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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

Version 1.2026 — June 24, 2025

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# NCCN Guidelines Version 1.2026
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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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**Updates in Version 1.2026 of the NCCN Guidelines for WM/LPL from Version 2.2025 include:**

**Global**
- References updated throughout Guidelines.

**WM/LPL-1**
- Workup, Useful in Certain Circumstances, 2nd bullet revised: CXCR4 gene mutation testing ~~for patients being considered for Bruton's tyrosine kinase (BTK) inhibitors.~~
- Footnote c, last sentence added: For classification of IgM monoclonal gammopathies, see Table 1 in Treon SP, et al. Semin Hematol 2023;60:97 and MGNS-1 in the NCCN Guidelines for Multiple Myeloma.

**WM/LPL-2**
- Indications for Treatment, line added: or if asymptomatic with high levels of IgM (>6000 mg/dL)
- Footnote m revised: Retinal examination once a year if serum IgM level >3000 mg/dL. ~~Consider therapy in asymptomatic patients with serum IgM level >6000 mg/dL.~~

**WM/LPL-3**
- Management After Primary Treatment
  - If treated with fixed-duration chemoimmunotherapy regimens pathway revised: Observe until *symptomatic* progressio~~n~~*ve* of disease
  - If treated with BTK inhibitor regimens pathway revised: Continue treatment until symptomatic ~~disease~~ progression *of disease* (beyond biochemical progression) or unacceptable toxicity
- Footnote p revised: Plasmapheresis should be performed for patients with symptomatic hyperviscosity *or severe cryoglobulin-related symptoms*, and before treatment with Rituximab-containing regimen in patients with IgM ≥4000 mg/dL.

**WM/LPL-A**
- Modified Staging System for Waldenström Macroglobulinemia (MSS-WM) replaces Revised IPSS Waldenström Macroglobulinemia Scoring System.

**WM/LPL-B (1 of 4)**
- Side Effects and Laboratory Tests, 2nd bullet revised: ~~Serial serum IgA and~~ IgG levels should be carefully monitored as these can be depleted with WM therapies. See Prevention and Treatment of Cancer-Related Infections.
- Substitutions, 1st bullet revised: A U.S. Food and Drug Administration (FDA)-approved biosimilar is an appropriate substitute for *any recommended systemic biologic therapy in the NCCN Guidelines* ~~rituximab~~.

**WM/LPL-B (2 of 4)**
- Primary Therapy for WM/LPL table
  - Regimen moved from Preferred to Other Recommended: Ibrutinib ± Rituximab (category 1)
- Footnote d added: Should not be used in first-line for patients with LPL-associated amyloidosis.

**WM/LPL-B (3 of 4)**
- Therapy for Previously Treated WM/LPL table
  - Regimen moved from Useful in Certain Circumstances to Other Recommended: Pirtobrutinib

**WM/LPL-B (4 of 4)**
- Reference removed: Morel P, Duhamel A, Gobbi P, et al. International prognostic scoring system for Waldenstrom macroglobulinemia. Blood. 2009;113:4163-4170.
- Reference removed: Owen RG, Kyle RA, Stone MJ, et al. Update from the VIth International Workshop on Waldenström macroglobulinaemia. Response assessment in Waldenström macroglobulinaemia: update from the VIth International Workshop. Br J Haematol 2013;160:171-176.
- Reference added: Treon SP, Tedeschi A, San-Miguel J, et al. Report of consensus Panel 4 from the 11th International Workshop on Waldenstrom's macroglobulinemia on diagnostic and response criteria. Semin Hematol 2023;60:97-106.
- Reference added: Zanwar S, Le-Rademacher J, Durot E, et al. Simplified risk stratification model for patients with Waldenström macroglobulinemia. J Clin Oncol 2024;42:2527-2536.



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## 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/abdomen/pelvis CT ± contrast and/or FDG-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[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

→ **Asymptomatic or minimally symptomatic** → **Monitoring plan (WM/LPL-2)**

→ **Symptoms[i] related to:**
- Hyperviscosity
- Neuropathy
- Organomegaly
- Amyloidosis
- Cold agglutinin disease
- Cryoglobulinemia
- Anemia and other cytopenias associated with disease
- Bulky adenopathy
- B symptoms
- Cytopenias

→ **Primary treatment (WM/LPL-3)**

[a] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.
[b] 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. For classification of IgM monoclonal gammopathies, see Table 1 in Treon SP, et al. Semin Hematol 2023;60:97 and MGNS-1 in the NCCN Guidelines for 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 Waldenström macroglobulinemia (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.**



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## ASYMPTOMATIC OR MINIMALLY SYMPTOMATIC WM

Asymptomatic or minimally symptomatic[j]

→ Calculate asymptomatic Waldenström macroglobulinemia (WM) risk score using[k]:
- Bone marrow involvement (%)
- Serum IgM level (mg/dL)
- Serum beta-2 microglobulin level (mg/L)
- Serum albumin level (g/dL)

## FOLLOW-UP

**Low Risk**
Median time to progression: 9.2 years
→ Monitor every 12 months with CBC, CMP, SPEP, serum immunoglobulins

**Intermediate Risk**
Median time to progression: 4.8 years
→ Monitor every 6 months with CBC, CMP, SPEP, serum immunoglobulins

**High Risk**
Median time to progression: 1.8 years
→ Monitor every 3 months with CBC, CMP, SPEP, serum immunoglobulins

## INDICATIONS FOR TREATMENT

Symptoms[l] related to:
- Hyperviscosity[m]
- Neuropathy
- Organomegaly
- Amyloidosis
- Cold agglutinin disease[n]
- Cryoglobulinemia[n]
- Anemia and other cytopenias
- Bulky adenopathy
- B symptoms
- Cytopenias

Or if asymptomatic with high levels of IgM (>6000 mg/dL)

→ Primary treatment (WM/LPL-3)

[j] Reserve therapy only for symptomatic patients, as untreated asymptomatic patients have similar survival compared to age- and sex-matched individuals of the general population.
[k] Risk score calculator is available at www.awmrisk.com. All values are 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.
[n] Detection of cold agglutinins or cryoglobulins in the absence of symptoms does not represent a criterion to treat.

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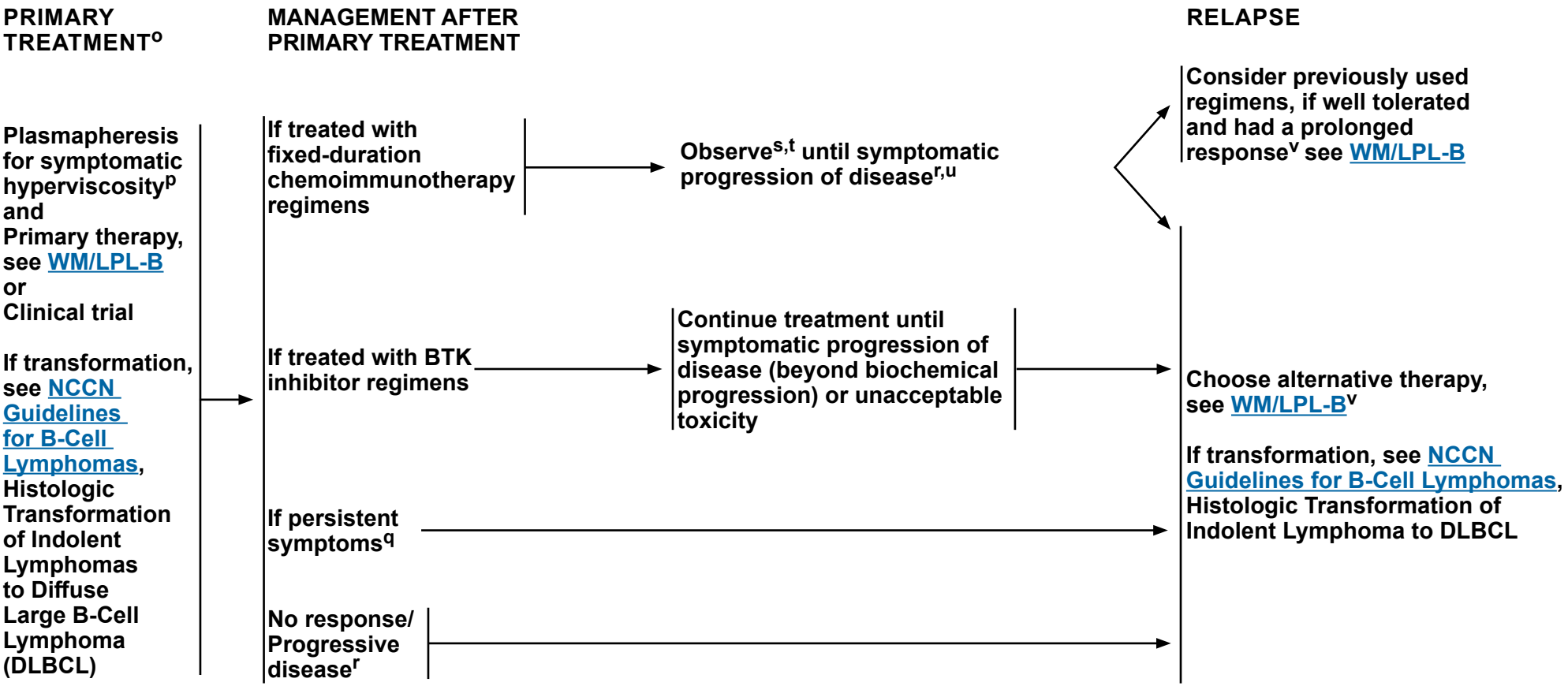


[o] Intent of therapy should be based on palliation of symptoms, not necessarily levels of IgM unless the patient is exhibiting evidence of symptomatic hyperviscosity.

[p] Plasmapheresis should be performed for patients with symptomatic hyperviscosity or severe cryoglobulin-related symptoms, 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. Red blood cell (RBC) transfusion, if indicated, should be done after plasmapheresis to prevent added hyperviscosity load.

[q] In patients with neuropathy, symptom stability might be the goal of therapy as neuropathy symptoms take time to improve.

[r] Response Criteria for WM/LPL (WM/LPL-C).

[s] NCCN Guidelines for Survivorship.

[t] CBC, CMP, and IgM every 3 months for 2 years, then every 4–6 months for an additional 3 years, then every 6–12 months. Progression based on IgM levels alone, without symptoms, should not be a reason to re-treat.

[u] Maintenance Rituximab may be considered in select patients after chemo-immunotherapy regimens.

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

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## 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 Waldenstrom's macroglobulinemia: Consensus panel recommendations from the Second International Workshop on Waldenstrom'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.

## MODIFIED STAGING SYSTEM FOR WALDENSTRÖM MACROGLOBULINEMIA (MSS-WM)

**Simplified Risk Stratification Model for Individuals with Waldenström Macroglobulinemia**

**Table 1**

| Criteria | Points |
|---|---|
| Age 66–75 | 1 |
| Age >75 | 2 |
| Elevated LDH | 2 |
| Serum albumin <3.5 g/dL | 1 |

**Table 2**

| Score* | Risk |
|---|---|
| 0 | Low |
| 1 | Low-Intermediate |
| 2 | Intermediate |
| ≥3 | High |

***Sum of total points in Table 1**

Adapted from Zanwar S, Le-Rademacher J, Durot E, et al. Simplified risk stratification model for patients with Waldenström macroglobulinemia. J Clin Oncol 2024;42:2527-2536.

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## 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.
- Plasmapheresis
  - In patients with symptomatic hyperviscosity, plasmapheresis should first be performed; plasmapheresis should also be considered before treatment with Rituximab for patients with asymptomatic WM with an IgM ≥4000 mg/dL or who are symptomatic to avoid aggravation of serum viscosity based on Rituximab-related IgM flare. Rituximab 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**
- Screen for HIV, hepatitis B, 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 older patients.
- IgG levels should be carefully monitored as these can be depleted with WM therapies. See Prevention and Treatment of Cancer-Related Infections.
- 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 (preferred) or twice weekly and at different doses.

**Substitutions**
- A U.S. Food and Drug Administration (FDA)-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
- 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.

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| PRIMARY THERAPY FOR WM/LPL[a,b]<br>(The regimens under each preference category are listed by order of NCCN Category of Evidence and Consensus alphabetically.) | |
|---|---|
| **Preferred** | |
| • Zanubrutinib[c,d] (category 1)<br>• Bendamustine/Rituximab | |
| **Other Recommended** | |
| • Ibrutinib[c,d] (category 1)<br>• Ibrutinib[c,d] + Rituximab (category 1)<br>• Bendamustine<br>• Bortezomib/Dexamethasone/Rituximab<br>• Carfilzomib/Rituximab/Dexamethasone<br>• Ixazomib/Rituximab/Dexamethasone | • Rituximab<br>• Rituximab/Cyclophosphamide/Dexamethasone<br>• Rituximab/Cyclophosphamide/Dexamethasone + Bortezomib<br>• Rituximab/Cyclophosphamide/Prednisone |

[a] General Considerations for Systemic Therapy for WM/LPL (WM/LPL-B 1 of 4).
[b] Obinutuzumab may be considered in patients who are unable to tolerate Rituximab (Wróbel T, et al. Hemasphere 2023;7:e4339598. doi: 10.1097/01.HS9.0000971308.43395.98).
[c] Rapid increases in IgM levels (IgM rebound) have been observed following discontinuation of BTK inhibitors. Consider continuing therapy with the BTK inhibitor until starting the next line of therapy or monitor for IgM rebound after discontinuation of BTK inhibitors.
[d] Should not be used in first-line for patients with LPL-associated amyloidosis.

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| THERAPY FOR PREVIOUSLY TREATED WM/LPL[a,b]<br>(The regimens under each preference category are listed by order of NCCN Category of Evidence and Consensus alphabetically.) | |
|---|---|
| **Preferred**<br>• Ibrutinib[c] (category 1)<br>• Ibrutinib[c] + Rituximab (category 1)<br>• Zanubrutinib[c] (category 1)<br>• Bendamustine/Rituximab<br>• Rituximab/Cyclophosphamide/Dexamethasone | |
| **Other Recommended**<br>• Acalabrutinib[c]<br>• Bortezomib/Dexamethasone/Rituximab<br>• Ixazomib/Rituximab/Dexamethasone | • Pirtobrutinib<br>• Rituximab/Cyclophosphamide/Prednisone<br>• Venetoclax |
| **Useful in Certain Circumstances**<br>• Bendamustine<br>• Cladribine[e]<br>• Cladribine + Rituximab[e]<br>• Everolimus<br>• Fludarabine[e]<br>• Fludarabine + Rituximab[e] | • Fludarabine/Cyclophosphamide/Rituximab[e]<br>• Rituximab<br>• RCHOP (Rituximab/Cyclophosphamide/Doxorubicin/Vincristine/Prednisone) |
| **Hematopoietic Cell Transplant**<br>• In selected patients HCT may be appropriate with either:<br>▸ Allogeneic HCT (ablative or nonablative)[f]<br>▸ Autologous HCT | |

[a] General Considerations for Systemic Therapy for WM/LPL (WM/LPL-B 1 of 4).
[b] Obinutuzumab may be considered in patients who are unable to tolerate Rituximab (Wróbel T, et al. Hemasphere 2023;7:e4339598. doi: 10.1097/01.HS9.0000971308.43395.98).
[c] Rapid increases in IgM levels (IgM rebound) have been observed following discontinuation of BTK inhibitors. Consider continuing therapy with the BTK inhibitor until starting the next line of therapy or monitor for IgM rebound after discontinuation of BTK inhibitors.
[e] May be associated with disease transformation and/or development of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) in patients with WM.
[f] Should ideally be undertaken in the context of a clinical trial.

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## RESPONSE CRITERIA FOR WM/LPL
## IWWM-11 RESPONSE CRITERIA FOR ASSESSMENT OF DISEASE RESPONSE IN WM/LPL[1]

| Response[a] | Serum Monoclonal IgM | Serum IgM Level | Bone Marrow Aspirate and Trephine Biopsy | Extramedullary disease |
|---|---|---|---|---|
| **Complete Response (CR)** | Absence of monoclonal IgM protein by SPEP and IFX. | Within normal range | Normal morphology; no evidence of LPL involvement. | Absence of extramedullary disease if present at baseline. See criteria for determination of resolution of extramedullary disease.[e] |
| **Very good partial response (VGPR)** | | ≥90% reduction in serum IgM levels or within normal range | | |
| **Partial response (PR)** | | ≥50% to <90% reduction in serum IgM levels | | |
| **Minor response (MR)** | | ≥25% to <50% reduction in serum IgM levels | | |
| **Stable disease (SD)** | | <25% reduction to <25% increase in serum IgM levels | | |
| **Progressive disease (PD)** | | ≥25% increase in serum IgM levels with a minimum increase of 500 mg/dL from nadir. Reconfirmation is required by 2 sequential (back-to-back) measurements if the serum IgM is being used to support PD. Demonstration of PD by imaging does not require re-confirmation.[b,c] | | Any new lesion (>1.5 cm in any axis) or unequivocal evidence of an increase by > 50% in any axis to >1.5 cm in size of previously involved extramedullary disease sites from their nadir measurements. Any new lesion consistent with transformed disease. |
| **Nonevaluable (NE)** | | Suspected IgM flare or IgM rebound, absence of data or suspected error in data reporting[d] | | |

[1] Reproduced with permission. Treon SP, Tedeschi A, San-Miguel J, et al. Report of consensus Panel 4 from the 11th International Workshop on Waldenstrom's macroglobulinemia on diagnostic and response criteria. Semin Hematol 2023;60:97-106.

[a] Categorical response assessment for CR, VGPR, PR, MR or SD assumes no signs or symptoms consistent with disease progression are present. The overall response rate includes MR, PR, VGPR, and CR responses, whereas the major response rate includes PR, VGPR and CR responses.

[b] Re-confirmation of CR, VGPR, PR, MR, or SD is not required. Progressive disease (PD) must be re-confirmed if the IgM is being used to support PD. To meet criteria for progressive disease, a ≥25% increase in serum IgM level with a minimum serum IgM increase of 500 mg/dL from the nadir is required on 2 sequential (back-to-back) measurements. In the event an IgM measurement meets PD criteria, and the subsequent measurement does not, the patient will not have met PD criteria until 2 back-to-back measurements show PD. Demonstration of PD by imaging does not require re-confirmation. In the event of discordant response findings, that is, IgM measurement shows a response but imaging shows PD related to WM, then the assessment should be considered PD.

[c] Suspected IgM flare or IgM rebound related to therapy will not be considered as progressive disease.

[d] A nonevaluable response assessment should be specified in cases of suspected IgM flare or IgM rebound; absence of data, or suspected error in data reporting (ie, contradictory central vs local laboratory measurements).

[e] For CR attainment, normalization of extramedullary disease if present at baseline will be considered complete resolution or decrease in size of lymph nodes (≤1.5 cm) or decrease in the size of spleen (≤15 cm), or complete resolution of any other non-lymph node or non-splenic extramedullary mass(es) related to WM disease consistent with revised response criteria for malignant lymphoma. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-586.

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## 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.

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## ABBREVIATIONS

| | |
|---|---|
| AML | acute myeloid leukemia |
| AS-PCR | allele-specific polymerase chain reaction |
| BUN | blood urea nitrogen |
| CBC | complete blood count |
| CMP | comprehensive metabolic panel |
| CNS | central nervous system |
| CR | complete response |
| CSF | cerebrospinal fluid |
| DLBCL | diffuse large B-cell lymphoma |
| EMG | electromyogram |
| GM1 | monosialotetrahexosylganglioside |
| HCT | hematopoietic cell transplant |
| HIV | human immunodeficiency virus |
| IgA | immunoglobulin A |
| IgG | immunoglobulin G |
| IgM | immunoglobulin M |
| IHC | immunohistochemistry |
| LDH | lactate dehydrogenase |
| LFT | liver function test |
| LPL | lymphoplasmacytic lymphoma |
| MAG | myelin-associated glycoprotein |
| MDS | myelodysplastic syndrome |
| MGUS | monoclonal gammopathy of undetermined significance |
| MR | minor response |
| MSS-WM | Modified Staging System for Waldenström Macroglobulinemia |
| NCS | nerve conduction study |
| NE | nonevaluable |
| PCR | polymerase chain reaction |
| PD | progressive disease |
| PJP | *pneumocystis jirovecii* pneumonia |
| PR | partial response |
| RBC | red blood cell |
| SD | stable disease |
| SIFE | serum immunofixation electrophoresis |
| SPEP | serum protein electrophoresis |
| UIFE | urine immunofixation electrophoresis |
| UPEP | urine protein electrophoresis |
| VGPR | very good partial response |
| WM | Waldenström macroglobulinemia |

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# NCCN Guidelines Version 1.2026
# Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

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| NCCN Categories of Evidence and Consensus | |
|---|---|
| **Category 1** | Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate. |
| **Category 2A** | Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate. |
| **Category 2B** | Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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** | Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability. |
| **Other recommended** | 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.

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# NCCN Guidelines Version 3.2025 Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

## Discussion

This discussion corresponds to the NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoblastic Lymphoma. Last updated: February 6th, 2025

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Discussion update in progress



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# NCCN Guidelines Version 3.2025 Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

## Overview

Waldenström macroglobulinemia (WM) is a B-cell disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells (LPCs) and 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 annually in the United States.[4,5] Review of the SEER database between 1980 and 2016 showed that white individuals, those assigned male at birth, and individuals aged >60 years are more likely to develop WM.[6]

## Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma, 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.[7]

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.

## Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

## Diagnosis

Key to the diagnosis of WM/LPL is the demonstration of bone marrow infiltration by a LPC population manifested by small lymphocytes with evidence of plasmacytoid/plasma cell differentiation. The bone marrow infiltration should be supported by immunophenotypic studies (flow

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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.[8] However, this should not exclude diagnosis as exceptions occur and approximately 10% to 20% of cases may express CD5, CD10, or CD23.[9,10] *MYD88* L265P mutations are present in >90% of patients with WM,[11] and can help differentiate WM/LPL from IgM myeloma or marginal zone lymphoma.

## Workup

### Essential Tests

History and physical (H&P) examination are essential components of initial evaluation. Laboratory studies include complete blood count (CBC) with differential, peripheral blood smear examination, and comprehensive metabolic panel (CMP), as well as creatinine clearance. CMP includes serum blood urea nitrogen (BUN)/creatinine, electrolytes, albumin, calcium, and liver function tests (LFTs) to assess kidney and liver function.[12] Serum uric acid, lactate dehydrogenase (LDH), and beta-2 microglobulin should also be included as part of the initial workup to assess risk of tumor lysis, tumor burden, and as a prognostic indicator.[13]

To establish the diagnosis of WM, it is necessary to demonstrate IgM monoclonal protein in the serum and histologic evidence of LPCs 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 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 have LPL managed like WM.

The International Prognostic Scoring System for WM (IPSS-WM) is useful for prognostication of WM at first-line treatment initiation.[14,15] Its value in making treatment-related decisions remains to be clarified.[14]

Bone marrow is almost always involved in WM; therefore, a unilateral bone marrow aspirate and biopsy should be performed to document clonal LPC population and confirmed by immunohistochemistry and/or flow cytometry.[1,8] Multiparametric flow cytometry may provide additional data on the immunophenotypic characterization of WM.[16]

The bone marrow aspirate should be tested for *MYD88* L265P mutation. Whole genome sequencing of bone marrow LPL cells has identified *MYD88* L265P as a commonly recurring mutation in patients with WM.[11,17,18] Absence of *MYD88* mutations should not be used to exclude diagnosis of WM if other criteria are met.[19] The NCCN Panel recommends allele-specific polymerase chain reaction (AS-PCR) for *MYD88* L265P detection.

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

### Tests 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 diagnosis. Many patients with WM will exhibit an elevated serum viscosity level of >1.8 centipoise (cP). Patients typically become symptomatic at serum viscosity levels of >4.0 cP. However, in some patients, lower levels of serum viscosity can cause retinal changes

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and hemorrhages that may necessitate intervention.[20] 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 <10% of patients with WM, monoclonal IgM may present with cold agglutinin activity, where the monoclonal IgM interact with specific red cell antigens below physiologic temperatures, producing complement-mediated hemolysis causing chronic hemolytic anemia.[21,22] The cold agglutinin titers are >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 ≤5% of 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.[23] Notably, cold agglutinins are also a key feature of primary cold agglutinin disease (CAD), part of the differential diagnosis of WM.[24,25]

Gene testing for the *CXCR4* mutation may be useful if patients are considered for Bruton's tyrosine kinase inhibitors (BTKis).[26] *CXCR4* mutations are present in ≤40% of patients with WM and are indicative of more aggressive disease. These mutations have a reduced sensitivity towards certain BTKis, specifically ibrutinib.

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.[27] Hepatitis C virus (HCV) should also be ruled out if cryoglobulinemia is suspected.[28]

Serologic screening for hepatitis B virus (HBV) is recommended, as certain agents, specifically rituximab, are known to induce severe, and potentially fatal, viral reactivation.[29] Individuals may also be screened for human immunodeficiency virus (HIV) as part of the workup.

Coagulation studies and/or von Willebrand disease testing can be considered if the patient presents with excessive bruising or bleeding, or if otherwise clinically indicated.

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.[23,30]

Serum anti-MAG antibodies can be evaluated in patients with sensory peripheral neuropathies[31]; in those with motor neuropathy, anti-ganglioside M1 antibodies may also be evaluated. In patients with peripheral neuropathy, referrals for neurologic consultation should be considered. Nerve conduction studies (NCS) or electromyography (EMG) may help determine if neuropathy is related to the monoclonal process or other causes.[32] Fat pad sampling and/or congo red staining of bone marrow for amyloid can also be performed in patients with suspected disease related to peripheral neuropathy. Amyloidosis should be ruled out in those presenting with nephrotic syndrome or unexplained cardiac conditions. If indicated, amyloid tissue subtyping with mass spectrometry may be performed.

The median age at the time of WM diagnosis ranges from 60 to 75 years.[23,33,34] Therefore, frailty assessment should be considered prior to treatment of older adults with WM as per the NCCN Guidelines for Older Adult Oncology (available at NCCN.org).

The manifestation of neurologic deficits is ambiguous and could be the result of underlying comorbidities. If CNS involvement is suspected in

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individuals with WM; imaging studies, cerebral spinal fluid (CSF) analysis, or tissue biopsy are needed to investigate Bing-Neel syndrome (BNS).

## Asymptomatic or Minimally Symptomatic

WM may be preceded by asymptomatic disease states such as IgM MGUS or smoldering WM (SWM).[35] Approximately 1.5% of patients with IgM MGUS and 12% of those with SWM have disease progression to WM per year.[11,36-38] The risk of disease progression is estimated using an asymptomatic risk score calculator, which takes the following diagnostic measurements into consideration: bone marrow involvement (%), serum IgM level (mg/dL), serum beta-2 microglobulin level (mg/dL), and serum albumin level (g/dL).[3] Based on the risk score, the risk of disease progression is categorized as low risk, intermediate risk, and high risk, with a median time to progression to symptomatic disease of 9.2 years, 4.8 years, and 1.8 years, respectively. The frequency of follow-up varies based on the risk status. Follow-up includes monitoring with diagnostic testing, including CBC, CMP, SPEP, and serum immunoglobulins, every 12 months for low risk, every 6 months for intermediate risk, and every 3 months for high risk.

## Primary Therapy Regimens for WM/LPL

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; B-symptoms; and presence of cytopenia.[14,39-41] Importantly, high IgM level by itself should not be considered a criterion for initiation of therapy in the absence of other indications. The NCCN Panel notes that it is important to rule out symptoms related to comorbidities before treatment initiation and detection of cold agglutinins or cryoglobulins in the absence of symptoms does not represent a criterion to treat, whereas treatment should be considered in asymptomatic patients with serum IgM level >6000 mg/dL.

Since WM is a rare disease, few randomized trials and limited data comparing different treatment approaches exist. Therefore, the treatment for WM has been primarily 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.

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 hematopoietic cell transplant (HCT) is being considered. Nucleoside analogs are associated with an increased risk of disease transformation, development of myelodysplastic syndromes (MDS), and secondary acute myeloid leukemia (AML).[43,44]

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

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 antibody (HBcAb) as clinically indicated. Prophylactic antiviral therapy with entecavir is recommended for those who have HBcAb to prevent HBV reactivation. In those with resolved HBV infection, who have antibodies to HBcAg, the Panel prefers prophylaxis with antiviral therapy. However, if

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there is a concurrent high-level HBcAb, 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 in the treatment of WM, because CD20 is expressed on LPCs in patients with WM. Bendamustine, an alkylating agent causing crosslinks in DNA bases resulting in apoptosis, is frequently used in chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin lymphoma (NHL).[45] A multicenter study by the French Innovative Leukemia Organization (FILO) showed favorable outcomes in 69 patients with WM, treated with bendamustine and rituximab (BR).[46] Progression-free survival (PFS) and overall survival (OS) after 5 years were 6.63% (95% CI, 56.09–79.17) and 80.01% (95% CI, 70.82–90.41), respectively. The Study Group Indolent Lymphomas (StiL) examined the activity of bendamustine plus rituximab (BR) versus cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (RCHOP) in a large, randomized, multicenter, phase III trial of previously untreated patients with indolent NHL.[47] Included in this study were 41 patients with WM/LPL, 40 of whom were available for response assessment.[47] After a median follow-up of 45 months, the median PFS was significantly longer with BR treatment, 69.5 versus 28.5 months with RCHOP.[48] 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 RCHOP as primary therapy for WM.[48] The results of the StiL NHL-2008 MAINTAIN trial, demonstrate a median PFS of 65.3 months in those receiving BR, which is consistent with the results of the StiL NHL1-2003 trial (69.5 months).[49]

Pneumocystis jirovecii pneumonia (PJP) prophylaxis should be considered for patients receiving BR.

The NCCN Panel has included BR as a Preferred Regimen for Primary Therapy.

*Ibrutinib With or Without Rituximab*: Signaling pathways from the B-cell antigen receptor and BTK are crucial in mediating the growth and survival of B-cell malignancies.[50-53]

A phase II study of 30 treatment-naïve patients with WM treated with ibrutinib monotherapy reported an ORR of 100%, a very good partial response (VGPR) rate of 30%, and a 48-month PFS rate of 76%.[52] Adverse events (AEs) associated with ibrutinib include bleeding and arrhythmia. Ibrutinib is approved by the FDA as single-agent therapy for patients with WM until disease progression or unacceptable toxicity.

The phase III iNNOVATE trial (n = 150) compared patients with newly diagnosed and relapsed/refractory WM treated with ibrutinib/rituximab or rituximab plus placebo.[53] At 30 months of follow-up, the ibrutinib/rituximab 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).[53] The rituximab-induced infusion reactions were markedly

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reduced in the ibrutinib/rituximab arm.[54] 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; $P = .64$). The ORR was 92% with ibrutinib/rituximab versus 44% with rituximab/placebo. *CXCR4* mutations affected VGPR rates (23% vs. 44%) but did not impact PFS. The most common grade 3/4 AEs with ibrutinib/rituximab over the 5-year study period were infections (29%), atrial fibrillation (16%), hypertension (15%), neutropenia (13%), anemia (12%), and pneumonia (11%).[55]

The NCCN Panel has included ibrutinib with or without rituximab as a Preferred Regimen for Primary Therapy (category 1).

*Zanubrutinib*: Zanubrutinib is a BTKi with a higher affinity to BTK than ibrutinib. In the phase III ASPEN trial, 201 patients with treatment-naïve or relapsed/refractory WM were randomized 1:1 to receive either zanubrutinib or ibrutinib. All patients had a *MYD88* (L265P) mutation and 26% had a *CXCR4* mutation. There was no statistical difference in VGPR between the zanubrutinib and ibrutinib groups (28% vs. 19%; $P = .09$).[56] The 42-month PFS rate for zanubrutinib was 78% and for ibrutinib was 70% (HR, 0.63; 95% CI, 0.36–1.12).[57] Zanubrutinib induced higher VGPR (21% vs. 10%) and 42-month PFS rates (73% vs. 49%) than ibrutinib in patients with *CXCR4* mutations.

The ASPEN safety data comparing zanubrutinib monotherapy showed a decrease in the incidence of atrial fibrillation (4% vs. 17%) and a lower incidence in most non-hematologic AEs compared with ibrutinib. The incidence of hematologic AEs was similar except for neutropenia, in which zanubrutinib was associated with a two-fold likelihood of any grade (29% vs. 13%) and grade ≥3 (20% vs. 8%) neutropenia compared to ibrutinib. A larger proportion of patients received granulocyte colony-stimulating factor (G-CSF) with zanubrutinib compared to ibrutinib.[56]

The NCCN Panel has included zanubrutinib as a Preferred Regimen for Primary Therapy (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,[58] bendamustine has been included as an option for primary therapy for WM. It is also a Useful in Certain Circumstances therapy option in patients previously treated for WM.

*Bortezomib/Dexamethasone/Rituximab*: Bortezomib has shown activity in the management of WM as a single agent,[59] in combination with rituximab,[60] or in combination with rituximab and dexamethasone.[61,62]

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

In another multicenter phase II trial, the activity of BDR (using once-weekly IV bortezomib) was evaluated in 59 newly diagnosed symptomatic patients with WM.[63] The ORR (including major and minimal response) was 85% (major response rate included: 3% complete

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response [CR], 7% VGPR, and 58% PR). In 11% of patients, an increase of IgM (≥25%) was observed after the administration of rituximab. After 32 months of follow-up, median PFS was 42 months, and 3-year OS was 81%. Peripheral neuropathy was observed in 46% (grade ≥3 in 7%) of patients; 8% discontinued bortezomib due to neuropathy.[63]

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.

The NCCN Panel has included bortezomib/dexamethasone/rituximab as a treatment 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 patients who are symptomatic (n = 31) with WM/LPL.[64] Long-term follow-up demonstrated an ORR of 87% and a median PFS of 46 months.[65] The study found that the response to this regimen was not impacted by *MYD88* (L265P) mutation status. Rituximab-associated IgM flare (increase of IgM ≥25%) was observed in 23% of patients. No significant peripheral neuropathy was observed in this study. IgA and IgG depletion were commonly observed and necessitated truncation of therapy and/or IV Ig 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.

*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.[66] All enrolled patients had the *MYD88* (L265P) mutation, and 58% had a *CXCR4* mutation. The median time to response was 8 weeks. The overall major and VGPR rates were 96%, 77%, and 19%, respectively, and the median time to response was 8 weeks.[66] The median PFS was 40 months, median duration of response (DOR) was 38 months, and the median time to next treatment (TTNT) was 40 months. PFS, DOR, and TTNT were not affected by *CXCR4* mutational profile.[67]

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%.[44,68,69] Transient increases in IgM levels (also called the IgM flare) have been reported in 40% to 50% of patients after initiation of rituximab therapy.[70,71] 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 disease progression but may necessitate plasmapheresis to reduce IgM levels. Prophylactic plasmapheresis can be considered in patients with high IgM levels (typically ≥4000 mg/dL)[72] before rituximab exposure to minimize the risk of symptomatic IgM flare. The risk of IgM flare may be decreased in patients receiving rituximab in combination with other agents.[61] Rituximab may be reasonable for treating patients with IgM anti-MAG antibody-related neuropathies.[73]

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*Rituximab/Cyclophosphamide/Dexamethasone With or Without Bortezomib*: In a prospective study of people with untreated WM (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 individuals and 80% for those whose disease responded to R-CD. The R-CD regimen was well-tolerated, with 9% of those experiencing grade 3 or 4 neutropenia and approximately 20% of individuals experiencing some form of toxicity related to rituximab.[74] The 8-year OS rates based on the IPSS-WM risk status for WM were 100%, 55%, and 27% for low-, intermediate-, and high-risk disease, respectively ($P$ = .005).[75] In a retrospective analysis of outcomes after treatment with R-CD in 50 people with untreated WM, the ORR was 96% and the median PFS was 34 months. The response rate and DOR were independent of *MYD88* mutational status.[76]

A prospective randomized, phase III, open-label clinical trial evaluated the efficacy and safety of R-CD versus R-CD plus bortezomib in 204 treatment-naïve patients with WM.[77] The 2-year PFS was 80.6% (95% CI, 69.5–88.0) and 72.8% (95% CI, 61.3–81.3) for R-CD plus bortezomib and R-CD, respectively. Results also indicated a shorter median time to first response at 3 months for R-CD plus bortezomib versus 5.5 months for R-CD. Both regimens were well tolerated, with grade ≥3 AEs occurring in 49.2% of participants.

The NCCN Panel has included R-CD with or without bortezomib as a treatment option under Other Recommended Regimens for Primary Therapy.

*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.[78] A single institutional retrospective study examined the outcomes of symptomatic patients with WM who received RCHOP (n = 23), cyclophosphamide/vincristine/prednisone plus rituximab (CVP-R; n = 16), 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 RCHOP ($P \leq .015$). The ORR and CR to the three regimens were: RCHOP (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 RCHOP and CVP-R versus CP-R ($P < .03$).[78]

*Maintenance Therapy*: Retrospective data supported PFS and OS benefits with maintenance rituximab after a rituximab-containing regimen.[79,80] However, a recent phase III study in WM patients who attained PR or better after six cycles of BR did not show PFS or OS benefit of maintenance rituximab over observation following induction therapy.[49] In the subset analysis, patients >65 years and patients with high IPSS risk for WM may have benefited from maintenance.[49]

### 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 Eleventh International Workshop on Waldenström's Macroglobulinemia,[81] a minor response is an IgM reduction of ≥25%; a PR is defined as a ≥50% reduction in IgM  a VGPR is a ≥90% reduction in IgM  and a CR is immunofixation negativity in the serum along with resolution of extramedullary disease and clearance of the bone marrow. Stable disease is defined as a <25% reduction and <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 Eleventh International Workshop on Waldenström's Macroglobulinemia,[81] has been



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included in the NCCN Guidelines (see *IWWM-11 Response Criteria for Assessment of Disease Response in WM/LPL* in the algorithm).

An important concern with the use of IgM as a surrogate marker of disease is that it can fluctuate independently 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 and lasts for several weeks to months.[23,70,71] Conversely, 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 persist in patients treated with selective B-cell–depleting agents such as rituximab, thus potentially skewing the relative response and assessment to treatment.[84] Therefore, in circumstances where the serum IgM levels appear to be out of context with the patient's clinical progress, 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 on *IWWM-11 Response Criteria for Assessment of Disease Response in WM/LPL* in the algorithm.

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.

If the primary treatment was with a fixed-duration chemoimmunotherapy regimen, patients should be observed for disease progression with tests including CBC, CMP, and IgM every 3 months for 2 years, then every 4–6 months for an additional 3 years, then every 6–12 months. Without symptoms, progression based on serum IgM levels alone should not be a reason to restart treatment.

If treatment is initiated with a BTKi regimen, treatment should be continued until symptomatic disease progression (beyond biochemical progression) or unacceptable toxicity. Rapid increases in IgM levels (IgM rebound) have been observed following discontinuation of BTKis. Consider continuing therapy with the BTKi until starting the next line of therapy or monitor for IgM rebound after discontinuing BTKis.

If symptoms persist or there is no response to primary treatment, an alternate therapy may be administered. If there is disease transformation, see *Histologic Transformation of Indolent Lymphomas to DLBCL* in the NCCN Guidelines for B-Cell Lymphomas.

## Therapy for Previously Treated WM

Many patients inevitably experience relapse after initial therapy and require further treatment.[85] 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 <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 HCT. 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.

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**Preferred Regimens for Previously Treated WM/LPL**

*Bendamustine/Rituximab:* Bendamustine-based therapy is effective in relapsed/refractory WM because it produces high and durable response rates. A phase II study of patients with relapsed/refractory WM who received bendamustine-based therapy reported an ORR of 83.3%.[58] The median PFS in patients with refractory WM/LPL was 13.2 months.[58] A phase I/II study analyzed the outcome of BR in patients with relapsed/refractory WM. Patients had previously received a median number of 2 lines of treatment (range 1–5). The ORR reported was 80.2%.[86] 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%; $P = .08$).[87]

Bendamustine combined with rituximab is listed as one of the preferred options for relapsed/refractory disease and single-agent bendamustine is listed under Useful in Certain Circumstances in the algorithm.

*Ibrutinib With or Without Rituximab:* 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% (10 with a VGPR, 36 with a PR, 11 with a minor response, and none with a CR) and a median time to response of 4 weeks.[88] At 5 years, the PFS and OS rates were 54% and 87%, respectively.[89] *CXCR4* mutations adversely impacted time to response, depth of response, and PFS duration. Treatment-related toxic effects of grade 3 or higher included neutropenia (in 16% of patients) and thrombocytopenia (in 11% of patients).[89]

The results of the phase III iNNOVATE trial that included patients with relapsed/refractory WM (trial details listed under *Primary Therapy for WM/LPL* in the algorithm) showed the benefit of adding ibrutinib to rituximab.

Based on the above trials, the NCCN Panel has added ibrutinib with or without rituximab as one of the Preferred Regimens for Therapy for Previously Treated WM/LPL (category 1).

*Rituximab/Cyclophosphamide/Dexamethasone*: A phase II study investigated symptomatic patients with WM (n = 100), of whom 50 patients received at least one cycle of therapy for relapsed/refractory WM and 50 patients received at least one cycle of the same regimen for newly diagnosed WM.[76] In the relapsed/refractory setting, the median PFS reported was 32 months (95% CI, 15–51) with 2- and 4-year PFS rates of 54% and 34%, respectively.[76]

The NCCN Panel has included R-CD as one of the Preferred Regimens for Therapy for Previously Treated WM/LPL.

*Zanubrutinib:* Based on the phase III ASPEN trial results that included relapsed/refractory WM (trial details listed under *Primary Therapy for WM/LPL* in the algorithm), the NCCN Panel has included zanubrutinib as one of the Preferred Regimens for Therapy for Previously Treated WM/LPL (category 1).

**Other Recommended Regimens for Previously Treated WM/LPL**

*Acalabrutinib:* Acalabrutinib is another BTKi 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 prior therapies, and 33 patients (31%) 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

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was 89% and the 24-month PFS was 82%. The most common grade 3/4 AEs were neutropenia (16%), pneumonia (7%), anemia (5%), and lower respiratory tract infection (5%).[90]

The NCCN Panel has included acalabrutinib as a treatment option under Other Recommended Regimens for Previously Treated WM/LPL.

*Bortezomib/Dexamethasone/Rituximab:* 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[59,82,83,91-93] with or without dexamethasone.[94] 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. Bortezomib/dexamethasone/rituximab is listed as one of the Other Recommended Regimens for Primary Therapy as well as Previously Treated WM/LPL.

*Ixazomib/Rituximab/Dexamethasone*: The results of a phase I/II study in patients (n = 59) who had received a median of two prior therapies treated with ixazomib/rituximab/dexamethasone showed an ORR of 71% (14% VGPR, 37% PR, and 20% minor response) after 8 cycles.[95] The median DOR reported was 36 months. The PFS and OS were 56% and 88%, respectively, after a median follow-up of 24 months.[95]

Based on these data, the NCCN Panel has included ixazomib/rituximab/dexamethasone as a treatment option under Other Recommended Regimens for Previously Treated WM/LPL.

*Rituximab/Cyclophosphamide/Prednisone:* A retrospective study examined the outcomes of patients with WM who received three separate rituximab-based regimens: RCHOP (n = 23), CVP-R (n = 16), or CP-R (n = 19).[78] The results reported the following ORR and CR rates to the regimens: RCHOP (ORR, 96%; CR, 17%); CVP-R (ORR, 88%; CR, 12%); and CP-R (ORR, 95%; CR, 0%). Therapy-related AEs such as neutropenic fever and treatment-related neuropathy were higher for RCHOP and CVP-R compared with CP-R ($P < .03$).[78]

The NCCN Panel has included CP-R as a treatment option under Other Recommended Regimens for Previously Treated WM/LPL.

*Venetoclax:* Venetoclax is an oral BCL2 antagonist approved for the treatment of CLL and 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 AE was neutropenia (42%).[97] The NCCN Panel has included venetoclax as a treatment option under Other Recommended Regimens for Previously Treated WM/LPL.

**Regimens Useful in Certain Circumstances for Previously Treated WM/LPL**

*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.[98-100] 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. Cladribine with or without rituximab is listed under Useful in Certain Circumstances for Therapy for Previously Treated WM/LPL.

*Everolimus:* Everolimus, an inhibitor of mTOR, is a potentially effective drug in treating WM, with high single-agent activity but substantial toxicity.

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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.[101] The response rate (minor response or better) was 73% with a PR rate of 50% and a minor response rate of 23%.[102] 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 frequently reported hematologic toxicities were cytopenias. Pulmonary toxicity was seen in 5% of patients.[102] The study reported that partial response to treatment was achieved after a median of 2 months. Everolimus is listed in the algorithm under *Useful in Certain Circumstances* for *Therapy for Previously Treated WM/LPL*.

*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 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), DOR (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).[103]

A prospective, multicenter trial evaluated treatment with fludarabine with rituximab in patients with WM (n = 43) who had received <2 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.[104] Fludarabine used alone or in combination with rituximab is listed in the algorithm under *Useful in Certain Circumstances* for *Therapy for Previously Treated WM/LPL.*

*Fludarabine/Cyclophosphamide/Rituximab:* A retrospective study of patients with relapsed/refractory WM reported an ORR of 80% after treatment with fludarabine, cyclophosphamide, and rituximab (FCR), with 32.5% (n = 13) of patients reaching at least a VGPR.[105] Another multicenter, prospective trial evaluated the quality of response in 43 patients with WM receiving FCR, who were either previously untreated or pretreated with chemotherapy.[106] Most of the participants in this study (65%) received FCR as first-line treatment, 28% of people 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.[107] Therefore, the NCCN Panel recommends PJP prophylaxis for those treated with the FCR regimen.

Nucleoside analogs have shown efficacy in relapsed/refractory WM/LPL either alone or in combination with rituximab.[100,104,106] All cladribine- and fludarabine-containing regimens have been listed in the algorithm under *Useful in Certain Circumstances* for *Therapy for Previously Treated WM/LPL*.

*Pirtobrutinib:* Pirtobrutinib, a highly selective, non-covalent BTKi has demonstrated favorable results in relapsed or refractory B-cell malignancies with a poor prognosis, including patients who have previously received covalent BTKis.[108] The phase I/II BRUIN study evaluated the efficacy of pirtobrutinib in individuals with WM who had received prior chemotherapy + anti-CD20 antibody, ≥1 prior BTKi, or chemotherapy + anti-CD20 antibody + BTKi. Of the response-evaluable patients (n = 72), the major response rate was 68% (95% CI, 56–79). In those who had received ≥1 prior BTKi, chemotherapy + anti-CD20 antibody, and chemotherapy + anti-CD20 antibody + BTKi, the major response rates were 64%, 68%, and 64%, respectively. The 6-month

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estimated DOR (regardless of previous treatment) was 86% (95% CI, 69–94). Two percent of patients discontinued the trial due to treatment-related AEs. Pirtobrutinib is listed in the algorithm under *Useful in Certain Circumstances* for *Therapy for Previously Treated WM/LPL*.

*Rituximab:* Treatment with single-agent rituximab has been reported to produce 40% to 50% response rates.[68,71,109] The NCCN Panel has included single-agent rituximab as a treatment option under Useful in Certain Circumstances for Previously Treated WM/LPL. For those individuals who are unable to tolerate rituximab, ofatumumab was previously listed as an option. [110] However, since it is no longer available for use in hematologic malignancies, it has been removed as an option. Results from an open-label, phase 2, single-arm study suggest that obinutuzumab may have clinical activity in WM.[111] A total of 23 patients were enrolled in the study with a median age of 66 years and a median of 1 prior treatment. The median follow-up duration was 20.7 months. The ORR at the end of induction was 52.2%, with 21.7% achieving a VGPR or better. The PFS and OS rates at 18 months were 68% and 90%, respectively. AEs occurred in 95.7% of patients, with the most common being infections, neutropenia, and thrombocytopenia. Severe AEs occurred in 69.6% of patients, and two deaths were reported, one due to cardiac insufficiency and another related to COVID-19. The NCCN Panel consensus was to add obinutuzumab as an option for consideration in patients who are unable to tolerate rituximab.

*RCHOP:* RCHOP is a stem cell–sparing regimen reported to be active and tolerated by patients with WM.[78,112,113] It has been reported as having a ≥90% response rate in patients with WM.[78,113,114] 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.[113] The addition of vincristine to cyclophosphamide-containing regimens is associated with risk of neuropathy in patients with WM.[61] 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), may be considered if cyclophosphamide-based therapy is being considered.

**Hematopoietic Cell Transplant**

HCT is also an option for relapsed WM in selected patients.[115-117] HCT options listed in the NCCN Guidelines for WM/LPL are for high-dose therapy with autologous stem cell rescue.[115,116] According to the NCCN Panel, myeloablative or non-myeloablative allogeneic HCT may be considered,[115] but in the context of a clinical trial.

## Management of Bing-Neel Syndrome

Bing-Neel syndrome (BNS) is a rare manifestation of WM that results in the migration of LPCs to the central nervous system (CNS).[118,119] Neurologic deficits concerning BNS include but are not limited to headaches, seizures, cranial nerve palsies, weakness in limbs, and atypical neuropathy. Differential diagnosis of BNS includes hyperviscosity syndrome (HVS) with CNS manifestation, which can present as new onset of neurologic symptoms such as headaches, visual impairment, and nose bleeds.[120,121] HVS with CNS involvement can be differentiated from BNS by confirming an appropriate increase in serum IgM consistent with levels detected in those with WM, in conjunction with abnormal imaging and/or the presence of clonal B cells in CSF or cerebral tissue.[122] Diagnostic criteria and workup of BNS includes histology, CSF analysis, molecular testing, radiology, and blood analysis.[120] Neuroimaging is encouraged in order to exclude differential diagnosis and aid in the selection of an appropriate site for biopsy.[120] Two forms of CNS involvement (diffuse and tumoral) can be best evaluated after gadolinium administration and MRI.[120] The diffuse form is associated with infiltration of lymphoid cells in the

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leptomeningeal sheath and perivascular space. This form presents as an enhancement or thickening of the meningeal sheath. Conversely, the tumoral form can be multifocal or unifocal and is found deep in the subcortical hemisphere.[120] CNS lymphoma histology cannot be detected on an MRI and thus BNS cannot be excluded in the absence of MRI findings. Diagnostic criteria for BNS include histologic biopsy of the cerebrum or meninges positive for clonal B cells with morphologic evidence of LPL. Analysis of the CSF should include cell count and differentiation, morphologic analysis, flow cytometry, and molecular testing to increase the sensitivity for detecting the presence of malignant B cells in the CSF. Analysis of CSF should be done routinely and should not precede the MRI to eliminate CSF sampling-induced meningeal enhancement.[120] Ig gene rearrangement assays can also be performed to determine clonal characteristics of a B-cell population. In addition, mutations in *MYD88* with an amino acid point mutation L265P have been detected in 93% to 97% of individuals with WM, using highly sensitive diagnostic techniques such as allele-specific PCR.[120] Definitive diagnosis of BNS includes presence of clonal B cells in CSF or within a tissue biopsy with a typical manifestation and presentation of systemic disease. Diagnosis can be confirmed with or without leptomeningeal enhancement or masses detected with an MRI. A probable diagnosis is made with abnormal MRI findings without evidence of clonal B cells in CSF or tissue biopsy.

If a person has abnormal test results but remains asymptomatic, their treatment will continue with routine observation. If a person is symptomatic, various systemic therapy options are recommended; preferred regimens include BTKis such as ibrutinib[123] and zanubrutinib. Other recommended regimens include chemotherapy agents such as bendamustine, cytarabine, fludarabine, and methotrexate. Regimens useful in certain circumstances include intrathecal methotrexate and radiotherapy. If systemic control is needed, rituximab can be added to any of the above regimens. BNS is a rare and usually a late manifestation in those with WM. It can develop when a person is in remission or less typically at the beginning of disease manifestation.[124] When BNS develops later in the disease, it is usually associated with a worse prognosis.[120,125]

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