

B-Cell Lymphomas Treatment Regimens: Follicular Lymphoma (Grade 1-2)

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.

► First Line Therapy^{1,a}

REGIMEN	DOSING
Preferred Regimens^b	
Bendamustine + Obinutuzumab ^{2,5,c-d}	<p>Day 1-2: Bendamustine 90mg/m² IV over 10-30 minutes</p> <p>Days 1,8,15 (Cycle 1): Obinutuzumab 1000mg IV, followed by:</p> <p>Day 1 (Cycles 2-6): Obinutuzumab 1000mg IV.</p> <p>Repeat cycle every 4 weeks for 6 cycles, followed by maintenance therapy with:</p> <p>Day 1: Obinutuzumab 1000mg IV.</p> <p>Repeat cycle every 8 weeks for a maximum of 2 years.</p>
Bendamustine + Rituximab ^{2,6-8,d,f}	<p>Days 1-2: Bendamustine 90mg/m² IV over 10-30 minutes</p> <p>Day 1: Rituximab 375mg/m² IV.</p> <p>Repeat cycle every 4 weeks for 6 cycles.</p>
CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) + Obinutuzumab ^{3,9-13,c,g-i}	<p>Day 1: Cyclophosphamide 750mg/m² IV over 30 minutes</p> <p>Day 1: Doxorubicin 50mg/m² IV push</p> <p>Day 1: Vincristine 1.4mg/m² (maximum 2mg) IV over 5-10 minutes</p> <p>Days 1-5: Prednisone 100mg orally once daily</p> <p>Days 1,8,15 (Cycle 1): Obinutuzumab 1,000mg IV, followed by:</p> <p>Day 1 (Cycles 2-6): Obinutuzumab 1,000mg IV.</p> <p>Repeat cycle every 3 weeks for 6 cycles.</p>
CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) + Rituximab ^{6,9-12,14,15,f,j}	<p>Day 1: Cyclophosphamide 750mg/m² IV over 30 minutes</p> <p>Day 1: Doxorubicin 50mg/m² IV push</p> <p>Day 1: Vincristine 1.4mg/m² (maximum 2mg) IV over 5-10 minutes</p> <p>Days 1-5: Prednisone 100mg orally once daily</p> <p>Day 1: Rituximab 375mg/m² IV.</p> <p>Repeat cycle every 3 weeks for 6-8 cycles.</p>
CVP (Cyclophosphamide, Vincristine, Prednisone) + Obinutuzumab ^{3,9-13,c,g-i}	<p>Day 1: Cyclophosphamide 750mg/m² IV over 30 minutes</p> <p>Day 1: Vincristine 1.4mg/m² (maximum 2mg) IV over 5-10 minutes</p> <p>Days 1-5: Prednisone 100mg orally once daily</p> <p>Days 1,8,15 (Cycle 1): Obinutuzumab 1000mg IV, followed by:</p> <p>Day 1 (Cycles 2-6): Obinutuzumab 1000mg IV.</p> <p>Repeat cycle every 3 weeks for 8 cycles.</p>
CVP (Cyclophosphamide, Vincristine, Prednisone) + Rituximab ^{6,9-12,16-18,f,i}	<p>Day 1: Cyclophosphamide 750mg/m² IV over 30 minutes OR</p> <p>Day 1: Cyclophosphamide 1,000mg/m² IV over 30 minutes.</p> <p>Day 1: Vincristine 1.4mg/m² (maximum 2mg) IV over 5-10 minutes</p> <p>Days 1-5: Prednisone 100mg orally once daily</p> <p>Day 1: Rituximab 375mg/m² IV.</p> <p>Repeat every 3 weeks for 6-8 cycles.</p>

continued

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► First Line Therapy^{1,a} (continued)

REGIMEN	DOSING
Preferred Regimens^b (continued)	
Lenalidomide + Rituximab ^{6,19-22,f,k}	<p>Days 2-22: Lenalidomide 20mg orally once daily Days 1,8,15,22 (Cycle 1): Rituximab 375mg/m² IV, followed by: Day 1 (Cycles 2-6): Rituximab 375mg/m² IV. Repeat cycle every 4 weeks for 6 cycles, conditionally followed by: Days 1-28: Lenalidomide 10mg once daily (for patients achieving a complete response [CR]). Repeat cycle every 4 weeks for 12 cycles, with: Day 1: Rituximab 375 mg/m² IV. Repeat cycle every 8 weeks for 6 cycles.</p> <p>OR</p> <p>Days 2-22: Lenalidomide 20mg orally once daily Days 1,8,15,22 (Cycle 1): Rituximab 375mg/m² IV, followed by: Day 1 (Cycles 2-6): Rituximab 375mg/m² IV Repeat cycle every 4 weeks for 6 cycles, conditionally followed by: Days 1-28: Lenalidomide 20mg orally once daily (for patients achieving a partial response [PR] until CR is achieved), followed by: Days 1-28: Lenalidomide 10mg orally once daily to complete a total of 12 cycles. Repeat cycle every 4 weeks for 3-6 cycles until complete clinical response followed by 6-9 cycles after CR achieved, with: Day 1: Rituximab 375mg/m² IV. Repeat every 8 weeks for 6 cycles.</p>
Other Recommended Regimens	
Lenalidomide + Obinutuzumab (Category 2B) ^{3,19,23,24,c,k}	<p>Days 1-21 (Cycles 1-6): Lenalidomide 20mg orally once daily Days 1,8,15 (Cycle 1): Obinutuzumab 1000mg IV, followed by: Day 1 (Cycles 2-6): Obinutuzumab 1000mg IV. Repeat cycle every 4 weeks for 6 cycles, followed by: Days 1-21 (Cycles 7-18): Lenalidomide 10mg orally once daily Day 1 (odd numbered cycles beginning with Cycle 7): Obinutuzumab 1000mg IV. Repeat cycle every 4 weeks for a maximum of 12 cycles, followed by: Day 1: Obinutuzumab 1000mg IV. Repeat cycle every 8 weeks for 6 cycles.</p>
Rituximab (consider for low tumor burden) ^{6,25-27f}	<p>Days 1,8,15,22: Rituximab 375mg/m² IV. Administer for one 4-week cycle.</p>

► First-Line Therapy for Elderly or Infirm (if none of the above regimens are expected to be tolerable in the opinion of the treating physician)^{1,a}

Preferred Regimens	
Rituximab ^{6,25-27f}	<p>Days 1,8,15,22: Rituximab 375mg/m² IV. Administer for one 4-week cycle.</p>
Other Recommended Regimens	
Chlorambucil ^{28-30,j}	<p>Days 1-28: Chlorambucil 0.1mg/kg orally once daily. Repeat cycle every 4 weeks.</p> <p>OR</p> <p>Day 1: Chlorambucil 40mg/m² orally once daily. Repeat cycle every 4 weeks.</p>
Chlorambucil + Rituximab ^{6,28,31,32,f,i}	<p>Days 1,8,15,22: Rituximab 375mg/m² IV, with: Day 1-42: Chlorambucil 6mg/m² IV orally once daily. Administer for one 6-week cycle, conditionally followed by consolidation therapy with: Day 1: Rituximab 375mg/m² IV, with: Days 1-14: Chlorambucil 6mg/m² IV orally once daily. Repeat cycle every 4 weeks for 4 cycles (for patients who have had a response after first cycle).</p>
Cyclophosphamide ^{9,33,i}	<p>Days 1-28: Cyclophosphamide 50-100mg/m² orally once daily. Repeat cycle every 4 weeks.</p>

continued

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► First-Line Therapy for Elderly or Infirm (if none of the above regimens are expected to be tolerable in the opinion of the treating physician)^{1,a} (continued)

REGIMEN	DOSING
Other Recommended Regimens (continued)	
Cyclophosphamide + Rituximab ^{6,9,33,f,i}	Day 1: Rituximab 375mg/m ² IV Day 1: Cyclophosphamide 750mg/m ² IV over 30 minutes OR Day 1: Cyclophosphamide 1000mg/m ² IV over 30 minutes. Repeat cycle every 3 weeks for 6-8 cycles.
Ibritumomab tiuxetan (Category 2B) ^{34,35,m}	See NCCN B-Cell Lymphoma guidelines (Follicular Lymphoma [grade 1-2]) ¹

► First-Line Consolidation or Extended Dosing (optional)^{1,a}

Preferred Regimens Following Chemoimmunotherapy	
Rituximab Maintenance (Category 1; for patients initially presenting with high tumor burden) ^{6,36-38,f}	Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 8-12 weeks for 2 years.
Obinutuzumab Maintenance ^{3-5,c}	Day 1: Obinutuzumab 1000mg IV. Repeat cycle every 8 weeks for 12 doses.
Other Recommended Regimens	
Rituximab Consolidation (if initially treated with single-agent Rituximab) ^{6,36-38,f}	Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 8 weeks for 4 cycles.
Ibritumomab tiuxetan (Category 2B) ^{34,35,m}	See NCCN B-Cell Lymphoma guidelines (Follicular Lymphoma [grade 1-2]) ¹

► Second-Line and Subsequent Therapy^{1,a}

Preferred Regimens ^b	
Bendamustine + Obinutuzumab (not recommended for patients treated with prior Bendamustine) ^{2-5,c-e,n}	Day 1-2: Bendamustine 90mg/m ² IV over 10-30 minutes Days 1,8,15 (Cycle 1): Obinutuzumab 1000mg IV, followed by: Day 1 (Cycles 2-6): Obinutuzumab 1000mg IV. Repeat cycle every 4 weeks for 6 cycles, followed by maintenance therapy with: Day 1: Obinutuzumab 1000mg IV. Repeat cycle every 8 weeks for a maximum of 2 years.
Bendamustine + Rituximab (not recommended for patients treated with prior Bendamustine) ^{2,6-8,d,f}	Days 1-2: Bendamustine 90mg/m ² IV over 10-30 minutes Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 4 weeks for 6 cycles.
CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) + Obinutuzumab ^{3,9-13,c,g,i,n}	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 Days 1,8,15 (Cycle 1): Obinutuzumab 1,000mg IV, followed by: Day 1 (Cycles 2-6): Obinutuzumab 1,000mg IV. Repeat cycle every 3 weeks for 6 cycles.
CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) + Rituximab ^{6,9-12,14,15,f,j}	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.
CVP (Cyclophosphamide, Vincristine, Prednisone) + Obinutuzumab ^{3,9-13,c,g-1,n}	Day 1: Cyclophosphamide 750mg/m ² IV over 30 minutes Day 1: Vincristine 1.4mg/m ² (maximum 2mg) IV over 5-10 minutes Days 1-5: Prednisone 100mg orally once daily Days 1,8,15 (Cycle 1): Obinutuzumab 1000mg IV, followed by: Day 1 (Cycles 2-6): Obinutuzumab 1000mg IV. Repeat cycle every 3 weeks for 8 cycles.

continued

B-Cell Lymphomas Treatment Regimens: Follicular Lymphoma (Grade 1-2)

► Second-Line and Subsequent Therapy^{1,a} (continued)

REGIMEN	DOSING
Preferred Regimens^o (continued)	
CVP (Cyclophosphamide, Vincristine, Prednisone) + Rituximab ^{6,9-12,16-18,f,i}	Day 1: Cyclophosphamide 750mg/m ² IV over 30 minutes OR Day 1: Cyclophosphamide 1,000mg/m ² IV over 30 minutes 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 every 3 weeks for 6-8 cycles.
Lenalidomide + Rituximab ^{6,19,39,f,k}	Days 1-21 (Cycles 1-12): Lenalidomide 20mg orally once daily. Day 1,8,15,22 (Cycle 1): Rituximab 375mg/m ² IV, followed by: Day 1 (Cycles 2-5): Rituximab 375mg/m ² IV. Repeat cycle every 4 weeks for 12 cycles.
Other Recommended Regimens^o	
Ibritumomab tiuxetan ^{34,40,41,m}	See NCCN B-Cell Lymphoma guidelines (Follicular Lymphoma [grade 1-2]) ¹
Lenalidomide (if not a candidate for anti-CD20 monoclonal antibody therapy) ^{19,42,k}	Days 1-21: Lenalidomide 25mg orally once daily. Repeat cycle every 4 weeks for 12 cycles.
Lenalidomide + Obinutuzumab ^{3,19,23,24,c,k}	Days 1-21 (Cycles 1-6): Lenalidomide 20mg orally once daily. Days 1,8,15 (Cycle 1): Obinutuzumab 1000mg IV, followed by: Day 1 (Cycles 2-6): Obinutuzumab 1000mg IV. Repeat cycle every 4 weeks for 6 cycles, followed by: Days 1-21 (Cycles 7-18): Lenalidomide 10mg orally once daily Day 1 (odd numbered cycles beginning with Cycle 7): Obinutuzumab 1000mg IV. Repeat cycle every 4 weeks for a maximum of 12 cycles, followed by: Day 1: Obinutuzumab 1000mg IV. Repeat cycle every 8 weeks for 6 cycles.
Obinutuzumab ^{3,43,c}	Days 1,8,15,22: Obinutuzumab 1000mg IV. Administer for one 4-week cycle, conditionally followed by: Day 1: Obinutuzumab 1,000mg IV. Repeat cycle every 8 weeks for a maximum of 12 cycles (stable disease or objective response to therapy).
Rituximab ^{6,25-27,l}	Days 1,8,15,22: Rituximab 375mg/m ² IV. Administer for one 4-week cycle.

► Second-Line and Subsequent Therapy for Elderly or Infirm (if none of the above regimens are expected to be tolerable in the opinion of the treating physician)^{1,a}

Preferred Regimens	
Rituximab ^{6,25-27,l}	Days 1,8,15,22: Rituximab 375mg/m ² IV. Administer for one 4-week cycle.
Other Recommended Regimens	
Chlorambucil ^{28-30,i}	Days 1-28: Chlorambucil 0.1mg/kg orally once daily. Repeat cycle every 4 weeks. OR Day 1: Chlorambucil 40mg/m ² orally once daily. Repeat cycle every 4 weeks.
Chlorambucil + Rituximab ^{6,28,31,32,f,i}	Days 1,8,15,22: Rituximab 375mg/m ² IV, with: Day 1-42: Chlorambucil 6mg/m ² IV orally once daily. Administer for one 6-week cycle, followed by consolidation therapy with: Day 1: Rituximab 375mg/m ² IV Days 1-14: Chlorambucil 6mg/m ² IV orally once daily. Repeat cycle every 4 weeks for 4 cycles (for patients who have had a response after first cycle).
Cyclophosphamide ^{9,33,i}	Days 1-28: Cyclophosphamide 50-100mg/m ² orally once daily. Repeat cycle every 4 weeks.

continued

B-Cell Lymphomas Treatment Regimens: Follicular Lymphoma (Grade 1-2)

▶ Second-Line and Subsequent Therapy for Elderly or Infirm (if none of the above regimens are expected to be tolerable in the opinion of the treating physician)^{1,a} (continued)

REGIMEN	DOSING
Other Recommended Regimens (continued)	
Cyclophosphamide + Rituximab ^{6,9,33,f,i}	Day 1: Rituximab 375mg/m ² IV Day 1: Cyclophosphamide 750mg/m ² IV over 30 minutes OR Day 1: Cyclophosphamide 1000mg/m ² IV over 30 minutes. Repeat cycle every 3 weeks for 6-8 cycles.
Ibritumomab tiuxetan (Category 2B) ^{34,40,41,m}	See NCCN B-Cell Lymphoma guidelines (Follicular Lymphoma [grade 1-2]) ¹

▶ Second-Line Consolidation or Extended Dosing (optional)^{1,a}

Preferred Regimens	
Rituximab Maintenance (Category 1) ^{6,36-38,f}	Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 12 weeks for 2 years.
Obinutuzumab Maintenance (for Rituximab-refractory disease) ^{3-5,c}	Day 1: Obinutuzumab 1000mg IV. Repeat cycle every 8 weeks for 12 doses.
Other Recommended Regimens	
<ul style="list-style-type: none"> • High-dose therapy with autologous stem cell rescue • Allogeneic hematopoietic cell transplant for highly selected patients 	

▶ Third-Line and Subsequent Therapy^{1,a}

Preferred Regimens	
Copanlisib (Relapsed/refractory after 2 prior therapies) ^{44-46,p}	Days 1,8,15: Copanlisib 60mg IV over 60 minutes. Repeat cycle every 4 weeks.
Duvelisib (Relapsed/refractory after 2 prior therapies) ^{47,48,q}	Days 1-28: Duvelisib 25mg orally twice daily. Repeat cycle every 4 weeks.
Idelalisib (Relapsed/refractory after 2 prior therapies) ^{49-51,r}	Days 1-28: Idelalisib 150mg orally twice daily. Repeat cycle every 4 weeks.
Umbralisib (Relapsed/refractory after 3 prior therapies) ^{52,53,s}	Day 1: Umbralisib 800mg orally once daily. Repeat every 4 weeks.
Tazemetostat (<i>EZH2</i> mutation positive relapsed/refractory disease after 2 prior therapies; <i>EZH2</i> wild type or unknown relapsed/refractory disease in patients who have no satisfactory alternative treatment options) ^{54,55,t}	Day 1: Tazemetostat 800mg orally twice daily. Repeat cycle every 4 weeks.
Axicabtagene ciloleucel ⁵⁶⁻⁵⁹	See NCCN B-Cell Lymphomas guidelines (Follicular Lymphoma [grade 1-2]) ¹

▶ Third-Line and Subsequent Therapy for Elderly or Infirm^{1,a}

Preferred Regimens	
Umbralisib (Relapsed/refractory after 3 prior regimens) ^{52,53,s}	Day 1: Umbralisib 800mg orally once daily. Repeat cycle every 4 weeks.

continued

B-Cell Lymphomas Treatment Regimens: Follicular Lymphoma (Grade 1-2)

► Histologic Transformation to Diffuse Large B-Cell Lymphoma (DLBCL)^{1,a}

REGIMEN	DOSING
Axicabtagene ciloleucel (only after ≥2 prior chemoimmunotherapy regimens) ^{57,59,u,v}	See NCCN B-Cell Lymphomas guidelines (Follicular Lymphoma [grade 1-2]) ¹
Lisocabtagene maraleucel (only after ≥2 prior chemoimmunotherapy regimens) ^{60,61,u,v}	See NCCN B-Cell Lymphomas guidelines (Follicular Lymphoma [grade 1-2]) ¹
Tisagenlecleucel (only after ≥2 prior chemoimmunotherapy regimens) ^{62,63,u,v}	See NCCN B-Cell Lymphomas guidelines (Follicular Lymphoma [grade 1-2]) ¹

- ^a The choice of therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT [high-dose therapy] with ASCR [autologous stem cell rescue]). Therefore, treatment selection is highly individualized.
- ^b Generally, a first-line treatment is not repeated
- ^c Obinutuzumab requires premedication with diphenhydramine, acetaminophen, and a corticosteroid.
- ^d This regimen may be associated with a risk of tumor lysis syndrome in patients with high-risk features, including extensive disease or underlying renal insufficiency.
- ^e Secondary malignancies have been associated with Bendamustine
- ^f Rituximab requires premedication with diphenhydramine and acetaminophen. Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for Rituximab after patients have received the first full dose of Rituximab by intravenous infusion. The substitution cannot be made with used in combination with ibritumomab tiuxetan.
- ^g Myeloid growth factor therapy may be considered as primary prophylaxis based on the febrile neutropenia risk of the regimen
- ^h Vincristine is for intravenous use only and usually results in death or serious neurological damage if given via other routes.
- ⁱ Cyclophosphamide has been associated with secondary malignancies.
- ^j Doxorubicin has been associated with secondary malignancies.
- ^k Lenalidomide can be taken with or without food. Secondary malignancies have been associated with Lenalidomide. Participation in the risk evaluation and mitigation strategy (REMS) program is required for Lenalidomide.
- ^l Chlorambucil should be taken on an empty stomach. Secondary malignancies have been associated with Chlorambucil.
- ^m Selection of patients requires adequate marrow cellularity >15% and <25% involvement of lymphoma in bone marrow, and platelets >100000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for ibritumomab tiuxetan.
- ⁿ Obinutuzumab is preferred in patients with Rituximab refractory disease, which includes disease progressing on or within 6 months of prior Rituximab therapy.
- ^o See second-line therapy for diffuse large b-cell lymphoma without regard to transplantability.
- ^p Copanlisib has multiple potential drug-drug and/or drug-food interactions. Review patient medical profile and drug package insert for specific drug and food interactions and recommendations.
- ^q Duvelisib has multiple potential drug-drug and/or drug-food interactions. Review patient medical profile and drug package insert for specific drug and food interactions and recommendations.
- ^r Idelalisib can be taken with or without food. Idelalisib has multiple potential drug-drug and/or drug-food interactions.
- ^s Umbralisib should be taken with food. Swallow tablet whole. Do not crush, break, cut, or chew tablets.
- ^t Tazemetostat can be taken with or without food. Tazemetostat has multiple potential drug-drug and/or drug-food interactions.
- ^u In patients intended to receive CAR T-cell therapy, Bendamustine should be used with caution unless after leukapheresis prior to CAR T-cell therapy, since it could impact the success of the patient's T-cell collection.
- ^v Patients should have received at least one anthracycline or anthracenedione-based regimen, unless contraindicated.

References

- Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for B-Cell Lymphomas V4.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed July 25, 2021.
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