

## NCCN Guidelines® Insights

# Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma, Version 2.2013

## Featured Updates to the NCCN Guidelines

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### Abstract

These NCCN Guidelines Insights highlight the important updates/changes specific to the management of Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma. These include the addition of regimens containing novel agents as primary and salvage therapy options, inclusion of the updated summary of response categories and criteria from the sixth international workshop on Waldenström's Macroglobulinemia, and a section on management of peripheral neuropathy in the accompanying discussion. (*JNCCN* 2012;10:1211–1218)

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### Disclosures for the NCCN Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma Panel

Individual disclosures of potential conflicts of interest for the NCCN Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma Panel members can be found online at [NCCN.org](http://NCCN.org).

### Please Note

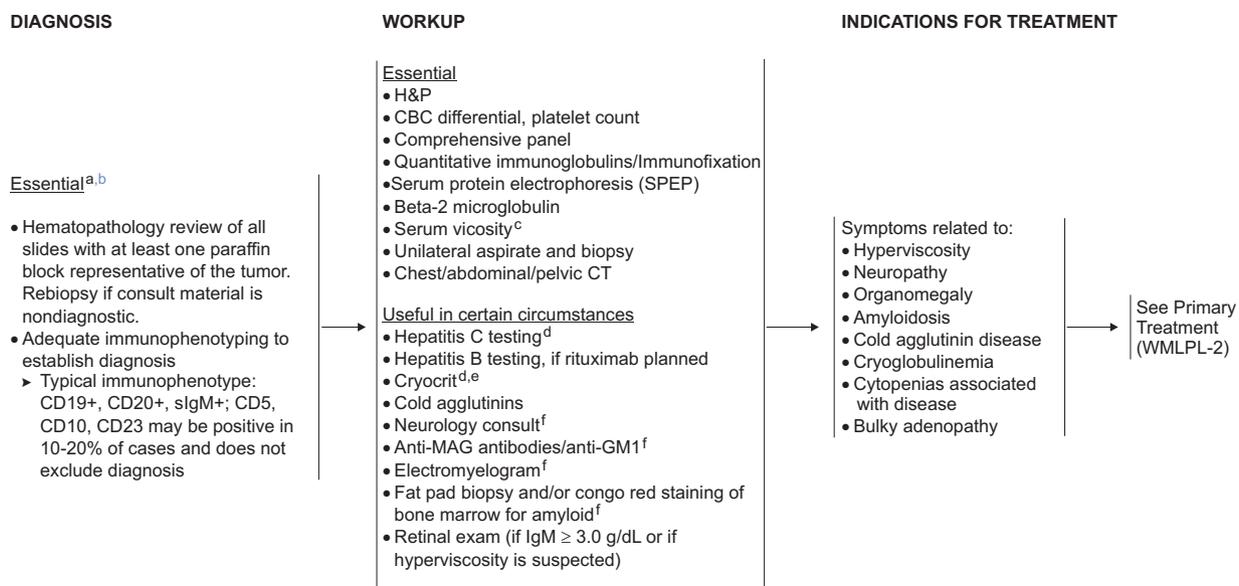
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## Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma, Version 2.2013



<sup>a</sup>See WHO Criteria for Lymphoplasmacytic Lymphoma and Waldenström's Macroglobulinemia (WMLPL-A).

<sup>b</sup>Lymphoplasmacytic lymphoma (LPL) does encompass IgG, IgA, and non secretory subtypes though make up <5% of all LPLs. The treatment non-IgM LPLs parallels that of IgM secreting LPLs, but these are less likely to have either hyperviscosity associated with them, or autoimmune related neuropathy.

<sup>c</sup>Most patients with serum viscosity of less than 4 cP will not have symptoms of hyperviscosity.

<sup>d</sup>Consider in patients with suspected cryoglobulinemia.

<sup>e</sup>If cryocrit positive, then repeat testing of initial serum IgM, and obtain all subsequent serum IgM levels under warm conditions.

<sup>f</sup>In patients presenting with suspected disease related peripheral neuropathy.

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WMLPL-1

### NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

**All recommendations are category 2A unless otherwise noted.**

**Clinical trials:** NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

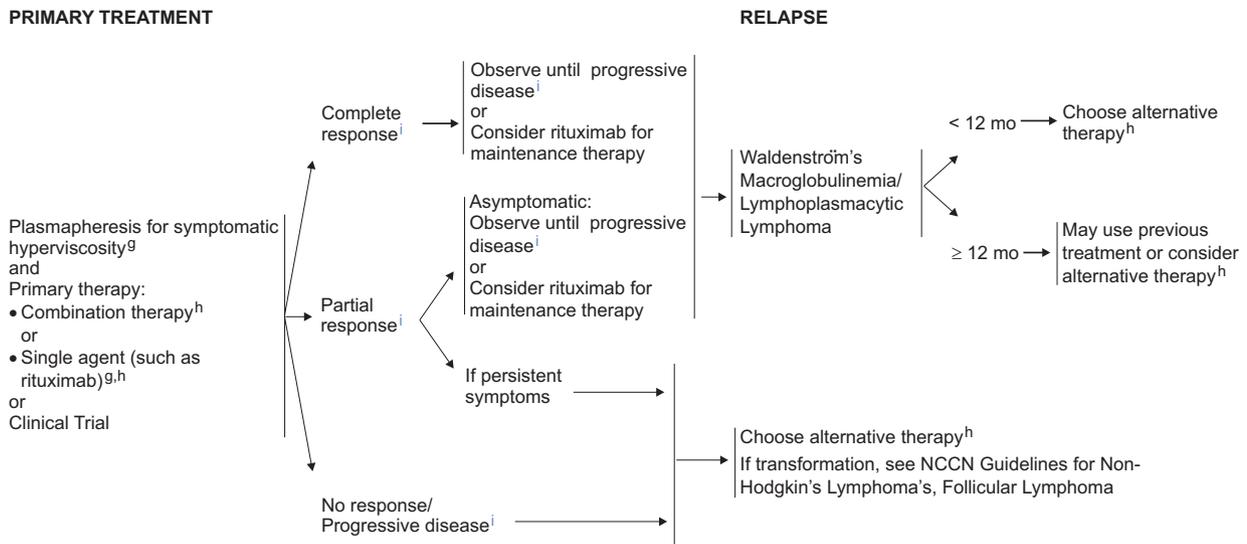
## Overview

Waldenström's macroglobulinemia (WM) is a B-cell disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of an IgM monoclonal gammopathy.<sup>1</sup> This condition is considered to be lymphoplasmacytic lymphoma (LPL) as defined by the Revised European-American Lymphoma and WHO classification systems.<sup>2,3</sup>

According to a recent SEER database report, the overall incidence of WM is 3 per million persons per year, with incidence increasing with age, and the median age at the time of presentation is in the seventh decade.<sup>4</sup> WM represents approximately 1% to 2% of all B-cell lymphomas.<sup>3,5</sup>

The NCCN multidisciplinary panel of leading experts in hematology-oncology and other related oncology fields continually update the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for WM/LPL along with those for oth-

## Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma, Version 2.2013



<sup>g</sup>Plasmapheresis should be performed for patients with symptomatic hyperviscosity, and before treatment with rituximab containing regimen in patients with IgM  $\geq$  5000 mg/dL. IgM should be monitored closely in these patients thereafter and plasmapheresis considered again if symptomatic hyperviscosity occurs or if IgM  $\geq$  5000 mg/dL while on rituximab containing therapy.

<sup>h</sup>See Suggested Treatment Regimens (WMLPL-B).

<sup>i</sup>See Response Criteria for WM/LPL (WMLPL-C).

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WMLPL-2

er plasma cell disorders, such as multiple myeloma and systemic light chain amyloidosis. The NCCN Guidelines for WM/LPL include diagnosis, workup, and management. These NCCN Guidelines Insights highlight important updates/changes specific to the management of WM/LPL in the NCCN Guidelines. These include the addition of regimens containing novel agents as primary and salvage therapy options; the inclusion of updated summary of response categories and criteria from the sixth international workshop on Waldenström's Macroglobulinemia; and a section on management of peripheral neuropathy in the accompanying discussion section. The latest full version of these guidelines is available on the NCCN Web site (NCCN.org).

### Primary Therapy

To establish the diagnosis of WM/LPL, it is necessary to demonstrate IgM monoclonal protein in the

serum, along with histologic evidence of lymphoplasmacytic cells in the bone marrow.<sup>1</sup> The NCCN panel clarified in a footnote that LPL encompasses IgG, IgA, and nonsecretory subtypes that constitute less than 5% of all LPLs. The treatment of non-IgM LPLs parallels that of IgM-secreting LPLs, but these are less likely to have either hyperviscosity or autoimmune-related neuropathy associated with them (see WMLPL-1, on page 1212).

The goal of therapy for WM/LPL is to provide symptomatic relief and reduce the risk of organ damage. Not all patients with WM/LPL require immediate treatment. The indicative symptoms for treatment include hyperviscosity; neuropathy; symptomatic adenopathy or organomegaly; amyloidosis; cryoglobulinemia; cold agglutinin disease; and presence of cytopenia.<sup>6,7</sup>

The primary treatment options for WM/LPL include oral alkylators (eg, chlorambucil), nucleoside analogs (cladribine or fludarabine), or rituximab alone, or rituximab in combination with cyclophos-

## Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma, Version 2.2013

**SUGGESTED TREATMENT REGIMENS**

(Order of regimens is alphabetical and does not indicate preference)

**Primary Therapy:****Non-stem cell toxic**

- Bortezomib ± rituximab<sup>1,2,3,4</sup>
- Bortezomib/dexamethasone<sup>3,4</sup>
- Bortezomib/dexamethasone/rituximab<sup>1,2,3,4</sup>
- Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab<sup>1,4</sup>
- Rituximab<sup>1</sup>
- Rituximab/cyclophosphamide/prednisone<sup>1</sup>
- Rituximab/cyclophosphamide/dexamethasone<sup>1</sup>
- Thalidomide ± rituximab<sup>1,4</sup>

**Possible stem cell toxicity and/or risk of transformation (or unknown)**

- Bendamustine ± rituximab<sup>1</sup>
- Cladribine ± rituximab<sup>1,5,6</sup>
- Chlorambucil<sup>5,6</sup>
- Fludarabine ± rituximab<sup>1,5,6</sup>
- Fludarabine/cyclophosphamide/rituximab<sup>1,5,6</sup>

<sup>1</sup>In patients with symptomatic hyperviscosity plasmapheresis should first be performed; plasmapheresis should also be considered before treatment with rituximab or ofatumumab for asymptomatic Waldenström's Macroglobulinemia patients with an IgM ≥ 5,000 mg/dL to avoid aggravation of serum viscosity on the basis of rituximab related IgM flare. Rituximab or ofatumumab may also be held in patients with elevated serum IgM levels for initial treatment cycles.

<sup>2</sup>Consider particularly for patients presenting with symptomatic hyperviscosity, or in whom rapid IgM reduction is required.

<sup>3</sup>Herpes zoster prophylaxis for patients treated with bortezomib.

<sup>4</sup>These regimens are associated with treatment-related neuropathy and should be avoided in patients with disease-related neuropathy. See Discussion.

**Salvage Therapy:****Non-stem cell toxic**

- Alemtuzumab
- Bortezomib ± rituximab<sup>1,2,3,4</sup>
- Bortezomib/dexamethasone<sup>3,4</sup>
- Bortezomib/dexamethasone/rituximab<sup>1,2,3,4</sup>
- Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab<sup>1,4</sup>
- Everolimus
- Ofatumumab (for rituximab intolerant individuals)<sup>1,7</sup>
- Rituximab<sup>1</sup>
- Rituximab/cyclophosphamide/prednisone<sup>1</sup>
- Rituximab/cyclophosphamide/dexamethasone<sup>1</sup>
- Thalidomide ± rituximab<sup>1,4</sup>

**Possible stem cell toxicity and/or risk of transformation (or unknown)**

- Bendamustine ± rituximab<sup>1</sup>
- Cladribine ± rituximab<sup>1,5,6</sup>
- Chlorambucil<sup>5,6</sup>
- Fludarabine ± rituximab<sup>1,5,6</sup>
- Fludarabine/cyclophosphamide/rituximab<sup>1,5,6</sup>

**Stem cell transplant**

- In selected cases stem cell transplantation may be appropriate with either:
  - ▶ High dose therapy with stem cell rescue
  - ▶ Allogeneic stem cell transplant (ablative or non-ablative)<sup>8</sup>

<sup>5</sup>May be associated with disease transformation and/or development of MDS/AML in Waldenström's Macroglobulinemia patients.

<sup>6</sup>Avoid in patients who are potential autologous stem cell transplant candidates.

<sup>7</sup>Ofatumumab may be used for rituximab intolerant individuals as a single agent or in combination therapy.

<sup>8</sup>Should ideally be undertaken in the context of a clinical trial.

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WMLPL-B  
(1 of 2)

phamide-based therapy, bortezomib-based therapy, nucleoside analogue-based therapy, thalidomide, or bendamustine.

Bortezomib has been shown to have high levels of activity in the management of WM as a single agent,<sup>8</sup> in combination with rituximab,<sup>9</sup> or in combination with rituximab and dexamethasone.<sup>10,11</sup> In a phase II study, bortezomib was administered to 27 patients with WM, 44% of whom were previously untreated and 56% who were previously treated with bortezomib.<sup>8</sup> The overall response rate was 78%, and major responses were seen in 44% of patients.<sup>8</sup> The combination of weekly bortezomib and rituximab has shown significant activity and minimal neurologic toxicity as primary therapy in patients with WM.<sup>9</sup> A phase II study of weekly bortezomib plus rituximab in patients with newly diagnosed WM reported an overall response rate of 88%, including a major response in 65% of patients. The estimated 1-year pro-

gression-free survival in this study was 79%.<sup>9</sup> A study using the combination of bortezomib (using a twice-weekly schedule) along with rituximab and dexamethasone in patients with newly diagnosed WM reported an overall response rate of 96%, including 83% who experienced a partial response.<sup>10</sup> The median time to progression exceeded 30 months in this study.<sup>10</sup> Grade 3 peripheral neuropathy was observed in 30% of the patients who used twice-weekly bortezomib administration. For rituximab-intolerant individuals, bortezomib with dexamethasone can be considered an alternate option. Sensory neuropathy is a primary toxicity observed with bortezomib-based regimens. Therefore, evaluation of patients for the development of bortezomib-related peripheral or autonomic neuropathy is important. To avoid reactivation of herpes zoster, prophylaxis is recommended.

The prospective randomized trial by the Study Group Indolent Lymphomas (STIL) group compared

## Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma, Version 2.2013

RESPONSE CRITERIA FOR WM/LPL<sup>1,2</sup>

Response categories and criteria for progressive disease in WM based on consensus recommendations are summarized in Table 1. An important concern with the use of IgM as a surrogate marker of disease is that it can fluctuate, independent of tumor cell killing, particularly with newer biologically targeted agents such as rituximab, bortezomib, and everolimus. Rituximab induces a spike or flare in serum IgM levels which can occur when used as monotherapy and in combination with other agents including cyclophosphamide, nucleoside analogues, thalidomide, and last for several weeks to months, whereas bortezomib and everolimus can suppress IgM levels independent of tumor cell killing in certain patients. Moreover, Varghese et al showed that in patients treated with selective B-cell depleting agents such as rituximab and alemtuzumab, residual IgM producing plasma cells are spared and continue to persist, thus potentially skewing the relative response and assessment to treatment. Therefore, in circumstances where the serum IgM levels appear out of context with the clinical progress of the patient, a bone marrow biopsy should be considered in order to clarify the patient's underlying disease burden.

Table 1. Summary of Updated Response Criteria adopted at the 6th International Workshop on Waldenström's Macroglobulinemia.

Complete Response	CR	IgM in normal range, and disappearance of monoclonal protein by immunofixation; no histological evidence of bone marrow involvement, and resolution of any adenopathy / organomegaly (if present at baseline), along with no signs or symptoms attributable to WM. Reconfirmation of the CR status is required by repeat immunofixation studies.
Very Good Partial Response	VGPR	A $\geq 90\%$ reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease.
Partial Response	PR	A $\geq 50\%$ reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease.
Minor Response	MR	A $\geq 25\%$ but $< 50\%$ reduction of serum IgM. No new symptoms or signs of active disease.
Stable Disease	SD	A $< 25\%$ reduction and $< 25\%$ increase of serum IgM without progression of adenopathy/organomegaly, cytopenias or clinically significant symptoms due to disease and/or signs of WM.
Progressive Disease	PD	A $\geq 25\%$ increase in serum IgM by protein electrophoresis confirmed by a second measurement or progression of clinically significant findings due to disease (i.e. anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever $\geq 38.4^{\circ}\text{C}$ , drenching night sweats, $\geq 10\%$ body weight loss, or hyperviscosity, neuropathy, symptomatic cryoglobulinemia or amyloidosis) attributable to WM.

<sup>1</sup>Treon SP, Merlini G, Morra E, et al. Report from the Sixth International Workshop on Waldenström's Macroglobulinemia. Clin Lymph Myeloma Leukemia 2011; 11:69-73.

<sup>2</sup>Varghese AM, Rawstron AC, Ashcroft AJ, et al. Assessment of bone marrow response in Waldenström's macroglobulinemia. Clin Lymph Myeloma 2009; 9:53-5.

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WMLPL-C

bendamustine plus rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (CHOP-R) in patients with low-grade lymphoma. A subset analysis of this study identified 41 patients with WM, among whom 22 received bendamustine and rituximab and 19 received CHOP-R.<sup>12</sup> In both groups, the response rate was 95%, but median progression-free survival was significantly prolonged with bendamustine. At the time of analysis, after a median follow-up time of 28 months for both groups, the median event-free survival for CHOP-R was 36 months, whereas it was not yet reached for bendamustine and rituximab ( $P < .0001$ ). Four relapses (18%) were identified in the bendamustine and rituximab group and 11 (58%) in the CHOP-R group. Bendamustine and rituximab was associated with lower incidences of grade 3 and 4 cytopenias, infectious complications, and alopecia. The role of bendamustine in the treatment of WM is evolving,

but it is clearly an active regimen.<sup>12</sup> The impact of bendamustine alone or with rituximab on stem cells is unknown.

### NCCN Recommendations

Based on the data described previously, regimens containing bendamustine alone or in combination with rituximab are listed in the NCCN Guidelines for WM/LPL (see WMLPL-B, on page 1214) as options for primary therapy (category 2A). The panel also included the following bortezomib-based regimens: bortezomib as a single agent; in combination with rituximab; in combination with rituximab; or in combination with dexamethasone (all are category 2A). The panel recommends prophylaxis against herpes zoster for patients treated with bortezomib. The panel has cautioned in a footnote that bortezomib-based regimens may be associated with an increased risk of treatment-related peripheral neuropathy in patients with WM/LPL and should be

## Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma, Version 2.2013

avoided in patients with disease-related peripheral neuropathy. A section on management of neuropathy has been included in the guidelines (see later discussion).

### Treatment of IgM-Related Peripheral Neuropathy

Paraprotein-related peripheral neuropathy is common in patients with WM/LPL, and may impact up to 22% of patients.<sup>13</sup> The treatment of IgM-related neuropathy may initially involve a course of plasmapheresis, particularly in patients with a more aggressive course of progressing peripheral neuropathy attributed to the IgM paraprotein. Typically, a course of 2 to 3 months of weekly plasmapheresis may be required before any impact on symptomatic neuropathy is seen. Plasmapheresis, however, should not be used as a permanent modality, and consolidation with chemotherapy must be considered. After plasmapheresis, IgM levels will return to baseline in 4 to 6 weeks.

Single-agent rituximab can be considered the first intervention in patients with mild, slowly progressive neuropathy. In patients with moderate to severe IgM-related neuropathy, or when the course of the IgM neuropathy appears aggressive, using the combination of either cyclophosphamide, prednisone, and rituximab, or rituximab, cyclophosphamide, and dexamethasone may be preferable to achieve more robust paraprotein reductions. Patients who experience a rituximab-related flare may also have a flare in their IgM-related neuropathic symptoms. Treatment directed at symptomatic improvement can also be considered with gabapentin, pregabalin, and duloxetine while the patient is undergoing plasmapheresis or is on therapy.<sup>14-16</sup> Results of one study<sup>13</sup> showed that symptomatic improvement was more likely with non-amyloid-related peripheral neuropathy (48.5% vs. 15.4%;  $P = .045$ ); in patients who achieved a major response (ie,  $\geq 50\%$  reduction in serum IgM; 79% vs. 35.5%;  $P < .0001$ ); those who received earlier therapy (ie,  $\leq 24$  months; 57.3% vs. 42.5%;  $P = .06$ ); and those who received a rituximab combination versus any monotherapy (59.3% vs. 37.0%;  $P = .007$ ;  $P = .06$  versus rituximab alone).

### Assessment of Response to Therapy

Consensus-based uniform response criteria for WM have been developed by the International Workshop on WM.<sup>17,18</sup> Response to therapy is defined as a reduction in the M protein. According to the updated

summary of response categories from the sixth International Workshop on WM, a minor response is an M-spike reduction of at least 25%; a partial response is defined as greater than or equal to a 50% reduction in M protein; a very good partial response is greater than or equal to a 90% reduction in M protein; and a complete response is immunofixation negativity in the serum. Stable disease is defined as a less than 25% reduction and less than 25% increase of serum IgM without progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms caused by disease and/or signs of WM. Progressive disease is defined as a 25% increase in serum IgM by protein electrophoresis, confirmed by a second measurement.

An important concern with the use of IgM as a surrogate marker of disease is that it can fluctuate, independent of tumor cell killing, particularly with newer biologically targeted agents, such as rituximab, bortezomib, and everolimus. Rituximab induces a spike or flare in serum IgM levels, which can occur when used as monotherapy and in combination with other agents, including cyclophosphamide, nucleoside analogues, and thalidomide, and lasts for several weeks to months.<sup>7,19,20</sup> On the other hand, bortezomib and everolimus can suppress IgM levels independent of killing tumor cells in certain patients.<sup>21-23</sup> The study by Varghese et al<sup>24</sup> showed that in patients treated with selective B-cell-depleting agents, such as rituximab and alemtuzumab, residual IgM-producing plasma cells are spared and continue to persist, thus potentially skewing the relative response and assessment to treatment. Therefore, when the serum IgM levels seem to be out of context with the clinical progress of the patient, a bone marrow biopsy should be considered to clarify the patient's underlying disease burden.

### NCCN Recommendations

The updated summary of response categories and criteria from the sixth International Workshop on WM<sup>25</sup> have been included in the NCCN Guidelines (see Table 1 on WMLPL-C, on page 1215). After primary therapy, the panel recommends assessing the response to treatment using the consensus panel criteria outlined in Table 1. Subsequent management options for patients with WM/LPL outlined in the NCCN Guidelines are based on the response assessment after therapy (see WMLPL-2, on page 1213).

## Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma, Version 2.2013

### Salvage Therapy

All regimens listed under primary treatment options are effective options for salvage therapy, keeping in mind that in patients for whom autologous transplantation is being considered, exposure to stem cell damaging agents, such as chlorambucil or nucleoside analogs, should be avoided.

The use of a bortezomib-based regimen as salvage therapy has reported response rates of 60% to 80%.<sup>8,21,22,26–29</sup> Prophylaxis against herpes zoster is important with bortezomib and steroid combinations, and so is evaluation of patients for the development of bortezomib-related peripheral or autonomic neuropathy.

Bendamustine-based therapy is also effective in relapsed/refractory WM. Bendamustine produces high response rates and durable responses both as monotherapy and in combination with rituximab. An outcomes study of patients with previously treated WM who then received bendamustine-based therapy reported an overall and major response rate of 83.3%.<sup>30</sup>

Everolimus is a potentially effective drug in WM with high single-agent activity and manageable toxicity, offering a new therapeutic strategy for patient with relapsed/refractory WM. Preclinical data show increased activity of the mTOR pathway in WM and significant cytotoxicity seen in WM cells lines in response to the mTOR inhibitor. Based on this, a phase II trial of single-agent everolimus was initiated in 50 patients with relapsed or relapsed/refractory WM.<sup>31</sup> In this study, the overall response rate to everolimus measured by paraprotein reduction alone was 70%. The estimated progression-free survival at 6 and 12 months was 75% and 62%, respectively. Common toxicities reported were mostly hematologic with cytopenias. Pulmonary toxicity was reported in 10% of patients. Discordance between serum IgM levels and underlying bone marrow disease burden is common in patients with WM treated with everolimus, and clinicians should consider repeating bone marrow biopsy when clinically indicated to assess treatment response.<sup>23</sup>

### Management of Patients Intolerant to Rituximab

Two studies recently addressed the role of ofatumumab in patients with WM, including patients who were intolerant to rituximab.<sup>30,32</sup> These studies show that ofatumumab is safe in patients with WM

intolerant to rituximab, and is associated with responses. Therefore, ofatumumab may be considered in rituximab-intolerant patients. As with rituximab, ofatumumab is associated with a risk of IgM flare, and therefore similar precautions should be considered with ofatumumab in patients who have evidence of hyperviscosity or elevated IgM levels.

**NCCN Recommendations:** In the NCCN Guidelines for WM/LPL, bendamustine alone or in combination with rituximab and everolimus are included as options for salvage therapy (category 2A; see page WMLPL-B, on page 1214). The panel also added the following bortezomib-based regimens: bortezomib as single agent; in combination with rituximab; in combination with rituximab; or in combination with dexamethasone (all are category 2A). The panel recommends prophylaxis against herpes zoster for patients treated with bortezomib and has cautioned in a footnote that bortezomib-based regimens may be associated with an increased risk of treatment-related peripheral neuropathy in patients with WM/LPL, and must be avoided in patients with disease-related peripheral neuropathy.

### For Rituximab-Intolerant Patients

In the NCCN Guidelines for WM/LPL, the panel has included ofatumumab as a salvage therapy option for rituximab-intolerant patients with WM (category 2A; see page WMLPL-B, on page 1214). In the recently updated 2013 version of the guidelines, the panel further clarified in a footnote (see page WMLPL-B, on page 1214) that ofatumumab may be administered either as a single-agent or as combination therapy. The latest full version of the NCCN Guidelines is available at [NCCN.org](http://NCCN.org).

### Conclusions

The important updates/changes in the NCCN Guidelines specific to the management of WM are highlighted in these NCCN Guidelines Insights. The NCCN Guidelines are in continuous evolution. They are updated annually, and sometimes more often if new high-quality clinical data become available in the interim. The recommendations in the NCCN Guidelines, with few exceptions, are based on the evidence from clinical trials. Expert medical judgment is required when applying these guidelines in the context of individual clinical circumstances to provide optimal care. Physicians and patients have

## Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma, Version 2.2013

the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the panel strongly encourages patient/physician participation in prospective clinical trials.

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## Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma, Version 2.2013

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