

# Treatment recommendations from the Eighth International Workshop on Waldenström's Macroglobulinemia

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**Waldenström macroglobulinemia (WM) is a distinct B-cell lymphoproliferative disorder for which clearly defined criteria for the diagnosis, initiation of therapy, and treatment strategy have been proposed as part of the consensus panels of the International Workshop on Waldenström's Macroglobulinemia (IWWM). At IWWM-8, a task force for treatment recommendations was impaneled to review recently published and ongoing clinical trial data as well as the impact of new mutations (MYD88 and CXCR4) on**

**treatment decisions, indications for B-cell receptor and proteasome inhibitors, and future clinical trial initiatives for WM patients. The panel concluded that therapeutic strategies in WM should be based on individual patient and disease characteristics. Chemoimmunotherapy combinations with rituximab and cyclophosphamide-dexamethasone, bendamustine, or bortezomib-dexamethasone provide durable responses and are still indicated in most patients. Approval of the BTK inhibitor ibrutinib in the United States**

**and Europe represents a novel and effective treatment option for both treatment-naïve and relapsing patients. Other B-cell receptor inhibitors, second-generation proteasome inhibitors (eg, carfilzomib), and mammalian target of rapamycin inhibitors are promising and may increase future treatment options. Active enrollment in clinical trials whenever possible was endorsed by the panel for most patients with WM. (*Blood*. 2016;128(10):1321-1328)**

## Introduction

Waldenström macroglobulinemia (WM) is a lymphoplasmacytic lymphoma in which the bone marrow (BM) is infiltrated by immunoglobulin M (IgM)-producing clonal lymphoplasmacytic cells.<sup>1</sup> At the Second International Workshop on WM (IWWM-2), criteria for the clinicopathologic diagnosis of WM and indications for initiation of therapy in WM were developed.<sup>2,3</sup> IWWM consensus panels have since provided updated treatment recommendations.<sup>4-7</sup> As part of IWWM-8, a consensus panel was formed to consider data from recent trials with novel agents and combinations. The updated recommendations for symptomatic untreated (Table 1) and previously treated (Table 2) patients are presented in this article.

## Treatment indications

Not all patients with a diagnosis of WM need immediate therapy. Criteria for the initiation of therapy (proposed in the IWWM-2 consensus panel and confirmed in IWWM-8) include IgM-related complications and/or symptoms related to direct BM involvement by tumor cells such as cytopenias, constitutional symptoms, and bulky extramedullary disease.

Some symptoms, such as symptomatic hyperviscosity, moderate to severe hemolytic anemia, and symptomatic cryoglobulinemia, need urgent therapy. Close observation is recommended for patients who do not fulfill the criteria for WM, and for whom laboratory evidence may be the only indicator of development of progressive disease (eg, a minor decrease in hemoglobin level with asymptomatic anemia or mild increases in IgM) or mild increase of lymphadenopathy or splenomegaly without discomfort for the patient.<sup>3</sup>

## Treatment options

Because of the rarity of WM, treatments have been adopted from data derived from phase 2 studies and more rarely from randomized studies that have included only patients with WM or other indolent B-cell malignancies.<sup>8,9</sup> More recently, a large randomized phase 3 study was undertaken to accelerate the study of ibrutinib in WM patients that met its accrual goal in less than 2 years (NCT02165397). The efficacy and toxicity of phase 2 and 3 studies in WM are summarized in Table 3.

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**Table 1. Consensus updates on the management of symptomatic, untreated WM patients**

Plasmapheresis	Plasmapheresis should always and immediately be used for patients with symptomatic hyperviscosity. Furthermore, plasmapheresis can be used to prevent flare in patients with high IgM level (typically >4000 mg/dL) before rituximab administration. Plasmapheresis alone is not an effective treatment of the disease and must be followed by a rapidly acting cytoreductive treatment.
Rituximab as a single agent	Because of the lower chance of response in WM patients with high IgM levels, and the risk of an IgM flare, rituximab single-agent therapy should be avoided in patients with high IgM levels, but rather should be considered for WM patients with immunologic disorders secondary to WM, such as anti-myelin-associated glycoprotein neuropathy or in frail patients less likely to tolerate chemoimmunotherapy.
Dexamethasone- rituximab- cyclophosphamide (DRC)	DRC is an active and safe treatment choice for first-line treatment of WM with a manageable toxicity, and it can be considered in frail patients requiring combination therapy.
Bendamustine- rituximab (Benda-R)	Benda-R is effective in treatment-naïve WM patients. Treatment is well tolerated even in elderly patients with limited episodes of myelosuppression and infections when compared with purine analog-based regimens. In elderly patients and those with renal impairment, the dose of bendamustine needs to be lowered. Four cycles of Benda-R may be sufficient to achieve adequate response in most WM patients.
Bortezomib-based therapy	Primary therapy with bortezomib is recommended for patients with high IgM levels, symptomatic hyperviscosity, cryoglobulinemia or cold agglutininemia, amyloidosis, and renal impairment or in young patients in whom avoidance of alkylator or nucleoside analog therapy is desired. The panel also recommends that bortezomib should ideally be given once per week and possibly by a subcutaneous route; in case urgent reduction of the IgM level is needed, bortezomib can be started at twice-per-week doses for 1 or 2 cycles and then be changed to once-per-week dosing to reduce risk of neurotoxicity.
Carfilzomib-based therapy	Carfilzomib-based therapy represents an emerging neuropathy-sparing option for proteasome-inhibitor based therapy for WM. Cardiac toxicity has been reported in 3% to 4% of multiple myeloma patients and could be an issue especially in elderly WM patients with preexisting cardiac conditions. Other open issues include the optimal dose of carfilzomib and the optimal schedule of administration.
Ibrutinib	Ibrutinib is an option in symptomatic WM patients. Ibrutinib is approved as primary therapy in WM patients by the US Food and Drug Administration, Health Canada, and the European Medicines Agency as primary therapy in WM patients who are not candidates for chemoimmunotherapy. Ibrutinib should not be stopped unless toxicity or disease progression is suspected. Increases in serum IgM and reductions in hemoglobin can occur if ibrutinib is held and should not be regarded as treatment failure. The optimal use of ibrutinib (ie, in first-line treatment or previously treated disease) as a single agent or in combination continues to be a subject of investigation.

### Monoclonal antibodies as a single agent

**Rituximab.** Rituximab is widely used in WM patients as a result of single-agent and combination studies in patients with WM and other indolent B-cell malignancies. Anti-CD20 monoclonal antibody therapy alone or in combination with chemotherapy is an important standard of care for most patients with WM.<sup>7,10-13</sup> Two schedules for rituximab monotherapy have been studied in WM: the standard schedule in which 1 once-per-week infusion of 375 mg/m<sup>2</sup> is administered for 4 weeks, and the extended schedule in which responsive patients received 4 more once-per-week infusions during weeks 12 to 16. With the standard schedule of rituximab administration, the overall response rates (ORRs) were 30% to 60%, and major responses were observed in 25% to 30% of patients. The duration of response (DOR) was 8 to 11 months in both untreated and previously treated patients in these studies.<sup>14,15</sup> Even for patients with minor responses, improvements in hemoglobin and platelet counts and reductions in lymphadenopathy and splenomegaly can be observed with rituximab. With the extended rituximab schedule, the ORR is 35% to 45% and the DOR has exceeded 16 to 29 months.<sup>16</sup> Rituximab is well tolerated although a transient increase in serum IgM levels (IgM flare) occurs in about 50% of patients.<sup>17</sup> The rituximab-induced IgM flare occurs mostly during the first months of treatment but may persist for several months. This phenomenon is not associated with a higher risk of treatment failure, but physicians should be cautioned to not interpret this phenomenon hastily as lack of response or even progression. In patients with baseline high serum IgM levels, the IgM flare can lead to hyperviscosity-related complications.<sup>18</sup> WM patients with high IgM levels (ie, 4000 mg/dL or higher) should undergo prophylactic plasmapheresis, or rituximab should be avoided during the first 1 or 2 courses of systemic therapy until IgM levels decrease to a safer level.<sup>18,19</sup> Late-onset neutropenia (LON) has also been described with rituximab, mostly when it is combined with chemotherapy.<sup>20</sup> The underlying mechanism of LON is not understood, but a

cellular immune mechanism and/or antibody-mediated complement cytotoxicity have been proposed.<sup>21</sup> An association between a specific polymorphism in the IgG Fc receptor (FcγRIIIa-V158F) and LON has been described.<sup>22</sup>

**Ofatumumab.** Ofatumumab is a fully human CD20-directed monoclonal antibody that targets a CD20 region at a different epitope than that of rituximab. Furman et al<sup>23</sup> studied ofatumumab as monotherapy in 37 treatment-naïve or previously treated patients. Ofatumumab was given at 300 mg during week 1 followed by either 1000 mg/week (low dose) or 2000 mg/week (high dose) during weeks 2 to 4. Patients with stable disease or a minor response at week 16 were eligible to receive a re-dosing cycle consisting of ofatumumab at 300 mg during week 1 and then 2000 mg/week for 4 weeks. The ORR was 59%, which included major responses in 35% of patients. The ORR was higher in rituximab-naïve patients and those with a serum IgM level of <4000 mg/dL in the low-dose but not high-dose ofatumumab cohort. Two patients with serum IgM levels >4000 mg/dL required plasmapheresis for renal insufficiency and hyperviscosity syndrome, and 2 patients experienced an IgM flare and subsequently responded. In patients with intolerance to rituximab, ofatumumab may represent a potential therapeutic option.<sup>24</sup> A therapeutic test dose with appropriate prophylaxis should be considered before administration of ofatumumab in a patient with rituximab intolerance.<sup>24</sup>

### Combinations with rituximab

Because rituximab is an active and nonmyelosuppressive agent, its combination with various chemotherapeutic agents has been explored in WM. The choice of chemotherapy depends on comorbidities, how fast disease control is required, and the manifestations of the disease.

**Table 2. Consensus updates on the management of symptomatic, previously treated WM patients**

Re-treatment	Treatment with any of the interventions listed for symptomatic, untreated patients can be considered for previously treated patients requiring therapy. Re-treatment may be considered with any of the above interventions if a response was achieved for 2 or more years with the prior regimen. Patients who progressed on first-line ibrutinib should not be retreated with ibrutinib.
Ofatumumab	In patients with intolerance to rituximab, ofatumumab is a potential therapeutic option.
Ibrutinib	Ibrutinib is an option in symptomatic WM patients. Ibrutinib is approved as primary therapy in WM patients by the US Food and Drug Administration, Health Canada, and the European Medicines Agency as primary therapy in WM patients who are not candidates for chemoimmunotherapy. Ibrutinib should not be stopped unless toxicity or disease progression is suspected. Increases in serum IgM and reductions in hemoglobin can occur if ibrutinib is held, and should not be regarded as treatment failure. The optimal use of ibrutinib (ie, as first-line treatment or in previously treated disease) as a single agent or in combination continues to be a subject of investigation.
Nucleoside analogs	Fludarabine-based combinations can be considered in fit WM patients with previously treated disease for whom other less toxic treatments have failed. In young patients who are eligible for autologous SCT (ASCT), stem cells should be collected before fludarabine administration.
Everolimus	Everolimus can be considered as a treatment option in the relapsed or refractory setting, although owing to the toxicities associated with this agent, everolimus is best considered in patients who are unresponsive or progressed after multiple lines of other better-tolerated therapies. Serial BM biopsies may help clarify underlying disease response or progression to everolimus, given the IgM discordance observed with this agent.
Immunomodulatory agents	On the basis of the current data, the use of lenalidomide and pomalidomide should be considered in the context of a clinical trial, given their potential adverse events.
Stem cell transplantation	The panel agrees that stem cell transplantation (SCT) should be discussed in selected WM cases, although physicians should take into account the numerous available alternative treatment options. ASCT is a feasible and effective treatment option for high-risk WM patients who are eligible for transplant, but should ideally be offered at early relapses. ASCT is not as beneficial for patients exposed to more than 3 lines of therapy or with chemotherapy refractory disease. Allogeneic SCT, when appropriate, should preferably be considered in the context of clinical trials.

### Rituximab with alkylators

The combination of dexamethasone, rituximab, and cyclophosphamide was evaluated in a prospective study of 72 untreated WM patients. An ORR of 83% was observed that included 7% complete responses (CRs) and 67% partial responses (PRs). The 2-year progression-free survival (PFS) was 67% for all evaluable patients and 80% for responders. Median time to response was long (4.1 months), suggesting that this combination is not appropriate if rapid control of disease is necessary. Toxicities were mild, with only 9% of patients having grade 3 to 4 neutropenia.<sup>25</sup> That study was recently updated to show a time to treatment failure of 35 months. The majority of relapsing patients were still sensitive to rituximab-based therapies, and long-term toxicity profile was favorable with only 1 patient with myelodysplastic syndrome and 2 patients with transformation to diffuse large B-cell lymphoma. The cause of death was prospectively evaluated in that study, and only 32% of deaths were related to WM at a median follow-up of 8 years. The 8-year overall survival (OS) based on the International Prognostic Scoring System (IPSS) WM score was 100%, 55%, and 27% for low-, intermediate-, or high-risk disease, respectively ( $P = .005$ ).<sup>25,26</sup>

### Rituximab with purine analogs

Most data on fludarabine-based regimens have been discussed in previous consensus guidelines and include fludarabine and rituximab combinations.<sup>5-7</sup> Both rituximab and fludarabine, as well as rituximab, fludarabine, and cyclophosphamide are effective as primary therapy, and salvage therapy has a median PFS exceeding 50 months.<sup>27-30</sup> However, because of the risk of long-lasting cytopenias and secondary malignancies with these combinations, first-line treatment is not recommended but could be an option in patients with a high-risk of relapsing.

### Rituximab with bendamustine

Rituximab and bendamustine (Benda-R) was compared with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in a phase 3 open-label trial. A total of 546 patients were enrolled in this study of indolent non-Hodgkin lymphoma, including 41 patients with WM (22 treated with Benda-R and 19 with R-CHOP).

Patients on the Benda-R arm received 6 cycles of bendamustine at 90 mg/m<sup>2</sup> on days 1 and 2 and rituximab at 375 mg/m<sup>2</sup> on day 1 every 4 weeks. A similar ORR (95%) but with a longer PFS was reported for the Benda-R arm (median, 69.5 months) versus R-CHOP (median, 28.1 months), along with a better tolerance (lower rates of grade 3 to 4 neutropenia, infectious complications, peripheral neuropathies, and alopecia).<sup>8</sup>

The outcome of 30 WM patients with relapsed/refractory disease who received bendamustine alone, or with a CD20-directed antibody has also been examined.<sup>31</sup> An ORR of 83% and a median PFS of 13 months was reported in that study. Overall, therapy was well tolerated, although prolonged myelosuppression occurred in patients who had received prior nucleoside analog therapy. Tedeschi et al<sup>32</sup> reported a retrospective study of Benda-R in 71 previously treated WM patients who received bendamustine at 50 to 90 mg/m<sup>2</sup> on days 1 and 2, with rituximab given on day 1. The ORR was 80%, and 75% of patients achieved a major response. The major toxicity was grade 3 to 4 neutropenia, which occurred in 13% of the patients. The median PFS was not reached after a median follow-up of 19 months. Among responders, the median time to 50% reduction in serum paraprotein was 3 months. No IgM flare was observed in this series. Sixty-six percent of patients completed the planned 6 courses. Ten patients discontinued because of toxicity. None of the patients developed aggressive lymphoma, secondary myelodysplastic syndrome, or acute myeloid leukemia, but a solid cancer was observed in 3 patients.

### Rituximab plus bortezomib

The Waldenström Macroglobulinemia Clinical Trials Group (WMCTG) studied bortezomib, dexamethasone, and rituximab in 23 untreated patients, with administration of intravenous bortezomib at 1.3 mg/m<sup>2</sup>, dexamethasone at 40 mg twice per week on days 1, 4, 8, and 11, and rituximab 375 mg/m<sup>2</sup> on day 11 for 4 cycles as induction treatment and 4 more cycles at 3 months as maintenance treatment.<sup>33</sup> The ORR and major response rates were 96% and 83%, respectively, with a median time to response of 1.4 months. Sixty percent of patients discontinued treatment after 4 cycles because of treatment-related peripheral neuropathy. The median PFS was 66 months.<sup>34</sup> Treatment with bortezomib once per week has also been investigated. Twenty-six

**Table 3. Summary of efficacy and toxicity for select phase 2 and 3 studies of therapeutic regimens for WM**

Combination	Reference	No. of patients	Treatment naive (%)	ORR (%)	Major RR (%)	CR (%)	Median		Safety
							TTP (mo)	PFS (mo)	
Rituximab + cyclophosphamide + dexamethasone	25, 26	72	100	83	74	7	35		Mild hematologic toxicity
Rituximab + fludarabine	27	43	63	95	86	4	51		Hematologic toxicity, infection
Rituximab + fludarabine + cyclophosphamide	28	43	65	79	74	11	NR		Hematologic toxicity, including prolonged cytopenias, infection, secondary malignancies
Rituximab + fludarabine + cyclophosphamide	30	82	33	81	74	10		79% at 3 y; 79 in relapse	Hematologic toxicity, including prolonged cytopenias, infection, secondary malignancies
Rituximab + fludarabine + cyclophosphamide	29	40	0	80	80	10	Median not reached at 52 mo		Hematologic toxicity, including prolonged cytopenias, infection, secondary malignancies
Rituximab + bendamustine	8	22	100	95	NA	NA	69.5		Hematologic toxicity, rash, fatigue
Rituximab + bendamustine	32	71	100	80	75	7	NR		Hematologic toxicity, rash, fatigue
Rituximab + bortezomib	35	26	100	88	65	4	NR		IgM flare, nausea, decreased incidence of peripheral neuropathy with once-per-week bortezomib dosing
Rituximab + bortezomib + dexamethasone	33, 34	23	100	96	83	13	66		Hematologic toxicity, high rate of peripheral neuropathy with twice-per-week bortezomib dosing
Rituximab + bortezomib	36	37	0	81	51	5	16	15.6	IgM flare, nausea, lymphopenia Low rate of peripheral neuropathy with once-per-week bortezomib dosing
Rituximab + bortezomib + dexamethasone	37	59	100	85	68	3		42	Low rate of peripheral neuropathy with twice-per-week dosing to once-per-week bortezomib dosing after first cycle, IgM flare
Carfilzomib + rituximab + dexamethasone (I)	38	31	90	87	68	3	64% at 15 mo		IgM flare, hypogammaglobulinemia, rare cardiomyopathy
Rituximab + lenalidomide (I)	43	16	75	50	25	0	17		Hematologic toxicity, IgM flare
Everolimus (I)	45	60	0	73	50	0	25	21	Hematologic toxicity, stomatitis, pneumonitis, rash
Ibrutinib	47	63	0	90.5	73	0		69% at 2 y	Bleeding, atrial fibrillation, mild hematologic toxicity

I, investigational outside United States; NA, not available; NR, not reached; RR, response rate; TTP, time to progression.

patients received bortezomib at 1.6 mg/m<sup>2</sup> intravenously on days 1, 8, and 15 during 6 cycles in a 28-day cycle and rituximab at 375 mg/m<sup>2</sup> at each cycle during 4 cycles.<sup>35</sup> Eighty-eight percent of patients obtained a response, with a 65% major response rate. The 1-year event-free survival was 79%. Neurologic complications were limited, and no grade 3 to 4 treatment-related neuropathy was reported. Grade 3 to 4 neutropenia was observed in 12% of patients. Among patients previously treated with this regimen, the ORR was 81%, with a 51% major response rate and a median PFS of 15.6 months. Sixteen percent of patients developed grade 3 neutropenia, and 5% of patients had grade 3 neuropathy.<sup>36</sup> Dimopoulos et al<sup>37</sup> reported the efficacy and toxicity of bortezomib, dexamethasone, and rituximab in 59 treatment-naive patients. To avoid IgM flare, the first induction cycle consisted of bortezomib 1.3 mg/m<sup>2</sup> intravenously on days 1, 4, 8, and 11 followed by 4 cycles of bortezomib 1.6 mg/m<sup>2</sup> intravenously once per week for 4 weeks with rituximab and dexamethasone in cycles 2 and 5. Peripheral neuropathy was observed in 46% of the patients (grade ≥3 in 7%), but only 5 patients (8%) discontinued bortezomib as a result of neuropathy. After a minimum follow-up of 32 months, the median PFS was 42 months, 3-year DOR for patients with PR was 70%, and 3-year survival was 81%.

In the previous IWWM recommendations, the panel noted that neurotoxicity was the major concern with bortezomib because of underlying IgM-related neuropathy resulting from WM or age-related comorbidities such as diabetes. Weekly dosing and subcutaneous

administration (as observed in myeloma patients) may reduce rates and severity of neuropathy and is being explored in a randomized phase 2 trial of subcutaneous bortezomib, cyclophosphamide, and rituximab versus fludarabine, cyclophosphamide, and rituximab for initial therapy of WM (NCT01592981). The impact of the addition of subcutaneous bortezomib to rituximab, cyclophosphamide, and dexamethasone is also being evaluated in a large European phase 3 study (NCT01788020). Bortezomib is not toxic to stem cells, and long-term follow-up in myeloma patients does not suggest a risk for secondary malignancies. Prophylaxis against herpes zoster is strongly recommended for WM patients receiving proteasome inhibitors.

#### Rituximab plus carfilzomib

Carfilzomib, a second-generation proteasome inhibitor, is associated with a low risk of neurotoxicity in multiple myeloma patients and was recently evaluated in combination with rituximab and dexamethasone, mainly in untreated WM patients.<sup>38</sup> The schedule of carfilzomib was attenuated (days 1 and 2 and days 8 and 9) compared with myeloma dosing, and maintenance therapy (days 1 and 2 only) was given every 8 weeks for 8 cycles. ORR was 87% (35% had a very good PR or better), MYD88 or CXCR4 mutation status did not have an impact, and no grade ≥3 neuropathy was observed. With a median follow-up of 15.4 months, 20 (65%) of 31 patients remain progression-free. Carfilzomib is currently available in the United States as an off-label

indication for WM, and in treatment options by the National Comprehensive Cancer Network (NCCN). However, it is not currently available for WM in many other countries.

### Maintenance rituximab

The role of maintenance therapy was addressed in a retrospective series of 248 rituximab-naïve WM patients who then received and responded to a rituximab-containing regimen.<sup>35</sup> Of these patients, 86 (35%) subsequently received maintenance rituximab. Maintenance treatment with rituximab appeared to extend PFS and OS in comparison with those patients who were observed. An increased incidence of sinobronchial infections (mainly grades 1 and 2) along with reduction of uninvolved immunoglobulins (IgA and IgG) was more pronounced in those patients who received maintenance therapy.<sup>39</sup> A randomized prospective study is ongoing in Germany (NCT00877214; Significance of Duration of Maintenance Therapy With Rituximab in Non-Hodgkin Lymphomas [MAINTAIN]) and is evaluating the impact of 2 years of rituximab maintenance versus observation alone after induction with rituximab and bendamustine in untreated patients.

### Stem cell transplantation

Stem cell transplantation (SCT) remains an option for salvage therapy in WM, particularly among younger patients who have had multiple relapses or those with primary refractory disease. In a European Bone Marrow Transplant Registry (EBMTR) study that included 155 evaluable WM patients who underwent autologous stem cell transplantation, the 5-year OS was 69%, PFS was 49%, incidence of relapse was 47%, and non-relapse mortality was 5.6%.<sup>40</sup> Incidence of relapse was significantly lower in patients receiving ASCT in first CR (CR1), first very good PR, and first PR (PR1) compared with transplantation in subsequent CRs or PRs or with refractory disease (39% vs 53%;  $P = .001$ ), translating into a significant disease-free survival (50% vs 40%;  $P = .004$ ) and OS benefit (71% vs 63%;  $P = .033$ ) for the patients who received transplants early in the course of their disease. The outcomes of previously treated WM patients who received myeloablative and reduced-intensity allogeneic SCT were also reported by the EBMTR.<sup>41</sup> The ORR was 76%, the 5-year PFS rate was 56%, and the 5-year OS rate was 62%. Among patients who received reduced-intensity allogeneic SCT, similar PFS and OS rates were observed (49% and 64%, respectively). NRM at 3 years was high at 33% for myeloablative transplantation and 23% for reduced-intensity allogeneic SCT. CRs occurred in about 20% of patients with allogeneic hematopoietic SCT.

## Novel treatment agents

### Immunomodulatory agents

In a phase 1/2 study, lenalidomide monotherapy was used at a low dose (starting at 15 mg) (trial RV-WM-0426) in 17 previously treated patients.<sup>42</sup> Dose-limiting toxicities occurred at the highest dose tested (20 mg); thus the dose of lenalidomide chosen for further testing was 15 mg/day for 21 of 28 days. Seven (50%) of 14 patients completed 1 year of single-agent lenalidomide treatment at 15 mg/day. In an intent-to-treat analysis, single-agent lenalidomide provided an ORR of 29%. Interestingly, all responses were obtained in cycles 9 to 12. An IgM flare was observed in 3 patients. With a median follow-up of 36 months, the median time to progression was 16 months, and the 5-year OS was 91%. The most frequent adverse events (grade  $\geq 3$ ) at 15 mg were 14%

anemia and 43% neutropenia; no grade 3 thrombocytopenia was reported. The combination of rituximab and lenalidomide (25 mg once per day for 3 weeks followed by 1 week of rest) was studied by the WMCTG<sup>43</sup> in 16 WM patients, 12 of whom were previously untreated. The ORR was 50%, and only 1 case of neuropathy was observed. Abrupt decreases in hematocrit were observed in 88% of patients, and they occurred despite reduction of lenalidomide to 5 mg/day. IgM flare was also observed and necessitated plasmapheresis in some patients.

The combination of pomalidomide, dexamethasone, and rituximab was also explored in previously treated WM patients in a dose-escalating phase 1 study.<sup>44</sup> Among the 7 enrolled patients, 3 (43%) attained a major response. The median time to response was 2.1 months. Three patients required emergent plasmapheresis for an IgM flare, which led to discontinuation of protocol therapy. The median response duration was 15.1 months, and all 3 patients continued to respond at study reporting.

### Mammalian target of rapamycin inhibitors

Ghobrial et al<sup>45</sup> reported the long-term results of a phase 2 trial with everolimus in 60 relapsed/refractory patients. The response rate was 50% PR and 23% minor responses. The median time to response was 2 months, and the median PFS was 21 months. Toxicity was hematologic, with 27% of the patients having grade 3 to 4 anemia and 20% having thrombocytopenia. Pulmonary toxicity was also reported. Among untreated, symptomatic WM patients, the ORR for everolimus was 72% and the major response rate was 60%.<sup>46</sup> Discordance between serum IgM levels and BM disease response was common, and it complicated response assessment. Oral ulcerations frequently occur with everolimus, and an oral dexamethasone swish-and-spit solution may be preventative. Toxicity resulting from everolimus was pronounced in this study and included cytopenias and pulmonary pneumonitis requiring frequent dose reductions. The results of a phase 1/2 study of everolimus in combination with rituximab with or without bortezomib in 46 patients was recently reported.<sup>47</sup> The response rate was 89% and the median PFS was 21 months in 36 patients who received full-dose therapy. Everolimus is currently available in the United States as an off-label indication for WM and in NCCN treatment options. However, it is not currently available for WM in many other countries.

### B-cell receptor (BCR) pathway inhibitors

Ibrutinib is a BTK inhibitor effective in high-risk patients with chronic lymphocytic leukemia (CLL) and mantle cell lymphoma. There is a strong rationale for using this drug in WM patients, given that BTK is activated by mutated MYD88 and enhances the survival of WM cells by activation of nuclear factor  $\kappa$ B. Treon et al<sup>48</sup> recently reported the results of a prospective study of ibrutinib in 63 symptomatic patients with WM who received at least 1 previous treatment. The median time to at least a minor response was 4 weeks. The ORR was 91%, the major response rate was 73%, and among all patients, the estimated 2-year PFS rate was 69% and the estimated 2-year OS rate was 95%. Treatment-related toxic effects of grade 2 or greater included neutropenia in 22% of the patients and thrombocytopenia in 14%, both of which were more common in heavily pretreated patients; there was also postprocedural bleeding in 3%, epistaxis associated with the use of fish oil supplements in 3%, and atrial fibrillation associated with a history of arrhythmia in 5%. The results of therapy with ibrutinib as a single agent are impressive, and the high rates of response and tolerance to therapy were confirmed in a study of single-agent ibrutinib in 31 relapsed/refractory WM patients by Dimopoulos et al.<sup>49</sup> In addition, Furman et al<sup>50</sup> reported on the durability of responses in previously

treated WM patients included in a phase 1 study who received ibrutinib at 12.5 mg/kg per day to 560 mg per day. Three of 4 WM patients included in that study achieved a major response and continued to respond >4 years after the start of ibrutinib therapy.

Overall treatment with ibrutinib is well tolerated in WM patients. An off-target effect of ibrutinib on platelet aggregation with bleeding complications has been described in CLL trials.<sup>51</sup> The use of ibrutinib in patients who require other anticoagulants or medicinal products that inhibit platelet function may increase the risk of bleeding, and particular care should be taken if anticoagulant therapy is used. Moreover, acquired von Willebrand disease associated with a high IgM level can be responsible for bleeding,<sup>52</sup> although patients with acquired von Willebrand disease showed benefit after treatment with ibrutinib.<sup>48</sup> The panel recommends that testing for von Willebrand activity in patients with a history of bleeding diathesis before starting ibrutinib is reasonable. In case of surgery, ibrutinib should be held at least 3 to 7 days pre- and postsurgery, depending upon the type of surgery and the risk of bleeding. Another potential off-target effect is the risk of atrial fibrillation. In a series of 112 WM patients receiving ibrutinib, the cumulative risk of atrial fibrillation at 1, 2, and 3 years was 5.4%, 7.1%, and 8.9%, respectively.<sup>53</sup> Patients with a prior history of atrial fibrillation had a shorter time to atrial fibrillation compared with those without a history (3.9 vs 33.4 months, respectively). Nearly all patients who developed atrial fibrillation were able to continue ibrutinib after cardiologic intervention and/or ibrutinib dose reduction.<sup>53</sup> In patients with preexisting atrial fibrillation that required anticoagulant therapy, alternative treatment options to ibrutinib can also be considered. Ibrutinib produces a mild decrease in QT interval. The underlying mechanism and safety relevance of this finding are not known. Clinicians should use clinical judgment when assessing whether to prescribe ibrutinib to patients at risk from further shortening of their QT interval. Ongoing randomized studies are comparing the efficacy of rituximab with either placebo or ibrutinib in relapsing and in treatment-naïve patients (NCT02165397). In CLL, resistance to ibrutinib with BTK C481S mutation or PLC $\gamma$ 2 mutations have been described in few patients and remain under investigation.<sup>54</sup>

Novel BTK inhibitors are in clinical development and may offer additional choices: CC-292, ONO-4059, ACP-196, and BGB-3111. The cost-effectiveness of these new compounds will invariably need to be addressed through pharmacoeconomic studies.

Both MYD88 and CXCR4 mutations can have an impact on ORRs and major responses to ibrutinib. WM patients who are wild-type for MYD88 had a lower ORR and no major response to ibrutinib.<sup>55</sup> CXCR4 mutations may also have an impact on the efficacy of this drug, with lower ORRs and major responses as well as delayed responses observed in WM patients with mutated CXCR4.<sup>55</sup> The panel recommends that testing for MYD88 should be considered for patients who are candidates for ibrutinib therapy, and that MYD88 and CXCR4 mutation status should be investigated in the context of clinical trials to clarify its impact on treatment outcome for novel agents. The panel also agrees that more data are needed for tailoring treatment options according to MYD88 and CXCR4 mutation status.

## Future options

### Which clinical trials should be prioritized in the first-line setting for symptomatic WM patients?

Many options are available in first-line treatment: chemoimmunotherapy with anti-CD20 monoclonal antibodies or the combination of anti-CD20

monoclonal antibodies with proteasome inhibitors. The aim of the first-line treatments is to reach a high response rate with a prolonged PFS. The panel agrees that there is need to perform clinical trials with chemotherapy-free combinations with new compounds alone or in combination with anti-CD20 antibodies. Ibrutinib is approved in the first-line setting, and first-line trials with ibrutinib and other BCR inhibitors are needed to assess the efficacy and tolerability of these agents in treatment-naïve patients.

### Which clinical trials should be prioritized in the salvage setting for symptomatic WM patients?

The panel agrees that investigation of BCR inhibitors along with existing and novel compounds in patients in the relapsed/refractory setting should be a priority. BCR inhibitors combined with proteasome inhibitors would be of interest for overcoming resistance by interfering with the 2 key pathways that are affected by MYD88. A randomized trial comparing the efficacy of BCR inhibitors alone to that of BCR inhibitors and proteasome inhibitors could answer this question. Obinutuzumab, which has shown efficacy in CLL and follicular lymphoma, is of interest as a combination partner in WM. The use of CXCR4 antagonists such as plerixafor or ulocuplumab as well as other antagonists in development may offer an opportunity to extend the activity of therapeutics impacted by the CXCR4 mutation in WM patients.

## Summary

Rituximab alone can be considered for WM patients with immunologic disorders secondary to WM, such as anti-myelin-associated glycoprotein neuropathy, or in frail patients who are less likely to tolerate chemoimmunotherapy. Rituximab should be avoided or withheld, or plasmapheresis should be performed before rituximab is given in patients with high IgM levels because of concerns regarding an IgM flare that could prompt symptomatic hyperviscosity. Chemoimmunotherapy combinations with rituximab, cyclophosphamide, and dexamethasone; Benda-R; or bortezomib and dexamethasone provide durable responses and are still indicated in most patients. The approval of the BTK inhibitor ibrutinib in the United States and Europe represents a novel and effective treatment option for both treatment-naïve and relapsing patients. Other BCR inhibitors, second-generation proteasome inhibitors (eg, carfilzomib), and mammalian target of rapamycin inhibitors are promising and may expand future treatment options. Active enrollment in clinical trials whenever possible was endorsed for most patients with WM.

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## Authorship

Contribution: V.L., M.A.D., and S.P.T. edited the final manuscript draft based on input from panel members. All authors participated on

consensus panel discussions that contributed to manuscript content and recommendations.

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## References

- Swerdlow SH, Campo E, Harris NL, et al, eds. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2008.
- Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol*. 2003;30(2):110-115.
- Kyle RA, Treon SP, Alexanian R, et al. Prognostic markers and criteria to initiate therapy in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol*. 2003;30(2):116-120.
- Gertz MA, Anagnostopoulos A, Anderson K, et al. Treatment recommendations in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol*. 2003;30(2):121-126.
- Treon SP, Gertz MA, Dimopoulos M, et al. Update on treatment recommendations from the Third International Workshop on Waldenstrom's macroglobulinemia. *Blood*. 2006;107(9):3442-3446.
- Dimopoulos MA, Gertz MA, Kastritis E, et al. Update on treatment recommendations from the Fourth International Workshop on Waldenstrom's Macroglobulinemia. *J Clin Oncol*. 2009;27(1):120-126.
- Dimopoulos MA, Kastritis E, Owen RG, et al. Treatment recommendations for patients with Waldenström macroglobulinemia (WM) and related disorders: IWWW-7 consensus. *Blood*. 2014;124(9):1404-1411.
- Rummel MJ, Niederle N, Maschmeyer G, et al; Study group indolent Lymphomas (StiL). Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381(9873):1203-1210.
- Buske C, Hoster E, Dreyling M, et al; German Low-Grade Lymphoma Study Group. The addition of rituximab to front-line therapy with CHOP (R-CHOP) results in a higher response rate and longer time to treatment failure in patients with lymphoplasmacytic lymphoma: results of a randomized trial of the German Low-Grade Lymphoma Study Group (GLSG). *Leukemia*. 2009;23(1):153-161.
- Buske C, Leblond V. How to manage Waldenstrom's macroglobulinemia. *Leukemia*. 2013;27(4):762-772.
- Buske C, Leblond V, Dimopoulos M, Kimby E, Jäger U, Dreyling M; ESMO Guidelines Working Group. Waldenstrom's macroglobulinaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24(Suppl 6):vi155-vi159.
- Buske C, Seymour JF. Immunochemotherapy in Waldenström macroglobulinemia - still the backbone of treatment. *Leuk Lymphoma*. 2015;56(9):2489-2490.
- Treon SP. How I treat Waldenström macroglobulinemia. *Blood*. 2015;126(6):721-732.
- Treon SP, Agus DB, Link B, et al. CD20-directed antibody-mediated immunotherapy induces responses and facilitates hematologic recovery in patients with Waldenstrom's macroglobulinemia. *J Immunother*. 2001;24(3):272-279.
- Gertz MA, Rue M, Blood E, Kaminer LS, Vesole DH, Greipp PR. Multicenter phase 2 trial of rituximab for Waldenström macroglobulinemia (WM): an Eastern Cooperative Oncology Group Study (E3A98). *Leuk Lymphoma*. 2004;45(10):2047-2055.
- Dimopoulos MA, Zervas C, Zomas A, et al. Treatment of Waldenström's macroglobulinemia with rituximab. *J Clin Oncol*. 2002;20(9):2327-2333.
- Treon SP, Emmanouilides C, Kimby E, et al; Waldenström's Macroglobulinemia Clinical Trials Group. Extended rituximab therapy in Waldenström's macroglobulinemia. *Ann Oncol*. 2005;16(1):132-138.
- Treon SP, Branagan AR, Hunter Z, Santos D, Tournhilac O, Anderson KC. Paradoxical increases in serum IgM and viscosity levels following rituximab in Waldenstrom's macroglobulinemia. *Ann Oncol*. 2004;15(10):1481-1483.
- Ghobrial IM, Fonseca R, Greipp PR, et al; Eastern Cooperative Oncology Group. Initial immunoglobulin M 'flare' after rituximab therapy in patients diagnosed with Waldenstrom macroglobulinemia: an Eastern Cooperative Oncology Group Study. *Cancer*. 2004;101(11):2593-2598.
- Wolach O, Bairey O, Lahav M. Late-onset neutropenia after rituximab treatment: case series and comprehensive review of the literature. *Medicine (Baltimore)*. 2010;89(5):308-318.
- Wolach O, Shpilberg O, Lahav M. Neutropenia after rituximab treatment: new insights on a late complication. *Curr Opin Hematol*. 2012;19(1):32-38.
- Li SC, Chen YC, Evens AM, et al. Rituximab-induced late-onset neutropenia in newly diagnosed B-cell lymphoma correlates with Fc receptor FcγRIIIa 158(V/F) polymorphism. *Am J Hematol*. 2010;85(10):810-812.
- Furman RR, Eradat H, DiRienzo CG, et al. A phase II trial of ofatumumab in subjects with Waldenstrom's macroglobulinemia [abstract]. *Blood*. 2011;118(21). Abstract 3701.
- Castillo JJ, Kanan S, Meid K, Manning R, Hunter ZR, Treon SP. Rituximab intolerance in patients with Waldenström macroglobulinaemia [published online ahead of print November 2, 2015]. *Br J Haematol*. doi:10.1111/bjh.13794.
- Dimopoulos MA, Anagnostopoulos A, Kyrtsolis MC, et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. *J Clin Oncol*. 2007;25(22):3344-3349.
- Kastritis E, Gaviatopoulou M, Kyrtsolis MC, et al. Dexamethasone, rituximab, and cyclophosphamide as primary treatment of Waldenström macroglobulinemia: final analysis of a phase 2 study. *Blood*. 2015;126(11):1392-1394.
- Treon SP, Branagan AR, Ioakimidis L, et al. Long-term outcomes to fludarabine and rituximab in Waldenström macroglobulinemia. *Blood*. 2009;113(16):3673-3678.
- Tedeschi A, Benevolo G, Varettoni M, et al. Fludarabine plus cyclophosphamide and rituximab in Waldenstrom macroglobulinemia: an effective but myelosuppressive regimen to be offered to patients with advanced disease. *Cancer*. 2012;118(2):434-443.
- Tedeschi A, Ricci F, Gordaniga MC, et al. Fludarabine, cyclophosphamide, and rituximab in salvage therapy of Waldenström's macroglobulinemia. *Clin Lymphoma Myeloma Leuk*. 2013;13(2):231-234.
- Souchet L, Levy V, Ouzegdouh M, et al; FILO (French Innovative Leukemia Organization). Efficacy and long-term toxicity of the rituximab-fludarabine-cyclophosphamide combination therapy in Waldenstrom's macroglobulinemia. *Am J Hematol*. 2016;91(8):782-786.
- Treon SP, Hanzis C, Tripsas C, et al. Bendamustine therapy in patients with relapsed or refractory Waldenström's macroglobulinemia. *Clin Lymphoma Myeloma Leuk*. 2011;11(1):133-135.
- Tedeschi A, Picardi P, Ferrero S, et al. Bendamustine and rituximab combination is safe and effective as salvage regimen in Waldenström

- macroglobulinemia. *Leuk Lymphoma*. 2015;56(9):2637-2642.
33. Treon SP, Ioakimidis L, Soumerai JD, et al. Primary therapy of Waldenström macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180. *J Clin Oncol*. 2009;27(23):3830-3835.
  34. Treon SP, Meid K, Gustine J, et al. Long-term outcome of a prospective study of bortezomib, dexamethasone and rituximab (BDR) in previously untreated, symptomatic patients with Waldenström's macroglobulinemia [abstract]. *Blood*. 2015;126(23). Abstract 1833.
  35. Ghobrial IM, Xie W, Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituximab in untreated patients with Waldenström Macroglobulinemia. *Am J Hematol*. 2010;85(9):670-674.
  36. Ghobrial IM, Hong F, Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituximab in relapsed or relapsed and refractory Waldenström macroglobulinemia. *J Clin Oncol*. 2010;28(8):1422-1428.
  37. Dimopoulos MA, García-Sanz R, Gaviatopoulou M, et al. Primary therapy of Waldenström macroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). *Blood*. 2013;122(19):3276-3282.
  38. Treon SP, Tripsas CK, Meid K, et al. Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenström's macroglobulinemia. *Blood*. 2014;124(4):503-510.
  39. Treon SP, Hanzis C, Manning RJ, et al. Maintenance Rituximab is associated with improved clinical outcome in rituximab naive patients with Waldenström Macroglobulinaemia who respond to a rituximab-containing regimen. *Br J Haematol*. 2011;154(3):357-362.
  40. Kyriakou C, Boumendil A, Finel H, et al. Autologous stem cell transplantation (ASCT) for the treatment of patients with Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL): a risk factor analysis by the European Society for Blood and Marrow Transplantation (EBMT) Lymphoma Working Party [abstract]. *Blood*. 2014;124(21). Abstract 678.
  41. Kyriakou C, Canals C, Cornelissen JJ, et al. Allogeneic stem-cell transplantation in patients with Waldenström macroglobulinemia: report from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2010;28(33):4926-4934.
  42. Fouquet G, Guidez S, Petillon MO, et al. Lenalidomide is safe and active in Waldenström macroglobulinemia. *Am J Hematol*. 2015;90(11):1055-1059.
  43. Treon SP, Soumerai JD, Branagan AR, et al. Lenalidomide and rituximab in Waldenström's macroglobulinemia. *Clin Cancer Res*. 2009;15(1):355-360.
  44. Treon SP, Tripsas C, Warren D, et al. Phase I study of pomalidomide, dexamethasone, rituximab (PDR) in patients with Waldenström's macroglobulinemia [abstract]. Proceedings of the 12th International Conference on Malignant Lymphoma. June 19-22, 2013. Lugano, Switzerland. Abstract 536.
  45. Ghobrial IM, Witzig TE, Gertz M, et al. Long-term results of the phase II trial of the oral mTOR inhibitor everolimus (RAD001) in relapsed or refractory Waldenström Macroglobulinemia. *Am J Hematol*. 2014;89(3):237-242.
  46. Tripsas CK, Meid K, Patterson C, et al. Prospective, multicenter study of the mTOR inhibitor everolimus (RAD001) as primary therapy in Waldenström's macroglobulinemia [abstract]. *Blood*. 2013;122(21). Abstract 1822.
  47. Ghobrial IM, Redd R, Armand P, et al. Phase I/II trial of everolimus in combination with bortezomib and rituximab (RVR) in relapsed/refractory Waldenström macroglobulinemia. *Leukemia*. 2015;29(12):2338-2346.
  48. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. *N Engl J Med*. 2015;372(15):1430-1440.
  49. Dimopoulos MA, Trotman J, Tedeschi A, et al. Ibrutinib therapy in rituximab-refractory patients with Waldenström's macroglobulinemia: initial results from an international, multicenter, open-label phase 3 substudy (INNOVATE™) [abstract]. *Blood*. 2015;126(23). Abstract 2745.
  50. Furman R, Bilotti E, Graef T. Single-agent ibrutinib demonstrates long-term activity and safety in patients with relapsed/refractory Waldenström's macroglobulinemia [abstract]. *Haematologica*. 2015;100(s1):705. Abstract PB1786.
  51. Levade M, David E, Garcia C, et al. Ibrutinib treatment affects collagen and von Willebrand factor-dependent platelet functions. *Blood*. 2014;124(26):3991-3995.
  52. Hivert B, Caron C, Petit S, et al. Clinical and prognostic implications of low or high level of von Willebrand factor in patients with Waldenström macroglobulinemia. *Blood*. 2012;120(16):3214-3221.
  53. Gustine JN, Meid K, Dubeau TE, Treon SP, Castillo JJ. Atrial fibrillation associated with ibrutinib in Waldenström macroglobulinemia. *Am J Hematol*. 2016;91(6):E312-E313.
  54. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med*. 2014;370(24):2286-2294.
  55. Treon SP, Xu L, Hunter Z. MYD88 Mutations and Response to Ibrutinib in Waldenström's Macroglobulinemia. *N Engl J Med*. 2015;373(6):584-586.