



## Lymphoma

# What is new in the treatment of Waldenstrom macroglobulinemia?

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## Abstract

Waldenstrom macroglobulinemia (WM) is a rare type of non-Hodgkin lymphoma. The diagnosis of WM is established by the presence of lymphoplasmacytic lymphoma in the bone marrow or other organs, a monoclonal IgM paraproteinemia and the recurrent MYD88 L265P somatic mutation. Some patients with WM can be asymptomatic, in which case treatment is not indicated. However, most patients with WM will become symptomatic during the course of the disease, due to anemia, hyperviscosity, neuropathy, or other processes, necessitating therapy. Current treatment options for symptomatic WM patients include alkylating agents, proteasome inhibitors and anti-CD20 monoclonal antibodies. The approval of the oral Bruton tyrosine kinase (BTK) inhibitor ibrutinib alone and in combination with rituximab has expanded the treatment options for WM patients. The present Perspective would focus on exciting treatment strategies under development for WM patients, such as proteasome inhibitors (e.g., ixazomib), BTK inhibitors (e.g., acalabrutinib, zanubrutinib, vecabrutinib), BCL2 inhibitors (e.g., venetoclax), and anti-CXCR4 antibodies (e.g., ulocuplumab), among others. It is certainly an exciting time for WM therapy development with novel and promising treatment options in the horizon.

## Introduction

Waldenstrom macroglobulinemia (WM) is a rare hematological malignancy characterized by the uncontrolled accumulation of malignant IgM-secreting lymphoplasmacytic lymphoma cells in the bone marrow and other organs [1]. The recurrent point mutation MYD88 L265P can be detected in over 90% of patients with WM, and its identification has helped gaining a better understanding of the underlying biology of the disease [2–5]. The minority of WM patients without MYD88 mutations have a higher risk of aggressive transformation to diffuse large B-cell lymphoma and a worse survival, when compared with WM patients who carry MYD88 mutations [6]. Recurrent mutations in CXCR4 have been detected in 30–40% of WM patients [7–10]. WM patients with CXCR4 mutations tend to have higher serum IgM levels, a higher risk of developing symptomatic hyperviscosity and lower rates of extramedullary disease (i.e., lymphadenopathy or hepatosplenomegaly) [11].

A large proportion of WM patients are diagnosed at an asymptomatic or “smoldering” stage, and these patients should not be treated, as curative therapy is not available and current standard treatment regimens seldom prolong the survival of WM patients. However, a large proportion of patients will become symptomatic during the course of the disease, requiring treatment to improve their quality of life. Most available treatment options are efficacious in WM patients; however, these treatments also are associated with toxicity. Given the incurable nature of WM, novel agents with higher efficacy, and lower toxicity rates are needed. In the present Perspective, current and novel treatment options for patients with WM will be discussed.

## Current treatment options for WM

### Anti-CD20 monoclonal antibodies

The chimeric anti-CD20 monoclonal antibody rituximab is one the most commonly agents used, alone or in combination, in the treatment of WM [12]. As a single agent, rituximab has been associated with an overall response rate (ORR, defined as minor response or better, at least a 25% decrease in serum IgM level from baseline) of 40–50% and median progression-free survival (PFS) ranging from 12–24 months in WM patients [13–16]. Despite its common

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use, rituximab has been associated with WM-specific adverse events, such as paradoxical IgM flares and rituximab intolerance [17–19]. The fully human anti-CD20 monoclonal antibody ofatumumab has also shown to be safe and effective in WM patients [20]. Ofatumumab therapy was associated with an ORR of 60% and a lower rate of IgM flare at 10%, when compared to rituximab. Ofatumumab can be used in patients with rituximab intolerance, although 25% of patients can also develop ofatumumab intolerance [19]. Available data on the humanized, glycoengineered anti-CD20 monoclonal antibody obinutuzumab in WM are limited to case reports. The Polish Myeloma Consortium is currently evaluating single agent obinutuzumab in previously treated WM patients (NCT03679455).

## Chemotherapy

Nucleoside analogs (i.e., fludarabine and cladribine) and alkylating agents (i.e., cyclophosphamide and bendamustine) are used in combination with the anti-CD20 monoclonal antibody rituximab. Given stem cell damage and other toxicities, nucleoside analogs are less frequently used for the treatment of WM [12]. Alkylating agent-based combinations, such as cyclophosphamide, dexamethasone and rituximab (CDR), and bendamustine and rituximab (Benda-R) have been evaluated in retrospective and prospective studies [21–25]. Overall, these regimens are associated with ORR at 80–90% and median PFS ranging between 36 and 60 months. Comparative analyses show better PFS with Benda-R than with cyclophosphamide-based regimens [23–25]. Alkylating agents have been associated with an increased risk of secondary myeloid neoplasms in about 3–5% of patients exposed [26].

## Proteasome inhibitors

The proteasome inhibitors bortezomib and carfilzomib, in combination with rituximab and dexamethasone are active in the treatment of WM. These combination regimens are associated with ORR of 90% and median PFS ranging between 48 and 60 months [27–31]. Bortezomib has been associated with high rates of peripheral neuropathy in WM patients, when administered twice a week [30]. The incidence of neuropathy can be reduced by administering bortezomib once a week [27–29]. Subcutaneous administration of bortezomib has been associated with lower rates of neuropathy in patients with multiple myeloma [32], but there are no published data on this approach in WM patients. Carfilzomib therapy is not associated with neuropathy in WM patients. Hyperlipasemia and hyperamylasemia prompted dose reductions in WM patients treated with carfilzomib.

## Bruton tyrosine kinase (BTK) inhibitors

The oral BTK inhibitor ibrutinib was approved by the United States Food & Drug Administration (FDA) for the treatment of patients with symptomatic WM in April 2015. The approval was based on ORR of 90% observed in a prospective study in 63 patients with previously treated WM [33]. The median PFS was not yet reached at 5 years of follow-up [34]. Depth of response and PFS are affected by the genomic profile of WM patients. Specifically, WM patients with MYD88 L265P as the only genomic abnormality tend to have deeper and more sustained responses to ibrutinib with major response rate (partial response or better, at least a 50% decreased in serum IgM level from baseline) of 80% and 5-year PFS rate of 75%, while WM patients with concurrent MYD88 and CXCR4 mutations had major response rate of 60% and median PFS of 4 years. None of the WM patients without MYD88 or CXCR4 mutations achieved a partial response, and the median PFS was shorter at 2 years.

Similar results were reported in prospective clinical trials in WM patients, who were refractory to rituximab and also in previously untreated WM patients. In 31 previously treated, rituximab-refractory WM patients, ibrutinib was associated with ORR, major response, and VGPR rates at 90%, 71%, and 13%, respectively [35]. The 18-month PFS rate was 86%. The major response rates in patients with and without CXCR4 mutations were 71% and 82%, respectively. A prospective study evaluating ibrutinib in 30 previously untreated WM patients reported ORR, major response, and VGPR rates were 100%, 83% and 20%, respectively [36]. VGPR rates were lower in patients with than without CXCR4 mutations (7% vs. 31%, respectively). The estimated 18-month PFS rate for the entire cohort was 92%.

Ibrutinib therapy is indefinite and should continue until disease progression or unacceptable toxicity. Ibrutinib has been associated with bleeding complications and atrial fibrillation, among other adverse events. The bleeding observed with ibrutinib is typically provoked (e.g., surgical procedures) and mediated by the anti-platelet adhesion and aggregation properties of the drug [37]. As most surgical procedures are elective, patients are instructed to hold ibrutinib for a few days before and after surgery, depending on the invasiveness of the procedure, to minimize the risk of bleeding. The mechanism by which ibrutinib induces atrial fibrillation remains to be clarified, but may be an off-target inhibitory effect on TEC kinase that promotes inhibition of cardiac phosphatidylinositol-3 kinase [38, 39]. The incidence of atrial fibrillation associated with ibrutinib is 4–6 times the risk of the general population and can occur in 8–10% of patients exposed to ibrutinib [40–42]. Most patients who develop atrial arrhythmia on ibrutinib can be

**Table 1** Response and progression-free survival rates reported in prospective clinical trials evaluating ibrutinib in patients with Waldenstrom macroglobulinemia

|                                   | Ibrutinib + rituximab [46] | Ibrutinib [33, 34] | Ibrutinib [35] | Ibrutinib [36] |
|-----------------------------------|----------------------------|--------------------|----------------|----------------|
| Study type                        | Phase III                  | Phase II           | Phase II       | Phase II       |
| Previously untreated ( <i>n</i> ) | 34                         | –                  | –              | 30             |
| Previously treated ( <i>n</i> )   | 41                         | 63                 | 31             | –              |
| Follow-up time                    | 30 months                  | 60 months          | 18 months      | 18 months      |
| ORR                               | 92%                        | 91%                | 90%            | 100%           |
| MRR                               | 72%                        | 73%                | 71%            | 83%            |
| VGPR                              | 23%                        | 27%                | 13%            | 20%            |
| PFS                               | 82%                        | 60%                | 86%            | 92%            |

ORR overall response rate, MRR major response rate, VGPR very good partial response, PFS progression-free survival

managed with beta-blockers, anticoagulants, and/or antiarrhythmic agents and continue ibrutinib [43]. Guidelines for the management of ibrutinib-related atrial fibrillation have been published [40]. More recently, rare events of ventricular arrhythmia have been reported with ibrutinib therapy [44, 45]. Patients who experience ventricular arrhythmias on ibrutinib should discontinue ibrutinib therapy.

## New developments in the treatment of WM

### Ibrutinib combinations

More recently, results from a randomized phase III study (INNOVATE) evaluating ibrutinib and rituximab versus placebo and rituximab have been published [46]. The study included 150 patients (75 per arm), of which 90 patients were previously untreated (45 per arm). At 30 months of follow-up, the combination of ibrutinib and rituximab showed superiority over placebo and rituximab on ORR (92% and 47%, respectively), major response rate (72% and 32%, respectively) and very good partial response rate (VGPR, 23 and 4%, respectively). VGPR is defined as at least a 90% decrease in serum IgM level from baseline. The 30-month PFS rate was also superior for the combination of ibrutinib and rituximab than for placebo and rituximab (82% and 28%, respectively). The median PFS was not reached on ibrutinib and rituximab, while it was 20 months for placebo and rituximab. The 30-month PFS rate appeared similar between patients with and without CXCR4 mutations (80% and 86%, respectively), preliminarily suggesting that the addition of rituximab to ibrutinib might negate the adverse outcomes previously described on WM patients with CXCR4 mutations treated with ibrutinib alone. However, updated data presented at the 2018 American Society of Hematology Annual Meeting showed 36-month PFS rates of 64% and 84% for patients with and without CXCR4 mutations [47]. No unexpected adverse events were reported with the combination of ibrutinib and rituximab.

Interestingly, in comparison with rituximab and placebo, there were lower than expected rates of IgM flare (8% vs. 47%, respectively) and somewhat lower rates of rituximab infusions reactions (43% vs. 59%, respectively) with ibrutinib and rituximab.

One of the major criticisms of the INNOVATE study is the lack of an ibrutinib monotherapy arm. The INNOVATE study, as it stands, supports increased efficacy when adding ibrutinib to rituximab. However, it does not answer the question whether rituximab adds value to ibrutinib alone. Such a comparative study, ibrutinib and rituximab versus ibrutinib alone in symptomatic WM patients, is unlikely to ever be done. Longer follow-up will be needed to clarify if ibrutinib and rituximab produce better PFS than ibrutinib alone, since median PFS with ibrutinib alone exceeds 5 years, with an estimated 5-year PFS rate of 75% in WM patients with MYD88 and without CXCR4 mutations. Longer follow-up will also delineate if PFS can be improved in WM patients with concurrent MYD88 and CXCR4 mutations, since response duration is shorter for this group with ibrutinib monotherapy. Table 1 shows reported clinical trial outcomes of ibrutinib alone and in combination with rituximab in WM patients. In addition, since WM patients can develop rituximab-related hypogammaglobulinemia, infections and intolerance, ibrutinib and rituximab should only be offered if there were compelling data for its superiority over ibrutinib monotherapy.

A number of prospective studies are evaluating ibrutinib in combination with other agents in WM patients. Accrual is ongoing for studies evaluating ibrutinib in combination with the anti-CXCR4 monoclonal antibody ulocuplumab in WM patients who carry CXCR4 mutations (NCT03225716) and with the oral proteasome inhibitor ixazomib (NCT03506373). Studies evaluating ibrutinib in combination with bortezomib and rituximab (NCT03620903), with the anti-CD38 monoclonal antibody daratumumab (NCT03679624), and with the ERK 1/2 inhibitor LY3214996 (NCT04043845) are not yet recruiting.

## Novel BTK inhibitors

The novel, oral BTK inhibitors acalabrutinib and zanubrutinib are undergoing clinical development in WM. Pre-clinically, both agents have shown to be more specific inhibitors to BTK than ibrutinib, with little to no impact on other ibrutinib off-targets such as HCK and EGFR [48–50]. Both agents are administered orally twice daily, and the duration of therapy with these agents is also indefinite, until disease progression or unacceptable toxicity.

Acalabrutinib is currently FDA-approved for the treatment of previously treated patients with mantle cell lymphoma. A phase II, single-arm, prospective study has evaluated acalabrutinib in 106 WM patients, of which 14 were treatment naïve and 92 were previously treated at the time of acalabrutinib exposure [51]. At a median follow-up time of ~2 years, acalabrutinib was associated with ORR of 94% in previously untreated and 93% in treatment naïve patients. Major response rates were 78% and 79%, respectively, VGPR rates were 32% and 7%, respectively, and 24-month PFS rates were 88% and 99%, respectively. MYD88 and CXCR4 mutational statuses were not obtained in most participants in this clinical trial, and the effect of genomic profiling on patient outcomes will be unknown. Unique adverse events with acalabrutinib include headaches, which tend to improve with caffeine consumption. Adverse events of bleeding and atrial fibrillation were observed with acalabrutinib.

Preliminary results of a phase I/II prospective study evaluating zanubrutinib in 77 WM patients, 24 treatment naïve and 53 previously treated [52]. At a median follow-up of 24 months, zanubrutinib was associated with ORR of 92%, major response rate of 82%, VGPR rate of 41%, and 24-month PFS rate of 82%. Most genotyped patients with MYD88 mutations in this series did not have CXCR4 mutations, which may have accounted for the impressive VGPR rate in this study. Adverse events of bleeding and atrial fibrillation were observed with zanubrutinib. Based on the higher VGPR rate observed with zanubrutinib in the single-arm study, a randomized, phase III study evaluating zanubrutinib versus ibrutinib in symptomatic WM patients is underway (ASPEN; NCT03053440). The study consists of three arms; zanubrutinib 160 mg by mouth twice daily (Arm A), ibrutinib 420 mg by mouth once daily (Arm B), and 160 mg by mouth twice daily in WM patients without MYD88 L265P mutations (Arm C). The study has completed accrual, and a total of 210 patients have been enrolled. Unusual for comparative randomized studies, the outcome of interest is the rate of VGPR or better, which might (or might not) encounter resistance by the approving authorities, as VGPR rate might be considered a weaker outcome in comparison with PFS, for example. Nevertheless, this study has the potential, if positive, of expanding

effective BTK-targeting treatment options with distinct adverse event profile for WM patients. Based on preliminary results of Arm C of the ASPEN study, zanubrutinib was reported to induce responses in patients without MYD88 mutations, with ORR of 77%, major response of 54% and VGPR rate of 15% [53].

Novel BTK inhibitors, such as vecabrutinib (NCT03037645), LOXO-305 (NCT03740529), and ARQ-351 (NCT03162536), do not interact with the BTK C481 site and can potentially overcome the resistance associated with this mutation. The highly selective, irreversible BTK inhibitor ONO/GS459 (tirabrutinib), alone or in combination, is also of interest for WM patients (NCT02457559, NCT02457598). These agents are undergoing clinical development in patients with B-cell lymphoproliferative disorders, including WM.

## Novel proteasome inhibitors

There is recently published clinical trial experience with the oral proteasome inhibitors ixazomib and oprozomib in patients with WM. Ixazomib is a boronic acid analog, similar to bortezomib, that selectively and reversibly binds to the proteasome [54]. Oprozomib, on the other hand, is an oral tripeptide epoxyketone proteasome inhibitor that is structurally analogous to carfilzomib and binds selectively and irreversibly to the proteasome [55].

The combination of the ixazomib, dexamethasone, and rituximab has shown to be safe and effective in WM patients [56]. In this single arm, phase II study, 26 previously untreated WM patients were treated with six induction cycles administered every 4 weeks followed by six maintenance cycles administered every 8 weeks. Twenty-six patients were enrolled, all had the MYD88 L265P mutation and 58% had a CXCR4 mutation. At a median follow-up of 22 months, the rates of ORR, major response and VGPR were 96, 77 and 15%, and the median PFS was not yet reached. There were no differences in ORR, major response, and PFS in patients with and without CXCR4 mutations, although the rate of VGPR was lower in patients with CXCR4 than in patients without CXCR4 mutations (7% vs. 27%, respectively). The adverse event profile of the combination was benign, with low rates of grade 1 or 2 neuropathy, and no reported grade 4 events.

Oprozomib was studied, as a single agent, in a phase Ib/II prospective study in patients with myeloma and WM [57]. Oprozomib was administered at escalating doses ranging from 150 mg to 330 mg by mouth, at two different schedules, two out of seven (2/7) days and 5 out of 14 (5/14) days until disease progression or unacceptable toxicity. Thirty-two patients with WM were enrolled, 15 in the 2/7 schedule and 17 in the 5/14 schedule. Oprozomib therapy was associated with ORR of 71% in patients on the 2/



7 schedule and 47% in patients on the 5/14 schedule. Major response rates were 50% (2/7 schedule) and 29% (5/14 schedule). VGPR rates were 21% (2/7 schedule) and 0% (5/14 schedule). The median PFS was 17 months (2/7 schedule) and 22 months (5/14 schedule), respectively. At the time of the report, 88% of patients had discontinued oprozomib therapy. Most common reasons for discontinuation included patient request (34%), adverse event (31%) and disease progression (22%). The most common grade 3 or higher adverse events included diarrhea, nausea, vomiting, and abdominal pain.

### BCL2 inhibitors

BCL2 inhibition is an attractive therapeutic strategy in WM, as there is positive expression of BCL2 in WM cells confirmed by immunohistochemical and transcriptome analysis [58, 59]. A phase I study showed responses in three of four previously treated WM patients exposed to the BCL2 inhibitor venetoclax [60]. A dedicated multicenter prospective phase II clinical trial evaluating venetoclax in WM patients has completed accrual (NCT02677324). A total of 30 patients were enrolled, of whom 15 were previously exposed to BTK inhibitors [61]. Venetoclax was administered, in the first six patients, at a dose of 200 mg by mouth once daily for 1 week, followed by 400 mg by mouth once daily for 1 week, followed by 800 mg by mouth once daily for a maximum of 2 years. In the subsequent 24 patients, venetoclax was administered at a dose of 400 mg by mouth once daily for 1 week, followed by 800 mg by mouth once daily for a maximum of 2 years. With a follow-up time of 12 months, preliminary results showed ORR, major response, and VGPR rates at 87%, 80% and 17%, respectively. Grade 4 neutropenia was observed in four patients. The most common grade 3 adverse events were neutropenia and anemia. There was only one reported event of laboratory tumor lysis syndrome. A prospective phase II study evaluating the combination of ibrutinib and venetoclax in previously untreated WM patients is undergoing planning.

### Phosphatidylinositol 3 kinase (PI3K) inhibitors

Other potential targets of interest with clinical data available in WM patients include PI3K. A phase II study in 125 patients with previously treated B-cell lymphomas reported responses in eight of ten patients with WM to the PI3K-gamma inhibitor idelalisib [62]. A dedicated phase II study aimed at evaluating idelalisib in 30 patients with WM was undertaken, but was terminated early due to grade 3 and higher elevation in serum liver enzymes in three patients that recurred upon re-exposure to idelalisib [63]. The French Innovative Leukemia Organization is currently evaluating idelalisib in combination with obinutuzumab in

previously treated WM patients (NCT02962401). A phase II study with the novel PI3K inhibitor umbralisib as a single agent in patients with previously treated WM is undergoing accrual (NCT03364231).

## Discussion

It is encouraging to see that, although a relatively rare disease, the field of emerging therapeutics for WM patients is expanding rapidly. The current management of patients with WM depends largely on alkylating agents, proteasome inhibitors, BTK inhibitors, and anti-CD20 monoclonal antibodies. We frequently get asked: “Which is the best treatment for patients with WM?” The long answer is that there is not a best treatment for all patients with WM, and that treatment decisions should be made taking into consideration a number of data points from each patient, such as age, performance status, comorbidities, concurrent medications, prior WM directed therapies, patient preferences, genomic profile and, in an increasing number of patients nowadays, insurance coverage. The short answer is that the best treatment option for a WM patient is a personalized one, made by weighing all the advantages of disadvantages of each approach in a thoughtful manner.

Our current treatment algorithm for previously untreated patients and patients with early relapses typically include alkylating agents (i.e., Benda-R), proteasome inhibitors (i.e., BDR), and ibrutinib with or without rituximab. In patients with MYD88 mutations as the sole genomic abnormality, we favor ibrutinib monotherapy. In patients with MYD88 and CXCR4 mutations, Benda-R, BDR or ibrutinib and rituximab are appropriate treatment options. In patients without MYD88 or CXCR4 mutations, we favor Benda-R or BDR. In general terms, we favor avoiding Benda-R in young patients to minimize risk of secondary myeloid neoplasms and BDR in patients presenting with peripheral neuropathy. In patients with late relapses, we consider nucleoside analogs and, in extraordinary situations, autologous stem cell transplantation. We encourage discussing clinical trial participation with all WM patients.

Within the next few years, we will see the results of the currently ongoing clinical trials evaluating combinations with BTK inhibitors, novel BTK inhibitors as well as BCL2 inhibitors in WM patients. We suspect that these new treatment options will change the treatment landscape of patients with WM. One could take as an example (a preview, if you will) the most recent version of the National Comprehensive Cancer Network guidelines for CLL, in which none of the preferred regimens, for young and elderly patients, in the frontline and relapsed settings, contain chemotherapeutic agents [64]. However, to provide thoughtful and compassionate care, one must familiarize

him/herself with the unique set of adverse events associated with these therapies, having in mind the indefinite nature of the duration of the treatment with several of the treatment options under investigation. On that topic, the use of combinations of targeted agents might induce the depth of response necessary to translate into durable responses, so stopping targeted therapy at some point could become a reality.

In addition to the several novel approaches discussed above, a selected list of other potential targets on interest in WM include CXCR4, CD38, IRAK1/IRAK4, HCK, and BCMA, just to name a few. As mentioned above, strategies targeting CXCR4 are underway in a study evaluating the anti-CXCR4 monoclonal antibody ulocuplumab in combination with ibrutinib. Small molecules targeting CXCR4, such as mavorixafor and AMD070, are under development and could be evaluated in clinical trials shortly. Preclinical data showed a high expression of CD38 in WM cells and an increased WM cell death induced by CD38 inhibition [65]. The anti-CD38 monoclonal antibody daratumumab is FDA approved for the treatment of patients with multiple myeloma. A phase II study evaluating daratumumab in previously treated WM patients is undergoing accrual (NCT03187262). Preclinically, IRAK1/IRAK4 support WM cell growth and survival and treatment of WM cells with ibrutinib and an IRAK1/IRAK4 inhibitor resulted in synergistic WM cell killing [66]. HCK is a member of the SRC family of tyrosine kinases and upregulated in WM cells, and HCK knockdown resulted in sustained reduction of WM cells viability [48]. HCK is a downstream target of MYD88 and promoted WM cell survival via BTK activation. Although ibrutinib targets HCK, the BCR/ABL tyrosine kinase inhibitor dasatinib has shown to also target HCK at nanomolar concentrations [67]. BCMA is highly expressed in multiple myeloma cells and also in the plasma cell compartment of WM, with lower expression rates in the B-cell compartment [68, 69]. Multiple strategies targeting BCMA, including bi-specific T-cell engagers, anti-BCMA antibody-drug conjugates, and chimeric antigen receptor (CAR) T-cells, are under clinical development in multiple myeloma [70–72].

CAR T-cell therapy targeting CD19 has proved to be safe and effective in patients with relapsed and/or refractory aggressive B-cell lymphomas [73, 74]. Axicabtagene ciloleucel and tisagenlecleucel have been approved by the FDA for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Lisocabtagene maraleucel is at late stages of development [75]. Clinical trials evaluating CAR T-cells targeting CD19 and CD20 are

enrolling patients with WM (NCT02153580 and NCT03277729, respectively).

It is safe to conclude that it is an exciting time for the development of novel therapies for WM patients. It is also exciting that these treatment strategies are based on strong scientific rationale promoted by cutting edge research. The thoughtful design of clinical trials is warranted to continue advancing the field towards more efficacious and safer options aimed at deepening and prolonging responses as well as improving the patients' quality of life.

## Compliance with ethical standards

**Conflict of interest** JJC received honoraria and/or research funds from Abbvie, Beigene, Janssen, Millennium, Pharmacyclics, and TG Therapeutics. SPT received honoraria and/or research funds from Bristol-Meyer-Squibb and Pharmacyclics.

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