

NON-HODGKIN LYMPHOMA TREATMENT REGIMENS: Follicular Lymphoma (Grade 1–2) (Part 1 of 3)

Clinical Trials: The National Comprehensive Cancer Network 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 healthcare 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 becomes 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.

General Treatment Notes¹

- Treatments listed in preference order
- The choice if initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with SCR). Therefore, treatment selection is highly individualized.
- 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. This substitution cannot be made for rituximab used in combination with ibritumomab tixetan.

First-line Therapy¹

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

REGIMEN	DOSING
Bendamustine + rituximab (Category 1) ^{2,3}	Day 1: Rituximab 375mg/m ² IV Days 1 and 2: Bendamustine 90mg/m ² IV over 30–60 minutes. Repeat every 4 weeks for 6 cycles.
Bendamustine + obinutuzumab ⁴	Days 1 and 2: Bendamustine 90mg/m ² IV Days 1, 8, 15 of Cycle 1: Obintuzumab 1000mg IV followed by: Days 1 and 2: Bendamustine 90mg/m ² IV Days 1 of Subsequent Cycles: Obintuzumab 1000mg IV. Repeat every 4 weeks for 6 cycles.
RCHOP (Category 1) ^{5,6}	Day 0: Rituximab 375mg/m ² IV Day 1: Cyclophosphamide 750mg/m ² IV + doxorubicin 50mg/m ² IV + vincristine 1.4mg/m ² IV (max 2mg) Days 1–5: Prednisone 100mg/m ² orally. Repeat every 3 weeks for 6 to 8 cycles.
CHOP + obinutuzumab ⁴	Day 1: Cyclophosphamide 750mg/m ² IV + doxorubicin 50mg/m ² IV + vincristine 1.4mg/m ² IV (max 2mg) Days 1–5: Prednisone 100mg/m ² orally Days 1, 8, 15 of Cycle 1: Obintuzumab 1000mg IV followed by: Day 1: Cyclophosphamide 750mg/m ² IV + doxorubicin 50mg/m ² IV + vincristine 1.4mg/m ² IV (max 2mg) Days 1–5: Prednisone 100mg/m ² orally Days 1 of Subsequent Cycles: Obintuzumab 1000mg IV. Repeat every 3 weeks for 6 to 8 cycles.
RCVP (Category 1) ⁷	Day 1: Rituximab 375mg/m ² IV + cyclophosphamide 750mg/m ² IV + vincristine 1.4mg/m ² IV (max 2mg) Days 1–5: Prednisone 40mg/m ² orally. Repeat every 21 days for a max of 8 cycles.
CVP + obinutuzumab ⁴	Day 1: Cyclophosphamide 750mg/v IV + vincristine 1.4mg/v IV (max 2mg) Days 1–5: Prednisone 40mg/v orally Days 1, 8, 15 of Cycle 1: Obintuzumab 1000mg IV followed by: Day 1: Cyclophosphamide 750mg/v IV + vincristine 1.4mg/v IV (max 2mg) Days 1–5: Prednisone 40mg/m ² orally Days 1 of Subsequent Cycles: Obintuzumab 1000mg IV. Repeat every 3 weeks for 6 to 8 cycles.
Rituximab ^{8–11}	Day 1: Rituximab 375mg/m ² IV. Repeat every 7 days for 4 cycles.
Lenalidomide + rituximab (Category 2B) ^{12,13}	Days 1–21: Lenalidomide 20mg orally, plus Cycle 1: Days 1, 8, 15, and 22: Rituximab 375mg/m ² IV Cycles 4, 6, 8, and 10: Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 28 days for 12 cycles.

continued

NON-HODGKIN LYMPHOMA TREATMENT REGIMENS: Follicular Lymphoma (Grade 1–2) (Part 2 of 3)

First-line Therapy for Elderly or Infirm (if none of the above are expected to be tolerable)¹

REGIMEN	DOSING
Rituximab (preferred) ⁸⁻¹¹	Day 1: Rituximab 375mg/m ² IV. Repeat every 7 days for 4 cycles.
Single agent alkylator ± rituximab ¹²	<ul style="list-style-type: none"> Chlorambucil 0.1mg/kg/day for 45 days then on days 1–15, monthly for 4 months Rituximab 375mg/m² weekly for 4 doses, then monthly for 4 infusions.
Radioimmunotherapy (Category 2B) ¹⁴	90Yttrium-ibritumomab-tixetan 15 MBq/kg (0.4 mCi/kg) single dose.

First-line Consolidation or Extended Dosing (optional)¹

Rituximab maintenance (Category 1) ¹⁵⁻¹⁶	Day 1: Rituximab 375mg/m ² IV. Repeat every 8 weeks for 12 cycles for patients initially presenting with high tumor burden.
Obinutuzumab maintenance ⁴	Day 1: Obinutuzumab 1000 mg IV. Repeat every 8 weeks for 12 cycles.
Rituximab ¹⁷	If initially treated with single-agent rituximab, consolidate with rituximab 375mg/m ² one dose every 8 weeks for 4 doses.
Radioimmunotherapy ¹⁸⁻¹⁹	After induction with chemotherapy or chemoimmunotherapy: Days –7 and 0: Rituximab 250mg/m ² followed by Day 0: 90Yttrium-ibritumomab-tixetan 14.9 MBq/kg (max 1184 MBq).

Second-line and Subsequent Therapy¹

Chemoimmunotherapy	As indicated under first-line therapy
Rituximab ^{17,28}	Days 1, 8, 15, and 22: Rituximab 375mg/m ² IV.
Lenalidomide ± rituximab ^{24,25}	Days 1–21: Lenalidomide 25mg orally; repeat every 28 days for 52 weeks, ± Days 1, 8, 15 and 22: Rituximab 375mg/m ² IV.
Bendamustine + obinutuzumab ²⁰	Days 1 and 2: Bendamustine 90mg/m ² IV Days 1, 8, 15 of Cycle 1: Obintuzumab 1000mg IV followed by: Days 1 and 2: Bendamustine 90mg/m ² IV Days 1 of Subsequent Cycles: Obintuzumab 1000mg IV. Repeat every 4 weeks for 6 cycles.
Radioimmunotherapy (Category 1) ²⁶⁻²⁷	Days 1 and 8: Rituximab 250mg/m ² IV Day 8: 90Yttrium-ibritumomab-tixetan 0.4 mCi/kg [15 MBq/kg (max 32 mCi [1.2 GBq])] immediately following second rituximab infusion.
Idelalisib (refractory to both alkylator and rituximab) ²³	Idelalisib 150mg orally twice daily.
Copanlisib (refractory to at least 2 prior therapies) ²¹	Days 1, 8, 15: Copanlisib 60mg IV. Repeat every 4 weeks until progressive disease or unacceptable toxicity.
Fludarabine + rituximab ²²	Days 1–5: Fludarabine 25mg/m ² ; repeat every 28 days for 6 cycles and Rituximab 375mg/m ² IV 4 days apart in weeks 1 and 26 and single infusions 72 hours before fludarabine infusions 2, 4, and 6.
RFND ²⁹	Days 1, 8, 15, and 22 (induction): Rituximab 375mg/m ² IV Days 1–3: Fludarabine 25mg/m ² IV + mitoxantrone 10mg/m ² IV for cycles 2–5 Days 1–5: Dexamethasone 20g/m ² IV or orally. Repeat every 28 days for 5 cycles.

Second-line Consolidation or Extended Dosing¹

Second-line Consolidation or Extended Dosing¹

Rituximab maintenance (Category 1; optional) ^{30,31}	Rituximab 375mg/m ² IV one dose every 12 weeks for 2 years.
Obinutuzumab maintenance for rituximab-refractory disease (Category 2B) ²⁰	Obinutuzumab 1g IV every 8 weeks for a total of 12 doses.

High-dose therapy with autologous stem cell rescue

Allogeneic stem cell transplant for highly selected patients

continued

NON-HODGKIN LYMPHOMA TREATMENT REGIMENS: Follicular Lymphoma (Grade 1–2) (Part 3 of 3)

References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Hodgkin's Lymphomas V7.2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf Accessed January 18, 2017.
2. Rummel M, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381:1203–1210.
3. Flinn IW, van der Jagt R, Kahl BS, et al. Open-label, randomized, noninferiority study of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of advanced indolent NHL or MCL: the BRIGHT study. *Blood*. 2014;124:2944–2952.
4. Marcus RE, Davies AJ, Ando K, et al. Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: primary results of the randomized phase 3 GALLIUM study [abstract]. *Blood*. 2017;128:Abstract 6.
5. Czuczman M, Weaver R, Alkuzweny B, et al. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. *J Clin Oncol*. 2004;22:4711–4716.
6. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*. 2005;106:3725–3732.
7. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol*. 2008;26:4579–4586.
8. Hainsworth JD, Litchy S, Burris HA, III, et al. Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma. *J Clin Oncol*. 2002;20:4261–4267.
9. Colombat P, Salles G, Brousse N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: Clinical and molecular evaluation. *Blood*. 2001;97:101–106.
10. Martinelli G, Schmitz SF, Utiger U, et al. Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98. *J Clin Oncol*. 2010;28:4480–4484.
11. Aredsha KM, Qian W, Smith P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. *Lancet Oncol*. 2014;15:424–435.
12. Martin P, Jung S-H, Johnson JL, et al. CALGB 50803 (Alliance): a phase II trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma [abstract]. *J Clin Oncol*. 2014;32:Abstract 8521.
13. Fowler N, Davis R, Rawal S, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial. *Lancet Oncol*. 2014;15:1311–1318.
14. Scholz CW, Pinto A, Linkesch W, et al. 90Yttrium ibritumomab tixetan as first line treatment for follicular lymphoma. first results from an international phase II clinical trial [abstract]. *Blood*. 2010;116:Abstract 593.
15. Salles GA, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): A phase 3, randomized controlled trial. *Lancet*. 2011;377:42–51.
16. Salles G, Seymour JF, Feugier P, et al. Updated 6 year follow-up of the PRIMA study confirms the benefit of 2-year rituximab maintenance in follicular lymphoma patients responding to frontline immunochemotherapy [abstract]. *Blood*. 2016;122:Abstract 509.
17. Ghielmini M, Schmitz SH, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly \times 4 schedule. *Blood*. 2004;103:4416–4423.
18. Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with Yttrium-90-Ibritumomab Tixetan compared with no additional therapy after first remission in advanced follicular lymphoma. *J Clin Oncol*. 2008;26:5156–5164.
19. Morschhauser F, Radford J, Van Hoof A, et al. 90Yttrium-ibritumomab tuxetan consolidation of first remission in advanced-stage follicular non-Hodgkin lymphoma: Updated results after a median follow-up of 7.3 years from the international, randomized, phase III first-line indolent trial. *J Clin Oncol*. 2013;31:1977–1983.
20. Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. *Lancet Oncol*. 2017;17:1081–1093.
21. Dreyling M, Santoro A, Leppa S, et al. Copanlisib in patients with relapsed or refractory indolent B-cell lymphoma: primary results of the pivotal Chronos-1 study [abstract]. AARC Meeting 2017;Abstract CT149.
22. Czuczman MS, Koryzna A, Mohr A, et al. Rituximab in combination with fludarabine chemotherapy in low-grade of follicular lymphoma. *J Clin Oncol*. 2005;23:694–704.
23. Gopal A, Kahl B, De Vos S, et al. PI3K α inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370:1008–1018.
24. Leonard J, Jung S-H, Johnson JL, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance). *J Clin Oncol*. 2015;33:3635–3640.
25. Witzig TE, Wiernik PH, Moore T, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's Lymphoma. *J Clin Oncol*. 2009;27:5404–5409.
26. Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tixetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol*. 2002;20:3262–3269.
27. Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tixetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2002;20:2453–2463.
28. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol*. 1998;16:2825–2833.
29. McLaughlin P, Hagemeister FB, Rodriguez MA, et al. Safety of fludarabine, mitoxantrone, and dexamethasone combined with rituximab in the treatment of stage IV indolent lymphoma. *Semin Oncol*. 2000;27:37–41.
30. van Oers MHJ, Van Glabbeke M, Gurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-hodgkin's lymphoma: Long-term outcome of the EORTC 20981 Phase III randomized Intergroup Study. *J Clin Oncol*. 2010;28:2853–2858.
31. Forstpointer R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). *Blood*. 2006;108:4003–4008.