgM LPL patients [3, 7, 19, 20]. Patients with *CXCR4* mutations, particularly those with nonsense mutations that result in protein truncation at the C-terminal domain such as S338X, have higher serum IgM levels, higher bone marrow disease burden, and higher risk of developing hyperviscosity and acquired von Willebrand disease than *CXCR4* wild-type ($CXCR4^{WT}$) patients [11, 20–23]. *CXCR4* mutations have also been associated with delayed treatment response and shortened progression-free survival in patients treated with ibrutinib [19–21].

It is important to note that there are several methods to assess *MYD88* and *CXCR4* mutational status in WM patients, and that there are differences in the methods followed by different research centers. The preferred tissue for genetic testing is the bone marrow. For *MYD88* mutations, the recommended method is AS-PCR [24]. At our center, we perform CD19 selection, which increases the sensitivity of the test [25]. Additionally, in cases without MYD88 L265P, we perform Sanger sequencing of the entire MYD88 gene to identify non-L265P mutations [17•]. Other centers perform AS-PCR assays for MYD88 L265P in non-selected samples, and others use next-generation sequencing (NGS) methods in non-selected samples, which can be associated with lower sensitivity rates. For *CXCR4* mutations, the methodology has not yet been standardized. At our center, we developed PCR assays for nonsense *CXCR4* mutations in CD19-selected cells [26]. We also perform Sanger sequencing and NGS looking for frameshift mutations. Other centers limit testing to NGS in non-selected samples. In addition to these differences in testing, the disease burden in the bone marrow sample might add an additional layer of complexity, as the sensitivity of the test is impacted by the amount of disease present in the sample. Samples with lower disease burden are more likely to render false negative results.

MYD88 mutated and *CXCR4* wild type

About 50 to 60% of patients with WM will have *MYD88* mutated and $CXCR4^{WT}$ disease. In these patients, the preferred first-line therapies may include either Bruton tyrosine kinase (BTK) inhibitors or rituximab-based regimens, and the decision should be based on patient-specific characteristics.

Due to the discovery of the *MYD88* mutation in WM, BTK inhibitors have become an important treatment option. Ibrutinib was approved in the USA for the treatment of WM in 2015. The success of this therapy was first reported in a trial of 63 previously treated patients with WM [27••]. The overall response rate (ORR) was 91%, although the responses varied based on the *MYD88* and *CXCR4* mutational status. At 59 months of follow-up, the ORR was 100% in those patients with $MYD88^{L265P}$ and $CXCR4^{WT}$ disease, the rates of major and very good partial response were 97% and 47%, respectively, and the 5-year progression-free survival (PFS) rate was 70% [28]. In treatment-naïve WM patients, at 15 months of follow-up, the ORR, major response rate, and VGPR rates were 100%, 94%, and 31%, respectively, in patients with $MYD88^{L265P}$ and $CXCR4^{WT}$ disease [29••]. Notable adverse events in these trials included bleeding and bruising, neutropenia, thrombocytopenia, infections, hypertension, and atrial fibrillation. At a median follow-up of 59 months, there was a 13% risk of atrial fibrillation and the majority of patients remained on treatment [28]. Most patients tolerate single-agent ibrutinib well and obtain a durable disease response.

The use of ibrutinib in combination with rituximab was studied in a phase III randomized trial of 150 patients comparing rituximab combined with placebo to a combination of rituximab with ibrutinib [30••]. This trial demonstrated a significant improvement in the 30-month PFS rate with the addition of ibrutinib to rituximab at 82% versus 28% for the placebo and rituximab combination. The PFS benefit was independent of *MYD88* and *CXCR4* mutational status. This study, however, did not include an ibrutinib plus placebo arm and, therefore, did not evaluate the benefit of the combination of ibrutinib and rituximab over ibrutinib

alone. Patients with mutated CXCR4 showed faster attainment of major responses, suggesting that this population may benefit from the addition of rituximab to ibrutinib. Since many of these patients have high serum IgM levels, it may be more prudent to initiate rituximab after a few weeks of ibrutinib to avoid an IgM flare that could be consequential.

Additional data for the more specific BTK inhibitors, acalabrutinib and zanubrutinib, have been published. The safety of zanubrutinib was demonstrated in a subset of patients with WM in a phase I trial of zanubrutinib in B-cell malignancies [31], as well as follow-up data from a phase I/II trial demonstrating an overall response rate of 96% in 77 patients with relapsed and treatment-naïve WM [32]. Additionally, the ASPEN study randomized 201 WM patients to ibrutinib or zanubrutinib [33••]. At 24 months of follow-up, the ORR, major response rate, and VGPR rates for zanubrutinib were 94%, 77%, and 28%, and for ibrutinib were 93%, 78%, and 19%. There was comparable efficacy between zanubrutinib and ibrutinib. Zanubrutinib was associated with lower rates of bleeding, atrial fibrillation, infections, and hypertension, but with higher rates of neutropenia and granulocyte colony stimulating factor use than ibrutinib. Acalabrutinib has not been directly compared to ibrutinib in patients with WM. The ORR, major response, and VGPR rates were 94%, 78%, and 28% at 27 months of follow-up [34•]. Acalabrutinib has a similar side effect profile as ibrutinib, though headaches are more common in the first few months of treatment. In contrast to ibrutinib's once daily dosing, acalabrutinib and zanubrutinib require twice daily dosing. The difference in dosing between BTK inhibitors should be discussed with patients, as more frequent dosing may lead to lower medication compliance.

BTK inhibitors are an ideal treatment option for patients with $MYD88^{MUT}$ and $CXCR4^{WT}$ disease, although there are some patient-specific characteristics that should be considered. In patients with a history of cardiovascular disease or pre-existing atrial arrhythmia, the risk of atrial fibrillation is higher and can occur at an earlier time point [35, 36], although this is not a contraindication for the use of a BTK inhibitor. In these cases, patients should be monitored closely, or other treatment options can be considered. Additionally, due to risk of bleeding associated with BTK inhibitors, alternative treatment options can be considered in those patients on therapeutic anticoagulation, although anticoagulation is also not a contraindication to BTK inhibitor therapy. Using direct oral anticoagulants, rather than vitamin K antagonists, may lower the risk of bleeding when used in combination with BTK inhibitors. Patients and clinicians should also be aware that BTK inhibitors are prescribed as indefinite therapy, which should be continued until the time of disease progression or development of intolerable adverse effects. Temporary or permanent cessation of BTK inhibitors can lead to withdrawal symptoms and a rapid serum IgM level rebound [37, 38]. Pauses in dosing should be avoided whenever possible.

If a BTK inhibitor is not the preferred treatment choice, then a rituximab-based regimen should be considered. Rituximab, an anti-CD20 monoclonal antibody, should be administered in combination with chemotherapy or a proteasome inhibitor. Although rituximab alone is a treatment option for patients with poor functional status or significant comorbidities, it is less preferred in our practice due to a longer time to response and lower response rates than BTK inhibitors or rituximab combination regimens [39, 40].

The combination of rituximab and bendamustine (Benda-R) has been successfully used for patients with WM. The efficacy and safety of Benda-R was reported in a prospective study comparing Benda-R to R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) in indolent lymphomas, including LPL [41••]. In this trial, 274 patients were randomized to receive R-CHOP or Benda-R. Forty-one patients had lymphoplasmacytic lymphoma of which 22 received Benda-R and 19 received R-CHOP. The median PFS was superior in those who received Benda-R with a median PFS of 70 months versus 28 months in those who received R-CHOP. Additionally, Benda-R was less toxic than R-CHOP and has now become a standard treatment regimen in indolent non-Hodgkin lymphomas. Similar results were reported in a series of retrospective studies [42, 43].

Due to the high rate of response with Benda-R, this regimen is used frequently as a first-line therapy in WM. It is beneficial for patients who prefer a finite course of therapy, as this treatment is generally given for 4 to 6 cycles and maintenance therapy might not be needed [44]. The most common adverse events associated with this regimen are hematologic toxicities, such as neutropenia and thrombocytopenia, in addition to constipation, infections, and dermatologic symptoms, all of which occur at a low rate. There is also a small risk (1–2%) of secondary myelodysplasia or acute myeloid leukemia which must be considered, especially in younger patients [45]. Additionally, the ORR of this regimen does not seem to be affected by the *MYD88* or *CXCR4* mutational status.

Proteasome inhibitors (PIs) are used in the treatment of newly diagnosed and relapsed WM patients. Multiple single-arm prospective studies have demonstrated the efficacy of bortezomib-based regimens, including a 23-patient trial of treatment-naïve, as well as previously treated, patients with WM [46]. In this trial, patients received twice weekly bortezomib, dexamethasone, and rituximab (BDR). The ORR in this trial was 96% with a median time to response of 1.4 months. Subsequent trials using once weekly bortezomib in combination with rituximab showed ORR between 80 and 90% in patients with WM who were previously treated and treatment-naïve [46–48].

With response and PFS rates similar to those of Benda-R, bortezomib-based therapies are a reasonable first-line treatment for WM patients. The common adverse effect of neuropathy must be considered prior to initiation of this therapy. Neuropathy is present in approximately 25% of patients with WM at the time of diagnosis and up to approximately 50% of patients during the course of their disease [49, 50]. New neuropathy can develop while on therapy or preexisting symptoms can worsen significantly with bortezomib-based therapy. Rates of neuropathy have been reported in up to 74% of patients receiving bortezomib [51]. This rate can be improved by administering once weekly bortezomib or administering bortezomib subcutaneously [47, 48, 52]. Treatment-induced neuropathy may resolve or improve in most patients after treatment is complete, but the symptoms may persist in some patients [46]. For this reason, symptoms of neuropathy should be monitored closely during treatment with dose adjustments and treatment changes made as needed. In the absence of neuropathy, additional adverse effect rates are low, but include toxicities frequently seen with other therapies, such as cytopenia, infections, and gastrointestinal symptoms.

Carfilzomib and ixazomib-based regimens are also effective in WM patients. In 31 treatment-naïve WM patients, the ORR, major response, and VGPR rates with carfilzomib, rituximab, and dexamethasone (CaRD) were 87%, 68%, and

36%, respectively, and the 18-month PFS rate was 65% [53]. Neuropathy was uncommon with CaRD. Carfilzomib has been associated with a higher rate of cardiopulmonary adverse events in elderly individuals [54]. The combination of ixazomib, dexamethasone, and rituximab (IDR) was evaluated in 26 treatment-naïve WM patients with ORR, major response rate, and VGPR rates of 95%, 77%, and 19%, with a median PFS rate of 40 months [55, 56]. The safety profile of IDR was favorable with no grade 4 adverse events. Median times to response and to major response were longer in patients with *CXCR4* mutations, but PFS, duration of response, and time to next treatment were not impacted by *CXCR4* mutational status. A prospective study evaluating IDR in previously treated WM patients is ongoing [57].

MYD88 mutated and *CXCR4* mutated disease

Patients with $CXCR4^{MUT}$ WM generally present with a distinct clinical phenotype due to higher serum IgM levels, higher bone marrow burden of disease, lower rate of extramedullary disease, and increased risk of hyperviscosity and acquired von Willebrand disease [11, 20, 22, 23, 58]. In cases of hyperviscosity, or other complications associated with circulating IgM, such as symptomatic cold agglutinins or cryoglobulinemia, rapid response to therapy may be required. The most rapid decline in IgM with potential improvement in symptoms can be achieved with plasmapheresis. Plasmapheresis provides only a temporary improvement in the IgM; and therefore, a more definitive therapy should be initiated after plasmapheresis.

In patients with $CXCR4^{MUT}$ disease, single-agent ibrutinib is less preferred as first-line therapy as patients with *CXCR4* mutations have a lower rate of major response, a prolonged time to response, and a shorter PFS [21, 59]. Benda-R or BDR is an appropriate option as a primary treatment. Data from a retrospective review of 63 patients, with known *CXCR4* mutational status in 49 patients, treated with bortezomib and rituximab showed no significant difference in PFS or OS when comparing patients with or without *CXCR4* mutations [60]. A prospective study of 69 patients treated with Benda-R also showed no difference in disease response or survival outcomes when analyzed based on the *CXCR4* mutational status [61]. Similar results were also reported in a pooled analysis of patients treated with bortezomib, carfilzomib, or ixazomib in the frontline setting [62•]. No difference in response rates, PFS, or OS after frontline treatment initiation was noted between patients with and without *CXCR4* mutations. Therefore, the rituximab-based regimens with a proteasome inhibitor or bendamustine can be administered as first-line therapy in WM patients with *CXCR4* mutations.

The combination of ibrutinib plus rituximab was proven to be safe and efficacious in the INNOVATE study [30••]. The low rate of IgM flare of 8% reported in this trial with no patients requiring plasmapheresis makes the combination of ibrutinib and rituximab a suitable option in patients with *CXCR4* mutations, who are known to present with higher serum IgM levels. Response rates were similar among patients with or without *CXCR4* mutation with 73% of patients with $MYD88^{L265P}$ and $CXCR4^{MUT}$ having a major response to treatment. Therefore, this regimen could be used in this cohort with consideration for the most common toxicities of infusion-related reactions to rituximab, in addition to the side effects expected with ibrutinib.

In the future, additional CXCR4-directed therapies that are currently in development may become available for use in WM patients with *CXCR4* mutations [19, 63].

MYD88 wild-type and CXCR4 wild-type disease

A minority of patients with WM are *MYD88*^{WT} and *CXCR4*^{WT}. It is uncommon to find a *CXCR4* mutation in the absence of an *MYD88* mutation [64]. In patients with *MYD88*^{WT} and *CXCR4*^{WT} disease, some specific clinical characteristics, such as shorter OS and increased risk of transformation to aggressive lymphoma, are often seen [16, 20, 65]. Benda-R should be considered an option for first-line therapy given reported efficacy in a retrospective study [43]. However, a prospective study suggested a shorter PFS in the six MYD88 WT patients [56]. Lower response rates to treatment were reported with single-agent ibrutinib in a study using an allele-specific polymerase chain reaction assay in addition to Sanger sequencing of the *MYD88* gene in CD19-selected bone marrow cells to assess MYD88 mutational status [17•]. In the INNOVATE study, the combination of ibrutinib plus rituximab was associated with an ORR of 81%, a major response rate of 63%, a VGPR rate of 27%, and a 30-month PFS rate of 80% in patients with *MYD88*^{WT} and *CXCR4*^{WT} disease [30••]. In this study, the MYD88 mutational status was assessed in 136 patients using a next-generation sequencing platform in unselected bone marrow cells. This platform may be less sensitive than AS-PCR, particularly for patients with low BM disease burden [66]. Twenty patients (15%) had *MYD88*^{WT} and *CXCR4*^{WT} disease. Prospective studies have reported that the novel BTK inhibitors acalabrutinib and zanubrutinib are effective in WM patients with *MYD88*^{WT} disease. In the acalabrutinib study, 50 of 106 (47%) of the participants were genotyped and 14 (28%) had *MYD88*^{WT} disease. MYD88 genotyping was performed at the discretion of the participating centers and used different methods of detection. The ORR and major response rate in these patients were 78% and 57%. In the ASPEN cohort 2 substudy, 28 WM patients with *MYD88*^{WT} disease were exposed to zanubrutinib [67•]. *MYD88* mutational status was assessed using NGS in unselected tissue. Zanubrutinib therapy was associated with ORR, major response rate, and VGPR rate of 80%, 50%, and 27%, with an 18-month PFS rate of 68%.

Alternative treatment regimens

In the setting of intolerance to the previously discussed regimens or in patients with multiple relapsed or refractory disease, there are many alternative treatment regimens. Rituximab, cyclophosphamide, and dexamethasone (DRC) is a well-tolerated regimen with response rates of 83 to 96% in treatment-naïve patients. The toxicity profile of DRC is comparable to Benda-R, although the PFS appears shorter [43, 68, 69]. This regimen can be considered in patients requiring a non-stem-cell toxic regimen. Response rates with DRC are independent of the mutational status of *MYD88* or *CXCR4* [70].

Due to the development of more targeted and less toxic therapies, the use of fludarabine has fallen out of favor as a first-line therapy but is still utilized in some cases of relapsed or refractory disease. Fludarabine can be used as a single agent [71] or in combination with cyclophosphamide and/or an anti-CD20 monoclonal antibody [72–74]. If using a fludarabine-based regimen, the provider and patient

must be aware of the high risk of myelosuppression, as well as the increased risk of myelodysplasia and transformation to a large cell lymphoma [75, 76].

Stem cell transplantation is not frequently used in WM but can be considered in some cases of refractory disease as there are data reporting prolonged remissions in patients with WM [77–79]. Both autologous stem cell transplantation and allogeneic stem cell transplant have been used in WM, but neither is a curative therapy. Therefore, the toxicity of this therapy should be considered prior to pursuing this treatment and it is recommended that allogeneic stem cell transplantation only be pursued in the context of a clinical trial.

The sequencing of therapies in WM

Data on how to sequence treatment options in WM are rather limited. A summary of the recommendations for the management of WM by the National Comprehensive Cancer Network (NCCN), the 10th International Workshop for WM (IWWM10), the Mayo Clinic (mSMART), and the European Society of Medical Oncology (ESMO) are shown in Table 1.

The most recent versions of the NCCN and the IWWM10 treatment guidelines endorse Benda-R, BDR, CDR, or ibrutinib +/- rituximab as preferred regimens for treatment-naïve and previously treated patients with WM [80, 81]. For NCCN, the only Category 1 recommendation is in favor of ibrutinib +/- rituximab. The Mayo Clinic Stratification for Myeloma & Risk-Adapted Therapy (mSMART) guidelines endorse Benda-R or BTK-inhibitor-based therapy in the frontline, while Benda-R, CDR, BDR, or BTK-inhibitor-based therapy are endorsed in the relapsed setting [82]. The ESMO guidelines endorse Benda-R (4-6 cycles), BDR, CDR, or ibrutinib in the frontline setting for fit patients, and ibrutinib, CDR, Benda-R (4 cycles), rituximab alone, fludarabine alone, or chlorambucil alone for unfit patients [83••]. In the relapsed setting, ESMO recommends repeating the previous rituximab-based regimen if PFS was longer than 3 years, and ibrutinib or an alternate rituximab-containing regimen in patients with shorter PFS to the previous regimen. It is important to note that high-dose chemotherapy followed by autologous stem cell rescue (ASCT) is endorsed in the relapsed setting and in selected cases. Clinical trial participation is endorsed and positively encouraged by all current guidelines.

In our practice, we favor BTK inhibitor monotherapy in patients with *MYD88* but without *CXCR4* mutations in the frontline and relapsed settings. Benda-R and BDR are reasonable options, however. We do not recommend maintenance rituximab in patients who attained PR or better to induction therapy based on the results of the STiL NHL7-2008 MAINTAIN trial [84]. Maintenance rituximab therapy may be considered in select cases, such as patients who attained a minor response to induction. Ibrutinib is the favored BTK inhibitor given the longer track record with this agent. The frontline experience with acalabrutinib is limited and NCCN recommends its use in the relapsed setting. Zanubrutinib is of interest given the initial data in the ASPEN study showing a similar efficacy to ibrutinib but lower rates of atrial fibrillation. However, the FDA has not yet approved its use in WM, and it has not yet been endorsed by published guidelines. In patients with *MYD88* and *CXCR4* mutations, Benda-R or BDR may be better considered but recent data on ibrutinib-R, based on the INNOVATE study, is encouraging and should be taken into consideration. Based on the ASPEN study, zanubrutinib

Table 1. Available guidelines for the treatment of patients with Waldenström macroglobulinemia

Setting	Selection	NCCN	IWWM10	mSMART	ESMO	
Frontline	Preferred regimens	Ibrutinib +/- R (Category 1) Benda-R BDR CDR	Ibrutinib +/- R Benda-R BDR CDR	Benda-R BTKi +/- R	Fit: CDR BDR Benda-R	Unfit: Ibrutinib Benda-R R alone
	Other regimens	Benda alone Bortezomib alone CaRD IDR Cladribine +/- R CHOP-R CVP-R CP-R Fludarabine +/- R FCR	Acalabrutinib CaRD IDR Fludarabine-R R-CHOP R-CVP Rituximab		Ibrutinib	Fludarabine Chlorambucil
Relapsed	Preferred Regimens	Ibrutinib +/- R (Category 1) Benda-R BDR CDR	Ibrutinib +/- R Benda-R BDR CDR	Benda-R CDR BTKi-R ASCT (in selected cases)	Repeat R-based regimen Alternate R-based regimen Ibrutinib	
	Other regimens	Acalabrutinib Benda alone Bortezomib alone Cladribine +/- R CHOP-R CVP-R CP-R Fludarabine +/- R FCR ASCT (in selected cases)	Acalabrutinib CaRD IDR Fludarabine-R R-CHOP R-CVP Rituximab ASCT (in selected cases)		ASCT (in selected cases)	

R, rituximab; *Benda-R*, bendamustine and rituximab; *BDR*, bortezomib, dexamethasone, and rituximab; *CDR*, cyclophosphamide, dexamethasone, and rituximab; *BTKi*, BTK inhibitor; *CaRD*, carfilzomib, dexamethasone, and rituximab; *IDR*, ixazomib; dexamethasone, and rituximab; *CHOP*, cyclophosphamide, doxorubicin, vincristine, and prednisone; *CVP*, cyclophosphamide, vincristine, and prednisone; *FCR*, fludarabine, cyclophosphamide, and rituximab; *ASCT*, autologous stem cell transplant

monotherapy also appears effective in WM patients with *CXCR4* mutations. Data on the efficacy of acalabrutinib in WM patients with *CXCR4* mutations are lacking, as the prevalence of *CXCR4* mutations was not assessed in this study. In patients without *MYD88* mutations, Benda-R or BDR may be more appropriate. However, ibrutinib-R, acalabrutinib, and zanubrutinib have also shown efficacy in this group of patients although the sensitivity of the methods used to obtain *MYD88* mutational status may have led to the inclusion of *MYD88* mutated patients in the subset analyses of these trials.

BTK inhibitor therapy is indefinite and should continue until disease progression, although unacceptable toxicities may also necessitate a change in therapy. In WM, there are limited data available to direct changes between different BTK inhibitors, but there are two studies in chronic lymphocytic leukemia in which patients who were intolerant to ibrutinib switched therapy to acalabrutinib with improvement in the symptoms that prompted the switch in two-thirds of the patients and with continued response to acalabrutinib therapy [85, 86]. A study evaluating zanubrutinib in patients who are intolerant to ibrutinib or acalabrutinib is ongoing (NCT04116437). The use of a covalent BTK inhibitor in a patient who is actively progressing on another covalent BTK inhibitor is not recommended, as the mechanism of resistance to one covalent BTK inhibitors (i.e., *BTK* or *PLCG2* mutations) may predict cross-resistance to the others [87, 88].

Table 2. Selected clinical trials with novel agents in patients with Waldenström macroglobulinemia

ClinicalTrials.Gov ID	Agents	Mechanism of action	Phase
NCT04263480	Ibrutinib Carfilzomib Ibrutinib	BTK inhibitor Proteasome inhibitor BTK inhibitor	III
NCT04061512	Ibrutinib Rituximab Cyclophosphamide Rituximab Dexamethasone	BTK inhibitor Anti-CD20 monoclonal antibody Alkylating agent Anti-CD20 monoclonal antibody Steroid	II/III
NCT03506373	Ibrutinib Ixazomib	BTK inhibitor Proteasome inhibitor	II
NCT03620903	Ibrutinib Bortezomib Rituximab	BTK inhibitor Proteasome inhibitor Anti-CD20 monoclonal antibody	II
NCT04273139	Ibrutinib Venetoclax	BTK inhibitor BCL2 antagonist	II
NCT03679624	Ibrutinib Daratumumab	BTK inhibitor Anti-CD38 monoclonal antibody	II
NCT03630042	Pembrolizumab Rituximab	Anti-PD1 monoclonal antibody Anti-CD20 monoclonal antibody	II
NCT02962401	Idelalisib Obinutuzumab	PI3K inhibitor Anti-CD20 monoclonal antibody	II
NCT03364231	Umbralisib	PI3K inhibitor	II
NCT03162536	ARQ-351	Non-covalent BTK inhibitor	I/II
NCT03740529	Pirtobrutinib	Non-covalent BTK inhibitor	I/II
NCT02952508	CLR-131	Phospholipid drug conjugate	I/II
NCT04274738	Ibrutinib Mavorixafor	BTK inhibitor CXCR4 antagonist	I
NCT04115059	Dasatinib	HCK inhibitor	Pilot

BTK, Bruton tyrosine kinase; *PD1*, programmed cell death protein 1; *PI3K*, phosphatidylinosiyol-3 kinase; *CXCR4*, C-X-C chemokine receptor type 4; *HCK*, hematopoietic cell kinase

Future directions

The goal of therapy in WM patients is to find a reasonable balance between inducing a (deep) response, prolonging PFS, and improving the patient's quality of life. Future studies will focus on trying to keep this balance. A list of selected clinical trials using novel agents in WM are shown in Table 2. Not surprisingly, numerous clinical trials are evaluating BTK inhibitors in combination with chemotherapy agents, proteasome inhibitors, BCL2 inhibitors, and anti-CD38 antibodies. A phase II study evaluating the BCL2 inhibitor venetoclax, as monotherapy, in patients with previously treated WM reported exciting results with ORR of 90% with an 18-month PFS rate of 82% [89]. On the other hand, the phase II study on daratumumab monotherapy was stopped early due to low ORR at 23% [90].

The development of non-covalent BTK inhibitors is of high interest, especially because these agents might be able to overcome the resistance mechanisms against the currently available covalent BTK inhibitors. Vecabrutinib showed initial activity but the clinical development of the drug has been halted. Data on pirtobrutinib (aka LOXO-305) was presented at the 2020 American Society of Hematology (ASH) Annual Meeting and showed ORR of 60% in 15 evaluable WM patients, of whom 60% were previously exposed to a covalent BTK inhibitor [91]. Data on ARQ531 was presented at ASH 2019 but no patients with WM had been included [92].

Other pathways of interest currently being investigated include PI3K, PD1/PDL1, CXCR4, and HCK. The safety of a single-agent PI3K inhibitor was demonstrated in a phase II study, utilizing copanlisib in patients with relapsed or refractory indolent lymphomas [93]. This trial included six patients with WM and showed an ORR of 17%. An additional phase II study evaluating the PI3K inhibitor idelalisib in combination with obinutuzumab reported a higher ORR of 90% but a median PFS of 25 months with high rates of grade ≥3 hepatotoxicity [94]. The anti-PD1 monoclonal antibody pembrolizumab, the CXCR4 inhibitor mavorixafor, and the HCK inhibitor dasatinib are undergoing clinical development.

Looking further into the future, antibody-drug conjugates, bispecific T-cell engagers, and chimeric antigen receptor T-cell therapy targeting CD19, CD20, CD38, or BCMA would be of great interest in WM patients.

Declarations

Conflict of Interest

Shayna Sarosiek declares that she has no conflict of interest. Steven P. Treon has received research funding from AbbVie/Pharmacyclics, Janssen, BeiGene, and Eli Lilly; and has received compensation for service as a consultant from AbbVie/Pharmacyclics, Janssen, BeiGene, and Bristol-Myers Squibb. Jorge J. Castillo has received research funding from AbbVie, BeiGene, Janssen, Pharmacyclics, and TG Therapeutics; and has received compensation for service as a consultant from AbbVie, BeiGene, Janssen, Pharmacyclics, and Roche.

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