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Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

Version 1.2023 — July 6, 2022

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NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

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NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

[NCCN Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Panel Members Summary of Guidelines Updates](#)

[Diagnosis and Workup \(WM/LPL-1\)](#)

[Asymptomatic or Minimally Symptomatic \(WM/LPL-2\)](#)

[Primary Treatment, Response, Relapse \(WM/LPL-3\)](#)

[WHO Criteria for Lymphoplasmacytic Lymphoma and Waldenström Macroglobulinemia](#)

[Waldenström Macroglobulinemia International Workshop Criteria \(WM/LPL-A\)](#)

[Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Therapy \(WM/LPL-B\)](#)

[Response Criteria for WM/LPL \(WM/LPL-C\)](#)

[Management of Bing Neel Syndrome \(BNS-1\)](#)

[Abbreviations \(ABBR-1\)](#)

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

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NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

NCCN Categories of Preference: All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

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NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

Updates in Version 1.2023 of the NCCN Guidelines for WM/LPL from Version 3.2022 include:

[WM/LPL-1](#)

- Workup:
 - ▶ Essential:
 - ◇ Third bullet removed: Liver function tests (LFTs) as clinically indicated
 - ◇ 4th bullet modified: *Comprehensive Metabolic Panel (CMP)* including serum blood urea nitrogen (BUN)/ creatinine, electrolytes, albumin, calcium, and liver function tests (LFTs)
 - ◇ 9th bullet modified: Chest/abdominal/pelvic CT with contrast *and/or PET-CT* when possible
 - ▶ Useful in Certain Circumstances:
 - ◇ 2nd bullet modified: CXCR4 gene mutation testing for patients being considered for ibrutinib *Bruton's tyrosine kinase (BTK) inhibitors*
 - ◇ Bullet removed: Brain/spine MRI, if CNS symptoms
 - ◇ 14th bullet added: If central nervous system (CNS) symptoms, [see BNS-1](#)
- Header removed: Indications for Treatment
- Added: Asymptomatic or minimally symptomatic

[WM/LPL-2](#)

- A new page has been added to the guidelines: Asymptomatic or Minimally Symptomatic

[WM/LPL-3](#)

- This page has been extensively revised.

[WM/LPL-B 2 of 4](#)

- Primary Therapy for WM/LPL
 - ▶ Preferred Regimens:
 - ◇ The following regimen has been moved to Other Recommended Regimens:
 - Rituximab/cyclophosphamide/dexamethasone
 - ▶ Other Recommended Regimens:
 - ◇ The following regimens have been removed:
 - Bortezomib ± rituximab
 - Bortezomib/dexamethasone
 - Cladribine ± rituximab
 - Fludarabine ± rituximab
 - Fludarabine/cyclophosphamide/rituximab

[CONTINUED](#)

UPDATES



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

Updates in Version 1.2023 of the NCCN Guidelines for WM/LPL from Version 3.2022 include:

[WM/LPL-B 3 of 4](#)

- Therapy for Previous Treated WM/LPL
 - ▶ Other Recommended Regimens:
 - ◇ The following regimens have been moved to Useful in Certain Circumstances:
 - Cladribine ± rituximab
 - Fludarabine ± rituximab
 - Fludarabine/cyclophosphamide/rituximab
 - ◇ The following regimen has been added to Other Recommended Regimens:
 - Ixazomib/rituximab/dexamethasone
 - ◇ The following regimens have been removed:
 - Bortezomib ± rituximab
 - Bortezomib/dexamethasone

[WM/LPL-B 4 of 4](#)

- References have been updated.

[BNS-1](#)

- A new page has been added to the guidelines: Management of Bing Neel Syndrome

[ABBR-1](#)

- A new section has been added to the guidelines: Abbreviations

NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

DIAGNOSIS

- Essential^{b,c}**
- Hematopathology review of all slides with at least one paraffin block representative of the tumor (Rebiopsy if consult material is nondiagnostic)
 - Adequate tissue biopsy for immunophenotyping to establish diagnosis
 - ▶ Typical immunophenotype: CD19+, CD20+, sIgM+; CD5, CD10, CD23 may be positive in 10%–20% of cases and does not exclude diagnosis

WORKUP^a

Essential

- History and physical examination
- Complete blood count (CBC), differential, platelet count
- Peripheral blood smear
- Comprehensive Metabolic Panel (CMP) including serum blood urea nitrogen (BUN)/creatinine, electrolytes, albumin, calcium, and liver function tests (LFTs)
- Serum uric acid, serum lactate dehydrogenase (LDH), and beta-2 microglobulin
- Creatinine clearance (calculated or measured directly)
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- Unilateral bone marrow aspirate and biopsy, including immunohistochemistry (IHC) and/or multi-parameter flow cytometry
- Chest/abdominal/pelvic CT with contrast and/or PET-CT when possible
- MYD88 L265P^d Allele Specific-polymerase chain reaction (AS-PCR) testing of bone marrow

Useful in Certain Circumstances

- Serum viscosity
- CXCR4 gene mutation testing for patients being considered for Bruton's tyrosine kinase (BTK) inhibitors^e
- Testing for hepatitis B (if rituximab planned), hepatitis C,^f and HIV
- Cryocrit^{f,g}
- Consider coagulation and/or von Willebrand disease testing if symptoms present (excess bruising or bleeding) or if clinically indicated
- Cold agglutinins
- Neurology consult^h
- Anti-myelin-associated glycoprotein (MAG) antibodies/anti-GM1^h
- Nerve conduction study (NCS)/electromyogram (EMG)^h
- Fat pad sampling and/or congo red staining of bone marrow for amyloid^h
- Retinal examination (if IgM ≥3.0 g/dL or if hyperviscosity is suspected)
- 24-h urine for total protein, urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis (UIFE)
- Amyloid tissue subtyping with mass spectrometry, if indicated
- If central nervous system (CNS) symptoms, [See BNS-1](#)

INDICATIONS FOR

Asymptomatic or minimally symptomatic

[See Monitoring Plan \(WM/LPL-2\)](#)

Symptomsⁱ related to:

- Hyperviscosity
- Neuropathy
- Organomegaly
- Amyloidosis
- Cold agglutinin disease
- Cryoglobulinemia
- Anemia and other cytopenias associated with disease
- Bulky adenopathy
- B symptoms

[See Primary Treatment WM/LPL-3](#)

^a Frailty assessment should be considered in older adults. [See NCCN Guidelines for Older Adult Oncology.](#)

^b [See WHO Criteria for Lymphoplasmacytic Lymphoma and Waldenström Macroglobulinemia \(WM/LPL-A\).](#)

^c Lymphoplasmacytic lymphoma (LPL) encompasses IgG, IgA, serum free light chain alone, and non-secretory subtypes, although makes up <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 associated with them, or autoimmune-related neuropathy. It is important to differentiate from IgM MGUS or IgM multiple myeloma.

^d MYD88 wild-type occurs in <10% of patients and should not be used to exclude diagnosis of WM if other criteria are met.

^e Studies have shown that mutations in this gene are found in up to 40% of patients with WM/LPL and can impact ibrutinib response.

^f Consider in patients with suspected cryoglobulinemia.

^g If cryocrit is positive, then repeat testing of initial serum IgM, and obtain all subsequent serum IgM levels under warm conditions.

^h In patients presenting with suspected disease related to peripheral neuropathy, rule out amyloidosis in patients presenting with nephrotic syndrome or unexplained cardiac problems.

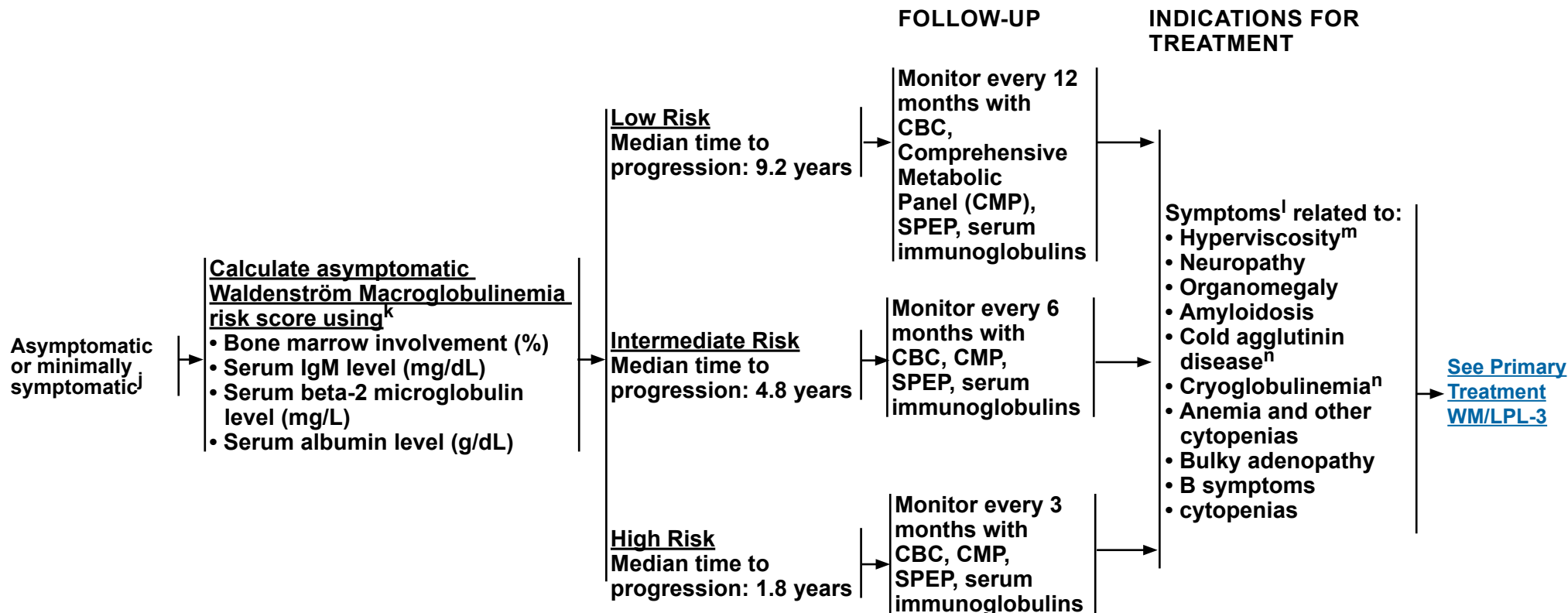
ⁱ Confirm symptoms are not related to or caused by comorbidities.

Note: All recommendations are category 2A unless otherwise indicated.

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



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^j Reserve therapy only for symptomatic patients, as untreated asymptomatic patients have similar survival than age and sex-matched individuals of the general population.

^k Risk score calculator available at www.awmrisk.com. All values taken at approximately the same time.

^l Confirm symptoms are not related to or caused by other comorbidities.

^m Retinal examination once a year if serum IgM level >3000 mg/dL. Consider therapy in asymptomatic patients with serum IgM level >6000 mg/dL.

ⁿ Detection of cold agglutinins or cryoglobulins in the absence of symptoms does not represent a criterion to treat.

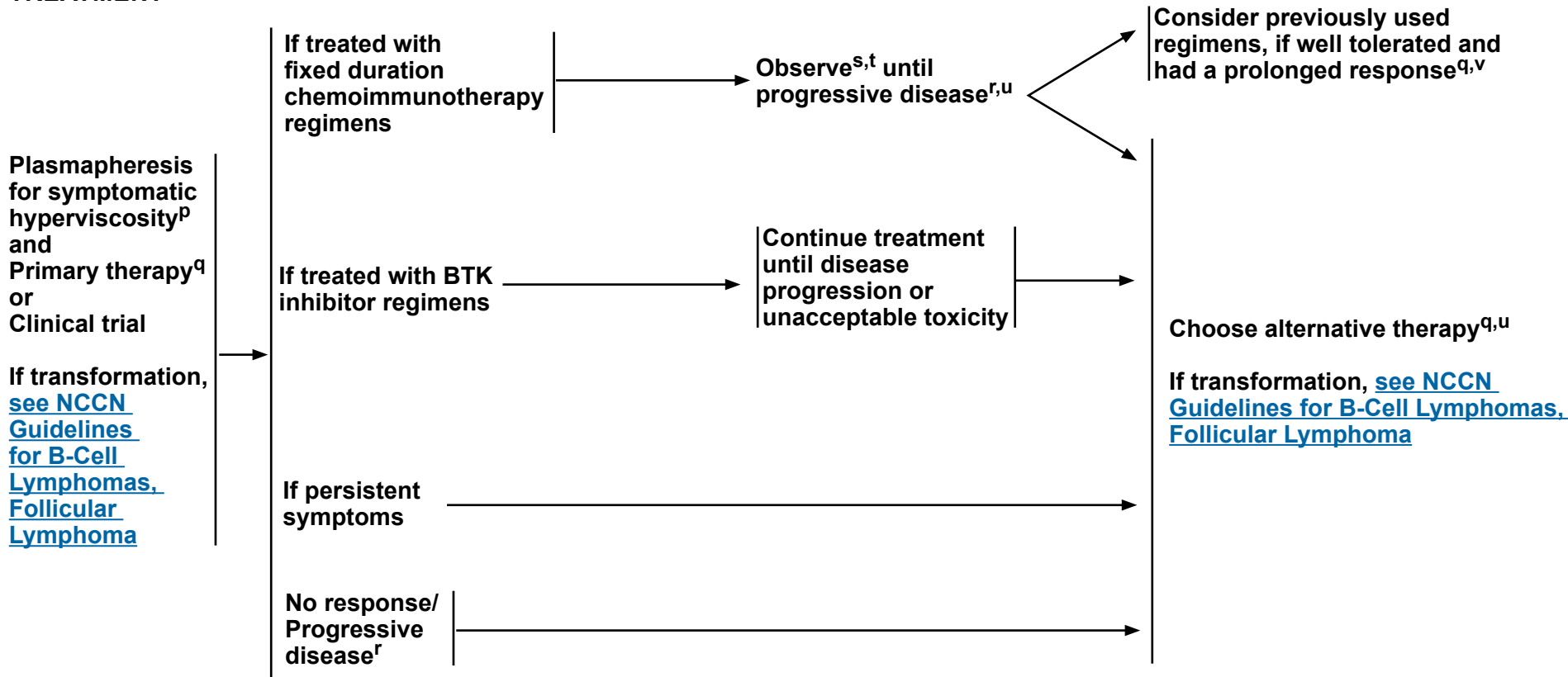
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PRIMARY TREATMENT^o

RELAPSE



^o Intent of therapy should be based on palliation of symptoms, not necessarily levels of IgM unless the patient is exhibiting evidence of symptomatic hyperviscosity.

^p Plasmapheresis should be performed for patients with symptomatic hyperviscosity, and before treatment with rituximab-containing regimen in patients with IgM ≥4000 mg/dL. IgM should be monitored closely in these patients thereafter and plasmapheresis should be considered again if symptomatic hyperviscosity recurs or if IgM is ≥4000 mg/dL while on rituximab-containing therapy. RBC transfusion, if indicated, should be done after plasmapheresis to prevent added hyperviscosity load.

^q [See Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Therapy \(WM/LPL-B\).](#)

^r [See Response Criteria for WM/LPL \(WM/LPL-C\).](#)

^s [See NCCN Guidelines for Survivorship.](#)

^t CBC, complete metabolic panel, and IgM every 3 months for 2 years, then every 4–6 months for additional 3 years, then every 6–12 months. Progression based on IgM levels alone, without symptoms, should not be reason to retreat.

^u Maintenance rituximab may be considered in select patients after chemoimmunotherapy regimens.

^v Caution should be used when re-treating with myelosuppressive regimens due to cumulative toxicities.

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NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

WHO CRITERIA FOR LYMPHOPLASMACYTIC LYMPHOMA AND WALDENSTRÖM MACROGLOBULINEMIA

- **Lymphoplasmacytic lymphoma:**
 - ▶ Neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells
 - ▶ Usually involving bone marrow and sometimes lymph nodes and spleen
 - ▶ Does not fulfill criteria of any other small B-cell lymphoid neoplasm that may also have plasmacytic differentiation

Reproduced with permission from Swerdlow SH, Campo E, Harris NL, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition. IARC, Lyon 2017.

- **Waldenström macroglobulinemia:**
 - ▶ Lymphoplasmacytic lymphoma with bone marrow involvement and IgM monoclonal gammopathy of any concentration

Adapted with permission. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological Definition of Waldenström's Macroglobulinemia: Consensus Panel Recommendations from the Second International Workshop on Waldenström's Macroglobulinemia. *Semin Oncol* 2003;30:110-115.

WALDENSTRÖM MACROGLOBULINEMIA INTERNATIONAL WORKSHOP CRITERIA

Proposed Criteria for the Diagnosis of Waldenström Macroglobulinemia

- IgM monoclonal gammopathy of any concentration
- Bone marrow infiltration by small lymphocytes, plasmacytoid cells, and plasma cells
- Diffuse, interstitial, or nodular pattern of bone marrow infiltration
- CD19+, CD20+, sIgM+; CD5, CD10, CD23 can be expressed in some cases of Waldenström macroglobulinemia and does not exclude diagnosis.

Reprinted with permission from Elsevier. Owen RG. Developing diagnostic criteria in Waldenström's macroglobulinemia. *Semin Oncol* 2003;30:196-200.

REVISED IPSS WALDENSTRÖM MACROGLOBULINEMIA SCORING SYSTEM

Criteria for the Diagnosis of Waldenström Macroglobulinemia (only at the time of initial treatment prognostication)

Table 1

	Points
Age <65	0
Age 66–75	1
Age >75	2
B2 microglobulin >4 mg/L	1
LDH >250 IU/L	1
Serum albumin <3.5 g/dL	1

Table 2

Score*	Stage
0	Very Low
1	Low
2	Intermediate
3	High
4–5	Very High

*Sum of total points in table 1

Adapted with permission from: Kastiris E, Morel P, Duhamel A, et al. A revised international prognostic score system for Waldenström's macroglobulinemia. *Leukemia* 2019;33:2654-2661.

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Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

GENERAL CONSIDERATIONS FOR SYSTEMIC THERAPY FOR WM/LPL

General Principles

- Frailty assessment should be considered in older adults. [See NCCN Guidelines for Older Adult Oncology.](#)
- If candidates for hematopoietic cell transplantation (HCT)
 - ▶ Exposure to nucleoside analogs (fludarabine and cladribine) should be avoided in patients who may be potential autologous HCT candidates.
- Plasmapheresis
 - ▶ In patients with symptomatic hyperviscosity, plasmapheresis should first be performed; plasmapheresis should also be considered before treatment with rituximab or ofatumumab for asymptomatic Waldenström macroglobulinemia patients with an IgM ≥ 4000 mg/dL or who are symptomatic to avoid aggravation of serum viscosity based on rituximab-related IgM flare. Rituximab or ofatumumab may also be held in patients with elevated serum IgM levels for initial treatment cycles. Blood warmers should be used for apheresis if cryoprecipitate or cryoglobulin are present.

Screening Recommendations

- Test for hepatitis B before starting carfilzomib, rituximab, or ofatumumab.
- Screen for HIV and hepatitis C, as clinically indicated.

Prophylaxis Recommendations

- Pneumocystis jiroveci pneumonia (PJP) prophylaxis should be considered for patients receiving bendamustine/rituximab or fludarabine/cyclophosphamide/rituximab.
- Administer herpes zoster prophylaxis for all patients treated with proteasome inhibitors and nucleoside analogs.
- Prophylactic antiviral therapy with entecavir is recommended for any patient who is hepatitis B surface antigen-positive and receiving anti-CD20 therapy. If there is active disease (PCR+), it is considered treatment/management and not prophylactic therapy. In cases of hepatitis B core antibody positivity, prophylactic antiviral therapy is preferred; however, if there is a concurrent high-level hepatitis B surface antibody, these patients may be monitored with serial hepatitis B viral load.

Side Effects and Laboratory Tests

- Carfilzomib can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
- Serial serum IgA and IgG levels should be carefully monitored as these can be depleted with WM therapies.
- Regimens containing bortezomib and vincristine are associated with higher risk of treatment-related peripheral neuropathy, especially in those with disease-related baseline neuropathy. Close monitoring or alternative therapies should be considered in some patients.

Dosing and Administration of Proteasome Inhibitors

- Subcutaneous bortezomib is the preferred method of administration.
- Both weekly and twice-weekly dosing schemas of bortezomib may be appropriate; weekly is preferred.
- Carfilzomib may be used once or twice weekly and at different doses.

Substitutions

- Rituximab and hyaluronidase human injection for subcutaneous administration may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion.
- An U.S. Food and Drug Administration (FDA)-approved biosimilar is an appropriate substitute for rituximab.

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Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

PRIMARY THERAPY FOR WM/LPL ^a (Order of regimens is alphabetical and does not indicate preference)	
Preferred Regimens	
<ul style="list-style-type: none"> • Bendamustine/rituximab • Bortezomib/dexamethasone/rituximab^b • Ibrutinib ± rituximab (category 1) 	<ul style="list-style-type: none"> • Zanubrutinib (category 1)
Other Recommended Regimens	
<ul style="list-style-type: none"> • Bendamustine • Carfilzomib/rituximab/dexamethasone • Ixazomib/rituximab/dexamethasone 	<ul style="list-style-type: none"> • Rituximab • Rituximab/cyclophosphamide/dexamethasone • Rituximab/cyclophosphamide/prednisone

^a See [General Considerations for Systemic Therapy for WM/LPL \(WM/LPL-B 1 of 4\)](#).

^b Consider for patients presenting with symptomatic hyperviscosity, or in whom rapid IgM reduction is required.

Note: All recommendations are category 2A unless otherwise indicated.
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[Continued
References](#)

WM/LPL-B
2 OF 4



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

THERAPY FOR PREVIOUSLY TREATED WM/LPL ^a (Order of regimens is alphabetical and does not indicate preference)	
Preferred Regimens	
<ul style="list-style-type: none"> • Bendamustine/rituximab • Bortezomib/dexamethasone/rituximab^b • Ibrutinib ± rituximab (category 1) 	<ul style="list-style-type: none"> • Rituximab/cyclophosphamide/dexamethasone • Zanubrutinib (category 1)
Other Recommended Regimens	
<ul style="list-style-type: none"> • Acalabrutinib • Bendamustine • Ixazomib/rituximab/dexamethasone • RCHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone) 	<ul style="list-style-type: none"> • Rituximab • Rituximab/cyclophosphamide/prednisone • Venetoclax
Useful in Certain Circumstances	
<ul style="list-style-type: none"> • Cladribine ± rituximab^c • Everolimus • Fludarabine ± rituximab^c • Fludarabine/cyclophosphamide/rituximab^c • Ofatumumab (for rituximab-intolerant individuals)^d 	
Hematopoietic Cell Transplant	
<ul style="list-style-type: none"> • In selected cases hematopoietic cell transplantation may be appropriate with either: <ul style="list-style-type: none"> ▶ Allogeneic HCT(ablative or nonablative)^e ▶ Autologous HCT 	

^a See [General Considerations for Systemic Therapy for WM/LPL \(WM/LPL-B 1 of 4\)](#).

^b Consider for patients presenting with symptomatic hyperviscosity, or in whom rapid IgM reduction is required.

^c May be associated with disease transformation and/or development of MDS/AML in patients with Waldenström macroglobulinemia.

^d Ofatumumab may be used for rituximab-intolerant individuals as a single agent or in combination therapy anywhere that rituximab is given. While ofatumumab is no longer commercially available, it may be obtained for clinical use.

^e Should ideally be undertaken in the context of a clinical trial.

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[References](#)



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

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Note: All recommendations are category 2A unless otherwise indicated.

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

RESPONSE CRITERIA FOR WM/LPL^{1,2}

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, and thalidomide, and can 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.² 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 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 Response³	CR	IgM in normal range, and disappearance of monoclonal protein by immunofixation; no histologic 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 ≥90% reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. ⁴ No new symptoms or signs of active disease.
Partial Response	PR	A ≥50% reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. ⁴ No new symptoms or signs of active disease.
Minor Response	MR	A ≥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 Disease³	PD	A ≥25% increase in serum IgM by protein confirmed by a second measurement or progression of clinically significant findings due to disease (ie, anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever ≥38.4°C, drenching night sweats, ≥10% body weight loss, or hyperviscosity, neuropathy, symptomatic cryoglobulinemia, or amyloidosis) attributable to WM.

¹ Reproduced with permission. Treon S. How I Treat Waldenström Macroglobulinemia. *Blood* 2015;126:721-732.

² Varghese AM, Rawstron AC, Ashcroft AJ, et al. Assessment of bone marrow response in Waldenström's macroglobulinemia. *Clin Lymph Myeloma* 2009;9:53-55.

³ Require two consecutive assessments made at any time before the institution of any new therapy.

⁴ CT scan may include chest/abdomen/pelvis with contrast.

Note: All recommendations are category 2A unless otherwise indicated.

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



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

MANAGEMENT OF BING NEEL SYNDROME

WORKUP

Neurological deficits concerning Bing Neel syndrome:

- Headaches
- Seizures
- Cranial nerve palsies
- Weakness in limbs
- Atypical neuropathy

Essential

- Brain and entire spine MRI with gadolinium enhancement
- Lumbar puncture for cerebrospinal fluid (CSF) analysis (cytology, multiparameter flow cytometry, PCR for *IgH* gene rearrangement, PCR for *MYD88 L265P*)

Useful in Certain Circumstances

- Biopsy of affected tissue
- Concurrent bone marrow aspiration and biopsy for *IgH* gene rearrangement and *MYD88 L265P* testing

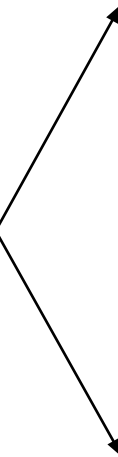
Definitive Diagnosis

- Presence of clonal B-cells in CSF or tissue biopsy with similar profile than systemic disease with or without leptomeningeal enhancement or masses in MRI

Probable Diagnosis

- Abnormal MRI findings without evidence of clonal B-cells in CSF or tissue biopsy

Asymptomatic → Observation



Symptomatic^{a,b} →

Preferred Regimens

- Ibrutinib
- Zanubrutinib

Other Recommended Regimens

- Bendamustine
- Cytarabine
- Fludarabine
- Methotrexate

Useful in Certain Circumstances

- Intrathecal methotrexate
- Radiotherapy

^a Rituximab can be added to these regimens if systemic control is needed.

^b Response criteria per Minnema MC, et al. Haematologica 2017;102:43-51.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

ABBREVIATIONS

AML	acute myeloid leukemia	IgA	immunoglobulin A	PCR	polymerase chain reaction
AS-PCR	allele-specific polymerase chain reaction	IgG	immunoglobulin G	PD	progressive disease
		IgM	immunoglobulin M	PJP	pneumocystis jirovecii pneumonia
BUN	blood urea nitrogen	IHC	immunohistochemistry	PR	partial response
		IPSS	International Prognostic Scoring System		
CBC	complete blood count			RBC	red blood cell
CMP	comprehensive metabolic panel	LDH	lactate dehydrogenase		
CNS	central nervous system	LFT	liver function test	SD	stable disease
CR	complete response	LPL	lymphoplasmacytic lymphoma	SIFE	serum immunofixation electrophoresis
CT	computed tomography			SPEP	serum protein electrophoresis
		MAG	myelin-associated glycoprotein		
EMG	electromyogram	MDS	myelodysplastic syndrome	UIFE	urine immunofixation electrophoresis
		MGUS	monoclonal gammopathy of undetermined significance	UPEP	urine protein electrophoresis
FDA	U.S. Food and Drug Administration	MR	minor response		
		MRI	magnetic resonance imaging	VGPR	very good partial response
GM1	monosialotetrahexosylganglioside				
HCT	hematopoietic cell transplantation	NCS	nerve conduction study	WM	Waldenström macroglobulinemia
HIV	human immunodeficiency virus				



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

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 indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/Lymphoplasmacytic

Discussion

This discussion corresponds to the NCCN Guidelines Waldenström Macroglobulinemia/Lymphoblastic Lymphoma. Last updated on 05/02/22

Table of Contents

Overview.....	MS-2
Literature Search Criteria and Guidelines Update Methodology.....	MS-2
Diagnosis.....	MS-2
Workup.....	MS-2
Essential Studies.....	MS-2
Studies Useful Under Certain Circumstances.....	MS-3
Primary Treatment Regimens.....	MS-4
Preferred Regimens for Primary Therapy.....	MS-5
Other Recommended Regimens for Primary Therapy.....	MS-7
Assessment of Response to Primary Treatment.....	MS-10
Follow-up After Primary Treatment.....	MS-10
Maintenance Therapy.....	MS-11
Therapy for Previously Treated WM.....	MS-11
References.....	MS-14

Discussion
update in
progress



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/Lymphoplasmacytic

Overview

Waldenström macroglobulinemia (WM) is a B-cell disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, along with immunoglobulin M (IgM) monoclonal gammopathy.¹ This condition is defined as “lymphoplasmacytic lymphoma” (LPL) by the Revised European-American Lymphoma (REAL) and World Health Organization (WHO) classification systems.^{2,3} WM is a rare disorder with approximately 1000 to 1500 new cases diagnosed every year in the United States.⁴

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Clinical Practice Guidelines (NCCN Guidelines®) for Waldenström Macroglobulinemia, an electronic search of the PubMed database was performed to obtain key literature in WM/LPL using the following search terms: Waldenström macroglobulinemia OR lymphoplasmacytic lymphoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.⁵

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel’s review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Diagnosis

Key to the diagnosis of WM/LPL is the demonstration of bone marrow infiltration by a lymphoplasmacytic cell population manifested by small lymphocytes with evidence of plasmacytoid/plasma cell differentiation. The bone marrow infiltration should be supported by immunophenotypic studies (flow cytometry and/or immunohistochemistry) showing the following profile: sIgM+, CD19+, CD20+, CD22+.¹ According to the current WHO classification, the lymphocytes in WM are typically negative for CD5, CD10, and CD23.⁶ However, this should not exclude diagnosis as exceptions occur and approximately 10% to 20% of cases may express CD5, CD10, or CD23.^{7,8} *MYD88* (L265P) mutations are present in greater than 90% of patients with WM,⁹ and can help differentiate WM/LPL from IgM myeloma or marginal zone lymphoma.

Workup

Essential Studies

History and physical (H&P) examination are essential components of initial evaluation. The essential laboratory studies include complete blood count (CBC) with differential, peripheral blood smear examination, and comprehensive metabolic panel to assess kidney and liver function.¹⁰

To establish the diagnosis of WM, it is necessary to demonstrate IgM monoclonal protein in the serum, along with histologic evidence of lymphoplasmacytic cells in the bone marrow.¹ Serum protein electrophoresis (SPEP), serum quantitative immunoglobulins, and serum immunofixation electrophoresis (SIFE) are used to identify and quantify the M-protein (IgM). While detection of a monoclonal IgM protein in the serum is a diagnostic criterion for WM, this monoclonal IgM may be found clinically either in the setting of clinical WM, IgM monoclonal gammopathy



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/Lymphoplasmacytic

of undetermined significance (IgM MGUS), or IgM multiple myeloma. It is important to make this distinction during diagnosis. Approximately 5% of patients with LPL can secrete non-IgM paraproteins (eg, IgG, IgA, kappa, lambda) or be non-secretory, and should be managed like WM.

Beta-2 microglobulin and the International Prognostic Scoring System for WM (IPSSWM) are useful for prognostication of WM at the time of first-line treatment initiation.^{11,12} Their use in making treatment-related decisions remains to be clarified.¹¹

Bone marrow is almost always involved in WM; therefore, a unilateral bone marrow aspirate and biopsy should be performed to document clonal lymphoplasmacytic cell population and confirmed by immunohistochemistry and/or flow cytometry.^{1,6} Multiparametric flow cytometry may provide additional data on the immunophenotypic characterization of WM.¹³

The bone marrow aspirate should be tested for *MYD88* (L265P) gene mutation. Whole genome sequencing of bone marrow LPL cells has identified *MYD88* (L265P) as a commonly recurring mutation in patients with WM.^{9,14,15} *Absence* of *MYD88* mutations should not be used to exclude diagnosis of WM if other criteria are met.¹⁶ The NCCN Panel recommends allele-specific polymerase chain reaction (AS-PCR) for *MYD88* (L265P).

CT scans of the chest, abdomen, and pelvis with intravenous (IV) contrast at time of diagnosis are useful to properly stage the patient and can assess adenopathy, splenomegaly, and other extramedullary disease sites.

Studies Useful Under Certain Circumstances

IgM is a pentamer and a common cause of hyperviscosity. Therefore, evaluation for characteristic clinical signs and symptoms of serum

viscosity should be done at the time of diagnosis. Many patients with WM will exhibit an elevated serum viscosity level, that is, more than 1.8 centipoise (cP). Patients typically become symptomatic at serum viscosity levels of more than 4.0 cP. However, in some patients, lower levels of serum viscosity can cause retinal changes and hemorrhages that may necessitate intervention.¹⁷ Serum viscosity results should not be used as the sole criterion for intervention, in part due to long turnaround time and potential technical issues.

In less than 10% of patients with WM, monoclonal IgM may present with cold agglutinin activity, where the monoclonal IgM interact with specific red cell antigens below physiological temperatures, producing chronic hemolytic anemia.¹⁸ The cold agglutinin titers are greater than 1:1000 in most cases. In up to 20% of patients with WM, the monoclonal IgM may behave as a cryoglobulin (type I), but will be symptomatic in less than or equal to 5% of the cases. The presence of cold agglutinins or cryoglobulins may affect determination of IgM levels; therefore, testing for cold agglutinins and cryoglobulins should be performed at diagnosis.¹⁹

When suspected, cryocrit, a test for cryoglobulins, should be obtained. The presence of cryoglobulins may render falsely low serum IgM levels. In such situations, maintaining the serum sample in a warm bath will provide a more reliable serum IgM level measurement.²⁰

Twenty-four-hour urine for total protein, creatinine clearance, urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis (UIFE) may be useful.

Patients with WM and peripheral neuropathy may harbor antibodies against myelin-associated glycoprotein (MAG) or other glycoproteins or lipids.^{19,21}



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/Lymphoplasmacytic

Serum anti-MAGs should be evaluated in patients with sensory peripheral neuropathies²²; in those with motor neuropathy, anti-ganglioside M1 (GM1) antibodies may also be evaluated. In patients with peripheral neuropathy, referral for neurologic consultation should be considered. Nerve conduction studies (NCS) or electromyography (EMG) may be helpful in determining if neuropathy is related to the monoclonal process or other causes.²³

Amyloidosis should be suspected in patients presenting with nephrotic syndrome, axonal neuropathy, or unexplained cardiac problems; a fat biopsy and/or evaluation of the bone marrow biopsy with Congo red can help establish the diagnosis. When detected, amyloid subtyping with mass spectrometry should also be performed, if indicated.

High von Willebrand factor levels have been associated with worse prognosis in patients with WM.²⁴ If unexplained clinical bleeding or bruising is present, the NCCN Panel recommends von Willebrand disease (VWD) testing, as acquired VWD has been identified in some cases of WM, usually with high serum IgM levels. Patients with WM, particularly those with cryoglobulinemia (especially type II), have been associated with having underlying hepatitis C; therefore, liver function tests and hepatitis C serology should also be obtained.²⁵⁻²⁷

Retinal examination is recommended if hyperviscosity is suspected or IgM levels are greater than or equal to 3.0 g/dL.²⁸

It is recommended that patients be screened for hepatitis B infection before initiation of carfilzomib, rituximab, or ofatumumab therapy. Hepatitis B carriers should be closely monitored for clinical and laboratory signs and symptoms of active hepatitis B virus infection during rituximab therapy and for several months following therapy.

WM patients may have recurrent mutations in the *CXCR4* gene. Studies have shown that mutations in this gene are found in up to 40% of patients with WM/LPL and can impact ibrutinib response.²⁹⁻³² Given that certain *CXCR4* mutations can confer resistance to ibrutinib,³³⁻³⁵ the NCCN Panel recommends consideration of *CXCR4* gene mutation testing for patients being initiated on ibrutinib therapy.

WM is a disease seen in older adults; the median age at the time of diagnosis ranges from 60 to 75 years.^{19,36,37} Therefore, frailty assessment should be considered prior to treatment of older adults with WM as per NCCN Guidelines for Older Adult Oncology (available at [NCCN.org](https://www.nccn.org)).

Primary Treatment Regimens

According to the NCCN WM/LPL Panel, treatment should be initiated for patients with a diagnosis of WM/LPL only in those who are symptomatic. The indicative symptoms of treatment include hyperviscosity; neuropathy; symptomatic adenopathy or organomegaly; amyloidosis; cryoglobulinemia; cold agglutinin disease; anemia; and presence of cytopenia.^{11,38-40}

Importantly, high IgM level per se should not be considered a criterion for initiation of therapy in the absence of other aforementioned indications. One must confirm that symptoms are not related to or caused by other comorbidities.

Treatment of WM is discussed in detail in several reviews.⁴¹ Since WM is a rare disease, there are very few randomized trials and limited data comparing different treatment approaches. Therefore, the treatment for WM has been largely adopted from data derived from phase II or retrospective studies.

According to the NCCN Panel, for patients requiring immediate disease control, such as those with symptomatic hyperviscosity, initial plasmapheresis is recommended.⁴² After plasmapheresis, systemic treatment should be initiated as soon as possible.



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/Lymphoplasmacytic

Agents that limit future treatment options should be avoided during initial therapy. Exposure to continuous oral alkylator therapy or nucleoside analogs should be avoided prior to stem cell harvest if an autologous stem cell transplant (SCT) is being considered. Nucleoside analogs are associated with increased risk of disease transformation, development of myelodysplastic syndromes (MDS), and secondary acute myeloid leukemia (AML) in patients with WM treated with nucleoside analog-containing therapy.^{43,44} Exposure to nucleoside analogs should therefore be limited, particularly in younger patients who may be potential SCT candidates.

The NCCN Panel recommends monitoring of serum IgG levels while on therapy. Herpes zoster prophylaxis should be considered for patients receiving proteasome inhibitor-based regimens and nucleoside-analogs.

Hepatitis B virus (HBV) reactivation is common in patients with hematologic malignancies. The NCCN Panel recommends screening for HBV infection by testing for hepatitis B surface antigen (HBsAg) or antibody to hepatitis B core antigen (HBcAb) especially before starting therapy with carfilzomib, rituximab, or ofatumumab. Prophylactic antiviral therapy with entecavir is recommended for those who have HBsAg to prevent HBV reactivation. In those with resolved HBV infection, who have antibody to hepatitis B core antigen (HBcAb), the panel prefers prophylaxis with antiviral therapy. However, if there is a concurrent high-level hepatitis B surface antibody, monitoring serially for hepatitis B viral load and giving antiviral therapy as soon as HBV DNA is detectable is also an option.

All treatment options for WM/LPL are listed alphabetically in the NCCN Guidelines. The NCCN Panel has categorized WM therapy regimens as: “preferred regimens,” “other recommended regimens,” and regimens “useful under certain circumstances.” The purpose of classifying regimens is to provide guidance on treatment selection considering the relative

efficacy, toxicity, and other factors that play into treatment selection such as pre-existing comorbidities (eg, peripheral neuropathy, rituximab intolerance). The NCCN Panel Members strongly encourage treatment in the context of a clinical trial when possible.

Preferred Regimens for Primary Therapy

Bendamustine/Rituximab

Rituximab, a monoclonal antibody that targets the B-lymphocyte antigen CD20, has been used successfully in the treatment of WM, because CD20 is expressed on lymphoplasmacytic cells in patients with WM. The Study Group Indolent Lymphomas (StiL) examined the activity of bendamustine plus rituximab (BR) versus cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab (CHOP-R) in a large, randomized, multicenter phase III trial of previously untreated patients with indolent non-Hodgkin lymphoma (NHL).⁴⁵ Included in this study were 41 patients with WM/LPL, 40 of whom were available for response assessment.⁴⁵ After a median follow-up of 45 months, the median progression-free survival (PFS) was significantly longer with BR treatment, 69.5 versus 28.5 months with CHOP-R.⁴⁶ BR was associated with a lower incidence of grade 3 or 4 neutropenia, infectious complications, and alopecia in this study. These results suggest that BR may be a preferable option to CHOP-R as primary therapy for WM.⁴⁶ The results of the StiL NHL-2008 MAINTAIN trial, demonstrate a median PFS of 65.3 months in those receiving bendamustine and rituximab, which is consistent with the results of the StiL NHL1-2003 trial (69.5 months).⁴⁷

Pneumocystis jirovecii pneumonia [PJP] prophylaxis should be considered for patients receiving bendamustine/rituximab.



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/Lymphoplasmacytic

Bortezomib/Dexamethasone/Rituximab

Bortezomib has shown excellent activity in the management of WM as a single agent,⁴⁸ in combination with rituximab,⁴⁹ or in combination with rituximab and dexamethasone.^{50,51}

The study by Waldenström Macroglobulinemia Clinical Trials Group (WMCTG) reported an overall response rate (ORR) of 96%, including 83% of patients achieving partial response (PR) with the combination of bortezomib (using a twice-a-week schedule), along with rituximab and dexamethasone (BDR) in newly diagnosed patients with WM.⁵⁰ With a median follow-up of 2 years, 80% of patients remained free of disease progression, including all patients achieving a very good partial response (VGPR) or better. However, grade 3 peripheral neuropathy was observed in 30% of patients in the study that used twice-a-week bortezomib administration. The development of peripheral neuropathy led to premature discontinuation of bortezomib in 61% of patients in this study, underscoring the difficulties encountered with the use of this agent in this patient population.

In another multicenter phase II trial, the activity of BDR (using once-weekly bortezomib) was evaluated in 59 newly diagnosed symptomatic patients with WM.⁵² The ORR was 85% (3% complete response [CR], 7% VGPR, and 58% PR). In 11% of patients, an increase of IgM ($\geq 25\%$) was observed after administration of rituximab. After 32 months of follow-up, median PFS was 42 months and 3-year overall survival (OS) was 81%. Peripheral neuropathy was observed in 46% (grade ≥ 3 in 7%) of patients; 8% discontinued bortezomib due to neuropathy.⁵² The high rate of peripheral neuropathy could be attributed to the IV administration of bortezomib in the trial. 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. Administering bortezomib subcutaneously and once weekly

reduces the risk of peripheral neuropathy. Therefore, this is the preferred method of administration. While both weekly and twice-weekly dosing schemas of bortezomib are appropriate, the weekly schema is preferred.

For patients who are intolerant to rituximab, subcutaneous bortezomib with dexamethasone can be considered as an alternate option to BDR (see *Other Recommended Regimens for Primary Therapy*).

Ibrutinib with or without Rituximab

Signaling pathways from the B-cell antigen receptor and Bruton's tyrosine kinase (BTK) play a crucial role in mediating growth and survival of B-cell malignancies, including WM.⁵³

A phase II trial of ibrutinib monotherapy in patients with symptomatic WM (n = 63) who received at least one prior treatment reported an ORR of 90.1% (10 with a VGPR, 36 with a PR, 11 with a minor response, none with a CR) and a median time to response of 4 weeks.³⁴ The study also investigated the effect of *MYD88* and *CXCR4* mutations on patient outcomes. A major response was seen in approximately 60% of patients with mutated *MYD88* and *CXCR4* mutations. At 5 years, the PFS and OS rates were 54% and 87%, respectively.⁵⁴ Treatment-related toxic effects of grade 3 or higher included neutropenia (in 15.9% of patients) and thrombocytopenia (in 11.1% of patients).⁵⁴ Similar results were observed in a phase II study on 30 treatment-naïve WM patients treated with ibrutinib, with an ORR of 100%, a VGPR rate of 30%, and 48-month PFS rate of 76%.⁵⁵ Other adverse events associated with ibrutinib include bleeding and arrhythmia. The U.S. Food and Drug Administration (FDA) has approved ibrutinib as single-agent therapy for patients with WM until disease progression or unacceptable toxicity.

The phase III iNOVATE trial (n = 150) compared both newly diagnosed and patients with relapsed/refractory WM treated with ibrutinib/rituximab or rituximab plus placebo.⁵⁶ At 30 months of follow-up, the ibrutinib/rituximab



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/Lymphoplasmacytic

treatment showed an ORR of 95% compared with 48% in those treated with rituximab/placebo. In newly diagnosed patients, treatment with ibrutinib/rituximab demonstrated an improved PFS at 24 months (84%) compared to the rituximab arm (59%) (hazard ratio [HR], 0.34; 95% CI, 0.12–0.95).⁵⁶ The rituximab-induced infusion reactions were markedly reduced in the ibrutinib/rituximab arm. The 30-month PFS rates were 79% with ibrutinib/rituximab versus 41% with rituximab/placebo.⁵⁷ At 50 months of follow-up, improvements in PFS were seen with ibrutinib/rituximab (median not reached) over rituximab/placebo (median PFS, 20 months), demonstrating a significant reduction in disease progression or death (HR, 0.25; 95% CI, 0.15–0.42; $P < .0001$). The estimated 54-month PFS rates were 68% with ibrutinib/rituximab versus 25% with rituximab/placebo. Median OS was not reached in either treatment arm (HR, 0.81; 95% CI, 0.33–1.99; $P = .6430$). The ORR was 92% with ibrutinib/rituximab versus 44% with rituximab/placebo. The most common grade 3/4 adverse events with ibrutinib/rituximab over the 5-year study period were infections (29%), atrial fibrillation (16%), hypertension (15%), neutropenia (13%), anemia (12%), and pneumonia (11%).⁵⁸

The NCCN Panel has included ibrutinib with or without rituximab as a *Preferred Regimen for Primary Therapy (category 1)* and as one of the *Preferred Regimens for Therapy for Previously Treated WM/LPL (category 1)*.

Rituximab/Cyclophosphamide/Dexamethasone

Another alternative to bortezomib-containing therapy is a cyclophosphamide-based regimen along with rituximab and a corticosteroid. In a prospective study of untreated WM patients ($n = 72$), treatment with rituximab/cyclophosphamide/dexamethasone (R-CD) resulted in an ORR of 83% that included a 7% CR and a 67% PR. The 2-year PFS was 67% for all evaluable patients and 80% for responders. The R-CD regimen was well-tolerated, with 9% of patients experiencing grade

3 or 4 neutropenia and approximately 20% of patients experiencing some form of toxicity related to rituximab.⁵⁹ The 8-year OS based on the IPSS risk status for WM was 100%, 55%, and 27% for low-, intermediate-, and high-risk disease, respectively ($P = .005$).⁶⁰

In a retrospective analysis of outcomes after treatment with R-CD in 50 patients with untreated WM, the ORR was 96% and the median PFS was 34 months. The response rate and duration of response were independent of *MYD88* mutation status.⁶¹

Zanubrutinib

Zanubrutinib is a BTK inhibitor that may be considered as an alternative to ibrutinib-based therapy. In the phase III ASPEN trial, 201 patients with treatment-naïve or relapsed/refractory WM were randomized 1:1 to receive either zanubrutinib monotherapy or ibrutinib monotherapy. All patients had a *MYD88* (L265P) mutation and 9.4% had a *CXCR4* (WHIM) mutation. There was no statistical difference in VGPR between the zanubrutinib and ibrutinib groups (28% vs. 19%; $P = .09$). Estimated 18-month OS/PFS was 97%/85% for the zanubrutinib arm and 93%/84% for the ibrutinib arm. No substantial differences in major response rates were seen between wildtype and mutated *CXCR4* patients in both treatment arms.⁶²

The ASPEN safety data comparing zanubrutinib monotherapy showed a decrease in incidence of atrial fibrillation (2% vs. 15%) and a lower incidence in most non-hematologic adverse events (AEs) compared with ibrutinib. The incidence of hematologic AEs was similar with the exception of neutropenia, in which zanubrutinib was associated with twofold greater likelihood of any grade (29% vs. 13%) and grade ≥ 3 (20% vs. 8%) neutropenia compared to ibrutinib. A greater proportion of patients received granulocyte colony-stimulating factor with zanubrutinib compared to ibrutinib (47% vs. 31%).⁶²



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/Lymphoplasmacytic

The NCCN Panel has included zanubrutinib as a *Preferred Regimen for Primary Therapy (category 1)* and as one of the *Preferred Regimens for Therapy for Previously Treated WM/LPL (category 1)*.

Other Recommended Regimens for Primary Therapy

Bendamustine

Based on the durable responses seen in previously treated WM, as monotherapy in rituximab-intolerant individuals,⁶³ bendamustine has been included as an option for primary therapy for WM.

Bortezomib

In a phase II study, bortezomib was administered to 27 patients with WM, 44% of whom were previously untreated and 56% of whom were previously treated.⁴⁸ Bortezomib was administered using the standard schedule until the patients demonstrated progressive disease or were two cycles beyond best response.⁴⁸ The ORR in this study was 78%, with major responses observed in 44% of patients. Sensory neuropathy occurred in 20 patients after two to four cycles of therapy. Among the 20 patients who developed neuropathy, it resolved in 14 patients and improved by one grade in one patient at 2 to 13 months.

Bortezomib/Rituximab

A phase II study of weekly bortezomib plus rituximab in newly diagnosed patients with WM reported an ORR of 88%, including a major response in 65% of patients. The estimated 1-year PFS in this study was 79%.⁴⁹

Bortezomib/Dexamethasone

While bortezomib/dexamethasone/rituximab is an active regimen and induces long-lasting responses in patients with newly diagnosed WM, bortezomib/dexamethasone without rituximab may be effective as initial therapy. Therefore, it is included as an option under *Other Recommended Regimens for Primary Therapy*.

Carfilzomib/Rituximab/Dexamethasone

A prospective phase II study studied the combination of carfilzomib/rituximab/dexamethasone in newly diagnosed symptomatic patients (n = 31) with WM/LPL.⁶⁴ Long-term follow-up demonstrated an ORR of 87% and a median PFS of 46 months.⁶⁵ The response rate seen in this study is comparable to those seen in studies using bortezomib-based regimens with an ORR of 85% to 96%.^{50,52} The study also found that the response to this regimen was not impacted by *MYD88* (L265P) mutation status. Rituximab-associated IgM flare (increase of IgM $\geq 25\%$) was observed in 22.7% of patients. With a median follow-up of 15.4 months, 64% remained progression-free. No significant peripheral neuropathy was observed in this study. IgA and IgG depletion were commonly observed and necessitated truncation of therapy and/or IV immunoglobulin use in several patients.⁶⁴

The NCCN Panel has included carfilzomib/rituximab/dexamethasone as a treatment option under *Other Recommended Regimens for Primary Therapy* and noted under general considerations that it can potentially cause cardiac and pulmonary toxicity, especially in older patients.

Cladribine Alone or with Rituximab

Cladribine, a nucleoside analogue, has been studied alone or in combination with rituximab and found to induce good ORRs with prolonged survivals.⁶⁶⁻⁶⁸ In a phase II trial of cladribine with rituximab in 29 patients with newly diagnosed or previously treated WM, reported ORRs and CR rates were 90% and 24%, respectively.

Fludarabine Alone or with Rituximab

Like cladribine, fludarabine is a nucleoside analogue and has been studied alone or in combination with rituximab and/or cyclophosphamide in patients with newly diagnosed WM. A recent phase III trial showed that monotherapy with fludarabine was more effective than chlorambucil in terms of PFS (36.3 vs. 27.1 months; $P = .012$), duration of response



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/Lymphoplasmacytic

(38.3 vs. 19.9 months; $P < .001$), and OS (not reached in the fludarabine arm vs. 69.8 months [95% CI, 61.6–79.8 months; $P = .014$] in the chlorambucil arm).⁶⁹

A prospective, multicenter trial evaluated treatment with fludarabine with rituximab in patients with WM ($n = 43$) who had received less than two prior therapies, of whom 63% had received no prior therapy. The ORR was 95%. The reported median time to progression for all patients was 51.2 months and was longer for untreated patients ($P = .017$) and those achieving at least a VGPR ($P = .049$). After a median follow-up of 40.3 months, 3 cases with transformation to aggressive lymphoma and 3 cases with MDS/AML were reported.⁷⁰

Fludarabine/Cyclophosphamide/Rituximab

Another multicenter, prospective trial treated previously untreated or pretreated chemotherapy patients with WM ($n = 43$) with the fludarabine, cyclophosphamide, and rituximab (FCR) regimen.⁷¹ Most of the patients in this study (65%) received FCR as first-line treatment, 28% of patients had relapsed disease, and 7% had disease that was refractory to a previous line of treatment. The results demonstrated that FCR produces rapid response rates of 79%, with high rates of CR and VGPR. There is a risk of PJP associated with FCR treatment, including late onset of PJP.⁷² Therefore, the NCCN Panel recommends PJP prophylaxis for those treated with the FCR regimen.

Ixazomib/Rituximab/Dexamethasone

A prospective phase II study, of patients ($n = 26$) with symptomatic WM studied the combination of ixazomib/rituximab/dexamethasone and found this regimen to be safe and effective as a primary therapy option.⁷³ All enrolled patients had the *MYD88* (L265P) mutation, and 58% of these had a *CXCR4* mutation. The median time to response was 8 weeks. Although the VGPR was 15%, the ORR was 96% and median time to response was 8 weeks. The median PFS was not reached after a median follow-up of 22

months.⁷³ Of note, the median time to response was longer in WM patients with *CXCR4* mutations (12 vs. 8 weeks; $P = .03$).⁷³

The NCCN Panel has included ixazomib/rituximab/dexamethasone as a treatment option under *Other Recommended Regimens for Primary Therapy*.

Rituximab

Single-agent rituximab is active in patients with WM; however, the response rates of single-agent rituximab using either standard or extended dosing vary between 25% and 45%.^{44,74,75} Transient increases in IgM titers (also called the IgM flare) have been reported in 40% to 50% of patients after initiation of rituximab therapy, including in circumstances where rituximab has been used in combination therapy.^{76,77} The rituximab-related IgM flare may lead to symptomatic hyperviscosity, as well as worsening of IgM-related neuropathy, cryoglobulinemia, and other IgM-related complications. These levels may persist for months and do not indicate treatment failure, but may necessitate plasmapheresis to reduce hyperviscosity. Prophylactic plasmapheresis can be considered in patients with high IgM levels (typically 4000 mg/dL or higher)⁷⁸ before rituximab exposure to minimize risk of symptomatic hyperviscosity. The risk of IgM flare may be decreased in patients receiving rituximab in combination with bortezomib and dexamethasone.⁵⁰ Rituximab may be regarded as a reasonable choice for treating patients with IgM anti-MAG antibody-related neuropathies.⁷⁹

Rituximab/Cyclophosphamide/Prednisone

The use of cyclophosphamide/prednisone/rituximab (CP-R) has been shown to be analogous to the more intense cyclophosphamide-based regimens with lesser treatment-related complications.⁸⁰ A single institutional retrospective study examined the outcomes of symptomatic patients with WM who received CHOP-R ($n = 23$), cyclophosphamide/vincristine/prednisone plus rituximab (CVP-R; $n = 16$),



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/Lymphoplasmacytic

or CP-R (n = 19). Baseline characteristics were similar for all three cohorts except for serum IgM levels, which were higher in patients treated with CHOP-R ($P \leq .015$). The ORR and CR to the three regimens were: CHOP-R (ORR, 96%; CR, 17%); CVP-R (ORR, 88%; CR, 12%); and CP-R (ORR, 95%; CR, 0%). A higher incidence for neutropenic fever and treatment-related neuropathy were reported for CHOP-R and CVP-R versus CP-R ($P < .03$).⁸⁰

Assessment of Response to Primary Treatment

Response to therapy in WM is defined by reduction in the IgM protein. According to the updated summary of response categories from the Sixth International Workshop on WM,⁸¹ a minor response is an IgM reduction of at least 25%; a PR is defined as a greater than or equal to 50% reduction in IgM immunoglobulin; a VGPR is a greater than or equal to 90% reduction in IgM immunoglobulin; and a CR is immunofixation negativity in the serum. Stable disease is defined as a less than 25% reduction and less than 25% increase of serum IgM by electrophoresis without progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms due to 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. The updated summary of response categories and criteria from the Sixth International Workshop on WM⁸¹ has been included in the NCCN Guidelines (see Table 1 on page WM/LPL-C).

An important concern with the use of IgM as a surrogate marker of disease is that it can fluctuate independent of tumor cell killing. Rituximab induces a spike or flare in serum IgM levels that 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.^{19,76,77} On the other hand, bortezomib and ibrutinib can suppress IgM levels independent of killing tumor cells in

certain patients.^{82,83} One study showed that residual IgM-producing plasma cells are spared and continue to persist in patients treated with selective B-cell-depleting agents such as rituximab and alemtuzumab, thus potentially skewing the relative response and assessment to treatment.⁸⁴ Therefore, in circumstances whereby the serum IgM levels appear 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.

Follow-up After Primary Treatment

After primary therapy, the NCCN Panel recommends assessing the response to treatment using consensus panel criteria outlined in the algorithm (Table 1).

The goal of treatment is symptom relief and reducing the risk of organ damage. When assessing responses, it is important to recognize that with some agents, responses (reduction of IgM) to initial therapies are often delayed and may result in underestimation of response.

According to the NCCN Panel, observation includes monitoring IgM every 3 months for 2 years, then every 4 to 6 months for an additional 3 years, and then every 6 to 12 months. Progression based on IgM levels alone, without symptoms, should not be a reason to restart treatment.

For patients showing a either complete or very good partial response to primary treatment, the follow-up options could include observation until the disease progresses.

For asymptomatic patients who have achieved a partial or minor response to induction therapy the NCCN Panel recommends observation until disease progression or considering maintenance rituximab in patients who might benefit from further deepening of the response.



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/Lymphoplasmacytic

For those patients who do not show any response to primary therapy or if symptoms persist, the panel recommends choosing an alternative therapy or following the NCCN Guidelines for B-Cell Lymphomas (available at [NCCN.org](https://www.nccn.org)) if there is disease transformation.

Subsequent management options for patients with WM/LPL outlined in the NCCN Guidelines are based on the response assessment after therapy.

Maintenance Therapy

Although a retrospective study in 248 patients with WM who responded to rituximab-containing regimens showed a benefit in PFS and OS of maintenance rituximab over observation,⁸⁵ the preliminary results of a prospective study have shown otherwise. The StiL NHL-2008 MAINTAIN trial randomized 218 patients with WM who attained a PR or better to 6 cycles of bendamustine and rituximab to rituximab maintenance every 2 months for 2 years (n = 109) versus observation (n = 109).⁴⁷ The median PFS in the maintenance group was 101 months and 83 months in the observation group. This difference, however, was not statistically significant ($P = .32$). Also, there was no difference in OS with the median not yet reached for both arms.

Therapy for Previously Treated WM

Many patients inevitably experience relapse after initial therapy and require further treatment.⁴¹ According to the NCCN Guidelines, administering the same regimen used for primary treatment is reasonable as therapy for relapsed disease, especially if the regimen was well-tolerated and the patient had a prolonged response. The panel notes that caution should be used when re-treating with myelosuppressive regimens due to cumulative toxicities.

For patients with remissions lasting less than 24 months or who show progressive disease/resistance to a first-line regimen, second-line

treatment may include agents of a different class of drugs, either alone or in combination. In addition, it is important to avoid exposure to stem cell-damaging agents, such as an alkylator or nucleoside analogs, in patients who are candidates for autologous SCT. Regimens that are not toxic to stem cells must be offered, especially if stem cells have not previously been harvested. All regimens listed under primary treatment options are effective options for consideration in patients with previously treated WM.

Bendamustine-based therapy is effective in relapsed/refractory WM because it produces high response rates and durable responses both as monotherapy and BR. A phase II study of patients with relapsed/refractory WM, who received bendamustine-based therapy, reported an ORR of 83.3%.⁶³ The median PFS in patients with refractory WM/LPL was 13.2 months.⁶³ Another study evaluated the efficacy of BR and R-CD. Of the 160 patients, 60 received BR (43 with relapsed/refractory WM) and 100 received R-CD (50 had relapsed/refractory WM). In patients with relapsed/refractory WM, ORR with BR was 95% versus 87% with R-CD, $P = .45$; median PFS with BR was 58 versus 32 months with R-CD (2-year PFS was 66% vs. 53%; $P = .08$).⁸⁶ Bendamustine in combination with rituximab is listed as one of the preferred options for relapsed/refractory disease and single-agent bendamustine is listed under *Other Recommended Regimens* in the algorithm.

The use of bortezomib as therapy for relapsed disease is associated with an ORR of 60% when administered as a single agent, and of 70% to 80% when in combination with rituximab^{48,82,83,87,88, 89} with or without dexamethasone.⁹⁰ Grade 3 peripheral neuropathy may occur in 30% of patients using the twice-a-week dosing schedule of bortezomib and in 10% of patients receiving once-a-week dosing. Therefore, evaluation of patients for the development of bortezomib-related peripheral or autonomic neuropathy is important. Prophylaxis against herpes zoster should be strongly considered with bortezomib and steroid combinations.



NCCN Guidelines Version 1.2023

Waldenström Macroglobulinemia/Lymphoplasmacytic

Bortezomib/dexamethasone/rituximab is listed as one of the preferred options for relapsed/refractory disease, and single-agent bortezomib or bortezomib in combination with rituximab or dexamethasone is listed under *Other Recommended Regimens* in the algorithm.

CHOP-R is a stem cell-sparing regimen reported to be active and tolerated by patients with WM.^{80,91,92} It has been reported as having at least a 90% response rate in patients with WM.^{80,92,93} In a randomized study involving 69 patients, most of whom had WM, the addition of rituximab to CHOP resulted in a higher ORR (94% vs. 67%) and median time to progression (63 vs. 22 months) in comparison to patients treated with CHOP alone.⁹² The addition of vincristine to cyclophosphamide-containing regimens is associated with risk of neuropathy in patients with WM.⁵⁰ According to the NCCN Panel, since vincristine is associated with a high risk of peripheral neuropathy in patients with WM/LPL, regimens without vincristine (eg, cyclophosphamide/dexamethasone/rituximab), it may be considered if cyclophosphamide-based therapy is being considered.

Treatment with single-agent rituximab has been reported to produce response rates of 50% to 70%.^{74,77,94} Other rituximab-containing chemotherapy regimens include: R-CD, CP-R, and CHOP-R. The NCCN Panel has listed R-CD in the algorithm under *Preferred Regimens*, and single-agent rituximab, CP-R, and CHOP-R are listed in the algorithm under *Other Recommended Regimens for Therapy for Previously Treated WM/LPL*.

Nucleoside analogs have shown efficacy in relapsed/refractory WM/LPL either alone or in combination with rituximab.^{68,70,71} All cladribine- and fludarabine-containing regimens have been listed in the algorithm under *Other Recommended Regimens for Therapy for Previously Treated WM/LPL*.

Acalabrutinib is another BTK inhibitor treatment option that may be considered. A single-arm phase II trial analyzed the usage of acalabrutinib in 106 patients with treatment-naïve or relapsed/refractory WM. Out of the total 106 enrolled, 14 patients (13%) were treatment-naïve, 41 patients (39%) had received 3 or more prior therapies, and 33 patients (31.1%) had refractory disease. In treatment-naïve patients, the 24-month OS was 92% and the 24-month PFS was 90%. In relapsed/refractory patients, the 24-month OS was 89% and the 24-month PFS was 82%. The most common grade 3/4 adverse events were neutropenia (16%), pneumonia (7%), anemia (5%), and lower respiratory tract infection (5%).⁹⁵ The NCCN Panel has included acalabrutinib as a treatment option under *Other Recommended Regimens for Previously Treated WM/LPL*.

Venetoclax is an oral BCL2 antagonist approved for the treatment of chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML). BCL2 is an anti-apoptotic protein that is shown to be overexpressed in primary WM cells.⁹⁶ A phase II trial analyzed venetoclax monotherapy in 33 patients with previously treated WM. All patients had a *MYD88* (L265P) mutation and 17 patients (53%) had a *CXCR4* mutation. At median follow-up of 33 months, the median PFS was 30 months. At time of data cutoff, the 30-month OS was 100% and the ORR was 84%. There was no difference in major response rate nor PFS on the basis of *CXCR4* mutational status. The most common grade 3/4 adverse event was neutropenia (42%).⁹⁷ The NCCN Panel has included venetoclax as a treatment option under *Other Recommended Regimens for Previously Treated WM/LPL*.

Everolimus, an inhibitor of mTOR, is a potentially effective drug in treating WM, with high single-agent activity but substantial toxicity. With a different mechanism of action, it offers an alternate therapeutic strategy for patients with relapsed/refractory WM. A phase II trial of single-agent everolimus was initiated in 60 patients with relapsed or relapsed/refractory WM.⁹⁸ The



response rate (minor response or better) was 73% with a PR rate of 50% and a minor response rate of 23%.⁹⁹ The median PFS was 21 months. Grade 3- or 4-related toxicities were reported in 67% of patients. Dose reductions due to toxicity were made in 62% of patients. The most commonly reported hematologic toxicities with everolimus treatment were cytopenias. Pulmonary toxicity was seen in 5% of patients.⁹⁹ The study reported that the patients who achieved a PR responded after a median of 2 months of treatment. Everolimus is listed in the algorithm under *Other Recommended Regimens for Therapy for Previously Treated WM/LPL*.

Ofatumumab is a human monoclonal antibody (IgG1) that binds specifically to a distinct epitope encompassing both the small and large extracellular loops of the CD20 molecule.^{100,101} In cells expressing low levels of CD20, it induces complement-dependent cytotoxicity in vitro that is more potent compared with rituximab.^{74,94} Studies demonstrated that ofatumumab could be successfully administered, either as a single agent or as combination therapy with meaningful responses in patients with WM.¹⁰² According to the NCCN Panel ofatumumab may be considered in patients who are intolerant to rituximab, either as single-agent or combination therapy. Therefore, it is listed as an agent that is “useful in certain circumstances.”

There is a risk of IgM flare with ofatumumab, as with rituximab. Therefore, similar precautions as with rituximab should be considered when using ofatumumab in those patients who have evidence of hyperviscosity or who have elevated IgM levels.

Hematopoietic Cell Transplant (HCT)

HCT is also an option for relapsed WM in selected patients.^{103,104} HCT options listed in the NCCN Guidelines for WM/LPL are for high-dose therapy with autologous stem cell rescue.^{103,104} According to the NCCN Panel, myeloablative or non-myeloablative allogeneic HCT may be considered,¹⁰³ but in the context of a clinical trial.



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NCCN Guidelines Version 1.2023

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Waldenström Macroglobulinemia/Lymphoplasmacytic

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References

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