

Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Treatment Regimens

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced health care team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are provided only to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data become available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

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

► Primary Therapy for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma (WM/LPL)^{1,a}

| REGIMEN | DOSING |
|---|---|
| Preferred Regimens | |
| Bendamustine + Rituximab ^{2-5,b,c,f} | <p>Days 1,2: Bendamustine 90mg/m² IV over 10-60 minutes daily Day 1 or 2: Rituximab 375mg/m² IV. Repeat cycle every 4 weeks cycle for 6 cycles.</p> <p>OR</p> <p>Days 1,2: Bendamustine 70mg/m² IV over 10-60 minutes daily (if advanced age, previously received nucleoside analogue, renal insufficiency) Day 1 or 2: Rituximab 375mg/m² IV. Repeat cycle every 4 weeks cycle for 6 cycles.</p> |
| Bortezomib + Dexamethasone + Rituximab ^{5-7,c-i} | <p>Days 1,4,8,11: Bortezomib 1.3mg/m² subcutaneous Days 1,4,8,11: Dexamethasone 20-40mg orally or IV Day 11: Rituximab 375mg/m² IV. Repeat cycle every 3 weeks for 4 cycles, followed by: Days 1,4,8,11: Bortezomib 1.3mg/m² subcutaneous Days 1,4,8,11: Dexamethasone 20-40mg orally or IV Day 11: Rituximab 375mg/m² IV. Repeat cycle every 12 weeks for 4 cycles starting 12 weeks after completion of the four 3-week cycles above.</p> |
| Ibrutinib (Category 1) ^{8-10,j} | <p>Days 1-28: Ibrutinib 420mg orally once daily. Repeat cycle every 4 weeks.</p> |
| Ibrutinib ⁱ + Rituximab (Category 1) ^{5,8,11} | <p>Days 1-28: Ibrutinib 420mg orally once daily Days 1,8,15,22 (Cycles 1 and 5): Rituximab 375mg/m² IV. Repeat cycle every 4 weeks for 5 cycles, followed by: Days 1-28: Ibrutinib 420mg orally daily. Repeat cycle every 4 weeks.</p> |
| Rituximab + Cyclophosphamide + Dexamethasone ^{5,12,13,c-f} | <p>Days 1-5: Cyclophosphamide 100mg/m² orally twice daily Day 1: Dexamethasone 20mg IV or orally Day 1: Rituximab 375mg/m² IV. Repeat cycle every 3 weeks for 6 cycles.</p> <p>OR</p> <p>Days 1-5: Cyclophosphamide 100mg/m² orally once daily Day 1: Dexamethasone 20mg IV or orally Day 1: Rituximab 375mg/m² IV. Repeat cycle every 3 weeks for 6 cycles.</p> |
| Zanubrutinib (Category 1) ^{14,15,j} | <p>Days 1-28: Zanubrutinib 160 mg orally twice daily. Repeat cycle every 4 weeks.</p> |
| Other Recommended Regimens | |
| Bendamustine ^{16,17} | <p>Days 1-2: Bendamustine 90mg/m² IV over 10-60 minutes daily. Repeat cycle every 4 weeks for 6 cycles.</p> <p>OR</p> <p>Days 1-2: Bendamustine 70mg/m² IV over 10-60 minutes daily (if advanced age, previously received nucleoside analogue, renal insufficiency). Repeat cycle every 4 weeks for 6 cycles.</p> |

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Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Treatment Regimens

► Primary Therapy for WM/LPL^{1,a} (continued)

| REGIMEN | DOSING |
|---|---|
| Other Recommended Regimens (continued) | |
| Bortezomib ^{6,18-20,g-i} | <p>Days 1,4,8,11: Bortezomib 1.3mg/m² IV subcutaneous. Repeat cycle every 3 weeks for 8 cycles.</p> <p>OR</p> <p>Days 1,8,15: Bortezomib 1.6mg/m² IV subcutaneous. Repeat cycle every 4 weeks for 6 cycles.</p> |
| Bortezomib + Dexamethasone ^{6,7,19-21,g,h} | <p>Days 1,4,8,11: Bortezomib 1.3mg/m² subcutaneous Days 1,4,8,11: Dexamethasone 20-40mg orally or IV. Repeat cycle every 3 weeks for 8 cycles.</p> <p>OR</p> <p>Days 1,8,15: Bortezomib 1.6mg/m² subcutaneous Days 1,8,15: Dexamethasone 20-40mg orally or IV. Repeat cycle every 4 weeks for 6 cycles.</p> <p>OR</p> <p>Days 1,8,15,22: Bortezomib 1.6mg/m² subcutaneous Days 1,8,15,22: Dexamethasone 20-40mg orally or IV. Repeat cycle every 5 weeks for 6 cycles.</p> |
| Bortezomib + Rituximab ^{6,20-22,c-i} | <p>Days 1,8,15: Bortezomib 1.6mg/m² IV subcutaneous Days 1,8,15,22 (Cycles 1 and 4): Rituximab 375mg/m² IV. Repeat cycle every 4 weeks for 6 cycles.</p> <p>OR</p> <p>Days 1,8,15,22: Bortezomib 1.6mg/m² IV subcutaneous Days 1,8,15,22 (Cycles 1 and 4): Rituximab 375mg/m² IV. Repeat cycle every 5 weeks for 6 cycles.</p> <p>OR</p> <p>Days 1,4,8,11: Bortezomib 1.3mg/m² IV subcutaneous Day 1: Rituximab 375mg/m² IV. Repeat cycle every 3 weeks for 6 cycles.</p> |
| Carfilzomib + Dexamethasone + Rituximab ^{23,24,c,g,k} | <p>Days 1-2,8-9: Carfilzomib 20mg/m² (maximum 44 mg) IV over 20 minutes daily Days 1-2,8-9: Dexamethasone 20mg orally or IV daily. Days 2,9: Rituximab 375mg/m² IV. Administer induction therapy for one 3-week cycle, followed by: Days 1-2,8-9: Carfilzomib 36mg/m² (maximum 79.2mg) IV over 30 minutes daily Days 1-2,8-9: Dexamethasone 20mg orally or IV daily Days 2,9: Rituximab 375 mg/m² IV. Repeat cycle every 3 weeks for 5 cycles (beginning with cycle 2), followed by maintenance therapy with: Days 1-2: Carfilzomib 36mg/m² (maximum 79.2mg) IV over 30 minutes daily Days 1-2: Dexamethasone 20mg orally or IV daily Day 2: Rituximab 375mg/m² IV. Repeat cycle every 8 weeks for 8 cycles beginning 8 weeks after completion of induction.</p> |
| Cladribine ^{25-28,g,l,m} | <p>Days 1-5: Cladribine 0.12mg/kg IV over 2 hours daily. Repeat cycle every 4 weeks for 2-4 cycles.</p> <p>OR</p> <p>Days 1-5: Cladribine 0.1mg/kg subcutaneous daily. Repeat cycle every 4 weeks for 2-4 cycles.</p> |
| Cladribine + Rituximab ^{5,25,29,c,g,l,m} | <p>Day 1: Rituximab 375mg/m² IV, followed by: Days 1-5: Cladribine 0.1mg/kg subcutaneous daily. Repeat cycle for 4 cycles for 2-4 cycles.</p> |
| Fludarabine ^{30-32,g,l,m} | <p>Days 1-5: Fludarabine 25-30mg/m² IV over 30 minutes daily. Repeat cycle every 4 weeks for 4-6 cycles.</p> |
| Fludarabine + Cyclophosphamide + Rituximab ^{3,33,34,b-g,l,m} | <p>Days 1-3: Fludarabine 25mg/m² IV over 30 minutes daily Days 1-3: Cyclophosphamide 250mg/m² IV over 30 minutes Day 1: Rituximab 375mg/m² IV. Repeat cycle every 4 weeks for 4-6 cycles.</p> |

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Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Treatment Regimens

► Primary Therapy for WM/LPL^{1,a} (continued)

| REGIMEN | DOSING |
|--|--|
| Other Recommended Regimens (continued) | |
| Fludarabine + Rituximab ^{5,35,36,c,g,l,m} | Days 1-5: Fludarabine 25mg/m ² IV over 30 minutes daily Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 4 weeks for 4-6 cycles. |
| Ixazomib ⁱ + Dexamethasone + Rituximab ^{5,37,38,c,g} | Days 1,8,15: Ixazomib 4mg orally once daily Days 1,8,15: Dexamethasone 20 mg orally or IV. Repeat cycle every 4 weeks for 2 cycles, followed by: Days 1,8,15: Ixazomib 4mg orally once daily Days 1,8,15: Dexamethasone 20mg orally or IV Day 1: Rituximab 375 mg/m ² IV. Repeat cycle every 4 weeks for 4 cycles beginning with cycle 3 (cycles 3-6) |
| Rituximab ^{5,39-41,c-f} | Day 1: Rituximab 375 mg/m ² IV. Administer for one 4-week cycle; may repeat cycle after 3 months for a total of 8 doses. |
| Rituximab + Cyclophosphamide + Prednisone ^{5,42,c-f} | Day 1: Cyclophosphamide 1000mg/m ² IV over 30 minutes Days 1-5: Prednisone 100mg orally once daily Day 1: Rituximab 375 mg/m ² IV. Repeat cycle every 3 weeks for 6 cycles. |

► Therapy for Previously Treated WM/LPL^{1,a}

| Preferred Regimens | |
|---|--|
| Bendamustine + Rituximab ^{2,5,b-f} | Days 1,2: Bendamustine 90mg/m ² IV over 10-60 minutes daily Day 1 or 2: Rituximab 375mg/m ² IV. Repeat cycle every 4 weeks cycle for 6 cycles. OR Days 1,2: Bendamustine 70mg/m ² IV over 10-60 minutes daily (if advanced age, previously received nucleoside analogue, renal insufficiency) Day 1 or 2: Rituximab 375mg/m ² IV. Repeat cycle every 4 weeks cycle for 6 cycles. |
| Bortezomib + Dexamethasone + Rituximab ^{5,7,c-i} | Days 1,4,8,11: Bortezomib 1.3mg/m ² subcutaneous Days 1,4,8,11: Dexamethasone 20-40mg orally or IV Day 11: Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for 4 cycles, followed by: Days 1,4,8,11: Bortezomib 1.3mg/m ² subcutaneous Days 1,4,8,11: Dexamethasone 20-40mg orally or IV Day 11: Rituximab 375mg/m ² IV. Repeat cycle every 12 weeks for 4 cycles starting 12 weeks after completion of the four 3-week cycles above. |
| Ibrutinib (Category 1) ^{8,10,j} | Days 1-28: Ibrutinib 420mg orally daily. Repeat cycle every 4 weeks. |
| Ibrutinib ⁱ + Rituximab (Category 1) ^{5,8,11,c-f} | Days 1-28: Ibrutinib 420mg orally daily Days 1,8,15,22 (Cycles 1 and 5): Rituximab 375mg/m ² IV. Repeat cycle every 4 weeks for 5 cycles, followed by: Days 1-28: Ibrutinib 420mg orally daily. Repeat cycle every 4 weeks. |
| Rituximab + Cyclophosphamide + Dexamethasone ^{5,12,13,c-f} | Days 1-5: Cyclophosphamide 100mg/m ² orally twice daily Day 1: Dexamethasone 20mg IV or orally Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for 6 cycles. OR Days 1-5: Cyclophosphamide 100mg/m ² orally once daily Day 1: Dexamethasone 20mg IV or orally Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for 6 cycles. |
| Zanubrutinib (Category 1) ^{14,15,i} | Days 1-28: Zanubrutinib 160mg orally twice daily. Repeat cycle every 4 weeks. |

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Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Treatment Regimens

► Therapy for Previously Treated WM/LPL^{1,a} (continued)

| REGIMEN | DOSING |
|--|--|
| Other Recommended Regimens | |
| Acalabrutinib ^{43,44,j} | Days 1-28: Acalabrutinib 100mg orally twice daily. Repeat cycle every 4 weeks. |
| Bendamustine ^{16,17} | Days 1-2: Bendamustine 90mg/m ² IV over 10-60 minutes daily. Repeat cycle every 4 weeks for 6 cycles. OR Days 1-2: Bendamustine 70mg/m ² IV over 10-60 minutes daily (if advanced age, previously received nucleoside analogue, renal insufficiency). Repeat cycle every 4 weeks for 6 cycles. |
| Bortezomib ^{6,18-20,g,i} | Days 1,4,8,11: Bortezomib 1.3mg/m ² IV subcutaneous. Repeat cycle every 3 weeks for 8 cycles. OR Days 1,8,15: Bortezomib 1.6mg/m ² IV subcutaneous. Repeat cycle every 4 weeks for 6 cycles. |
| Bortezomib + Dexamethasone ^{6,7,19-21,g,h} | Days 1,4,8,11: Bortezomib 1.3mg/m ² subcutaneous Days 1,4,8,11: Dexamethasone 20-40mg orally or IV. Repeat cycle every 3 weeks for 8 cycles. OR Days 1,8,15: Bortezomib 1.6mg/m ² subcutaneous Days 1,8,15: Dexamethasone 20-40mg orally or IV. Repeat cycle every 4 weeks for 6 cycles. OR Days 1,8,15,22: Bortezomib 1.6mg/m ² subcutaneous Days 1,8,15,22: Dexamethasone 20-40mg orally or IV. Repeat cycle every 5 weeks for 6 cycles. |
| Bortezomib + Rituximab ^{6,20-22,c-i} | Days 1,8,15: Bortezomib 1.6mg/m ² IV subcutaneous Days 1,8,15,22 (Cycles 1 and 4): Rituximab 375mg/m ² IV. Repeat cycle every 4 weeks for 6 cycles. OR Days 1,8,15,22: Bortezomib 1.6mg/m ² IV subcutaneous Days 1,8,15,22 (Cycles 1 and 4): Rituximab 375mg/m ² IV. Repeat cycle every 5 weeks for 6 cycles. OR Days 1,4,8,11: Bortezomib 1.3mg/m ² IV subcutaneous Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for 6 cycles. |
| Cladribine ^{25-28,g,l,m} | Days 1-5: Cladribine 0.12mg/kg IV over 2 hours daily. Repeat every 4 weeks for 2-4 cycles. OR Days 1-5: Cladribine 0.1mg/kg subcutaneous daily. Repeat cycle every 4 weeks for 2-4 cycles. |
| Cladribine + Rituximab ^{5,25,29,c-g,l,m} | Day 1: Rituximab 375mg/m ² IV, followed by: Days 1-5: Cladribine 0.1mg/kg subcutaneous daily. Repeat cycle every 4 weeks for 2-4 cycles. |
| CHOP (Cyclophosphamide + Doxorubicin + Vincristine + Prednisone) ^{5,42,h,l,m} | Day 1: Cyclophosphamide 750mg/m ² IV over 30 minutes Day 1: Doxorubicin 50mg/m ² IV push Day 1: Vincristine 1.4mg/m ² (maximum 2 mg) IV over 5-10 minutes. Days 1-5: Prednisone 100mg orally once daily. Repeat cycle every 3 weeks for 6-8 cycles. |
| CHOP (Cyclophosphamide + Doxorubicin + Vincristine + Prednisone) + Rituximab ^{5,42,c-t,h,l,m} | Day 1: Cyclophosphamide 750mg/m ² IV over 30 minutes Day 1: Doxorubicin 50mg/m ² IV push Day 1: Vincristine 1.4mg/m ² (maximum 2mg) IV over 5-10 minutes. Days 1-5: Prednisone 100mg orally once daily Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for 6-8 cycles. |
| Fludarabine ^{30-32,g,l,m} | Days 1-5: Fludarabine 25-30mg/m ² IV over 30 minutes daily. Repeat cycle every 4 weeks for 4-6 cycles. |

continued

Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Treatment Regimens

► Therapy for Previously Treated WM/LPL^{1,a} (continued)

| REGIMEN | DOSING |
|--|---|
| Other Recommended Regimens (continued) | |
| Fludarabine + Cyclophosphamide + Rituximab ^{5,33,34,b-g,i,m} | Days 1-3: Fludarabine 25mg/m ² IV over 30 minutes daily Days 1-3: Cyclophosphamide 250mg/m ² IV over 30 minutes Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 4 weeks for 4-6 cycles. |
| Fludarabine + Rituximab ^{5,35,36,c-g,i,m} | Days 1-5: Fludarabine 25mg/m ² IV over 30 minutes daily Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 4 weeks for 4-6 cycles. |
| Rituximab ^{5,39-41,c-f} | Day 1: Rituximab 375mg/m ² IV. Administer for one 4-week cycle; may repeat cycle after 3 months for a total of 8 doses. |
| Rituximab + Cyclophosphamide + Prednisone ^{5,42,c-f} | Day 1: Cyclophosphamide 1000mg/m ² IV over 30 minutes Days 1-5: Prednisone 100mg orally once daily Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for 6 cycles. |
| Useful in Certain Circumstances | |
| Everolimus ^{45-47j} | Days 1-28: Everolimus 10 mg orally once daily. Repeat cycle every 4 weeks. |
| Ofatumumab (for Rituximab-intolerant individuals) ^{48-50,f,n} | Day 1 (Cycle 1): Ofatumumab 300mg IV Administer for one weekly cycle, followed by: Day 1 (Cycle 2 and beyond): Ofatumumab 1,000 mg IV. Repeat cycle every week for 3 cycles OR Day 1 (Cycle 1): Ofatumumab 300mg IV Administer for one weekly cycle, followed by: Day 1 (Cycle 2 and beyond): Ofatumumab 2,000mg IV. Repeat cycle every week for 4 cycles. |
| Hematopoietic Cell Transplant^a | |

In selected cases HCT may be appropriate with either:

- Allogeneic stem cell transplant (ablative or nonablative): ideally undertaken in the context of a clinical trial.
- Autologous stem cell transplant

^a AML = acute myeloid leukemia; HCT = hematopoietic cell transplantation; MDS = myelodysplastic syndrome.

^b *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis should be considered for patients receiving bendamustine/rituximab or fludarabine/cyclophosphamide/rituximab.

^c Premedication for hypersensitivity reactions is required. The recommended regimen includes diphenhydramine and acetaminophen.

^d An FDA-approved biosimilar is an appropriate substitute for rituximab.

^e 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.⁵¹⁻⁵⁵

^f Prophylactic antiviral therapy with entecavir is recommended for any patient who is HgsAg-positive and receiving anti-CD20 therapy.

^g Administer herpes zoster prophylaxis for all patients treated with proteasome inhibitors and nucleoside analogs.

^h 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.

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

^j This agent has multiple drug-drug and/or drug-food interactions.

^k Carfilzomib can potentially cause cardiac and pulmonary toxicity, especially in elderly patients. Premedication (dexamethasone) for infusion reactions is required.

^l Exposure to nucleoside analogs (fludarabine and cladribine) should be avoided in patients who may be potential autologous HCT candidates.

^m Nucleoside analogs may be associated with disease transformation and/or development of MDS/AML in patients with Waldenström macroglobulinemia.

ⁿ 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. Premedication (diphenhydramine; acetaminophen; prednisolone) for hypersensitivity and/or infusion reactions is required.

References

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Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Treatment Regimens

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