NON-HODGKIN LYMPHOMA TREATMENT REGIMENS: Follicular Lymphoma (Grade 1-2) (Part 1 of 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 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 National Comprehensive Cancer Network 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.

whatsoever regarding their content, us	se, or application and disclaims any responsibility for their application or use in any way.
First-line Therapy ¹	
Note: All recommendations are C	Category 2A unless otherwise indicated.
REGIMEN	DOSING
Bendamustine + rituximab (Category 1) ²	Day 1: Rituximab 375mg/m² IV Days 1 and 2: Bendamustine 90mg/m² IV over 30–60 minutes. Repeat every 4 weeks for 6 cycles.
RCHOP (Category 1) ^{3,4}	Day 0: Rituximab 375mg/m² IV Day 1: Cyclophosphamide 750mg/m² IV + doxorubicin 50mg/m² IV + vincristine 1.4mg/m² IV (max 2mg) Days 1-5: Prednisone 100mg/m² orally. Repeat every 3 weeks for 6 to 8 cycles.
RCVP (Category 1) ^{5,6}	Day 1: Rituximab 375mg/m² IV + cyclophosphamide 750mg/m² IV + vincristine 1.4mg/m² IV (max 2mg) Days 1-5: Prednisone 40mg/m² orally. Repeat every 21 days for a max of 8 cycles.
Rituximab ^{7,8}	Day 1: Rituximab 375mg/m² IV. Repeat every 7 days for 4 cycles.
Lenalidomide + rituximab (Category 3) ^{9,10}	Days 1-21: Lenalidomide 20mg orally, <u>plus</u> <u>Cycle 1:</u> Days 1, 8, 15, and 22: Rituximab 375mg/m² IV <u>Cycles 4, 6, 8, and 10:</u> Day 1: Rituximab 375mg/m² IV. Repeat cycle every 28 days for 12 cycles.
First-line Therapy for Elderly	or Infirm (if none of the above are expected to be tolerable) ¹
Radioimmunotherapy (Category 2B) ¹¹	90Yttrium-ibritumomab-tiuxetan 15 MBq/kg (0.4 mCi/kg) single dose.
Rituximab (preferred) ^{7,8}	Day 1: Rituximab 375mg/m² IV. Repeat every 7 days for 4 cycles.
Single agent alkylator ± rituximab ¹²	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.
First-line Consolidation or E	extended Dosing (optional) ¹
Radioimmunotherapy ¹³⁻¹⁵	After induction with chemotherapy or chemoimmunotherapy: Days -7 and 0: Rituximab 250mg/m² followed by Day 0: 90Yttrium-ibritumomab-tiuxetan 14.9 MBq/kg (max 1184 MBq).
Rituximab maintenance (Category 1) ¹⁶	Day 1: Rituximab 375mg/m² IV. Repeat every 8 weeks for 12 cycles for patients initially presenting with high tumor burden.
Rituximab ¹⁷	If initially treated with single-agent rituximab, consolidate with rituximab 375mg/m² one dose every 8 weeks for 4 doses.
Second-line and Subsequen	nt Therapy¹
Chemoimmunotherapy	As indicated under first-line therapy
Fludarabine + rituximab ¹⁸	Days 1–5: Fludarabine 25mg/m²; repeat every 28 days for 6 cycles <u>and</u> Rituximab 375mg/m² IV 4 days apart in weeks 1 and 26 and single infusions 72 hours before fludarabine infusions 2, 4, and 6.
Lenalidomide ± rituximab ^{19,20}	Days 1-21: Lenalidomide 25mg orally; repeat every 28 days for 52 weeks, ± Days 1, 8, 15 and 22: Rituximab 375mg/m² IV.
Radioimmunotherapy (Category 1) ^{21,22}	Days 1 and 8: Rituximab 250mg/m² IV Day 8: 90Yttrium-ibritumomab-tiuxetan 0.4 mCi/kg [15 MBq/kg (max 32 mCi [1.2 GBq]) immediately following second rituximab infusion.
Rituximab ^{23,24}	Days 1, 8, 15, and 22: Rituximab 375mg/m ² IV.
RFND ²⁵	Days 1, 8, 15, and 22 (induction): Rituximab 375mg/m² IV Days 1-3: Fludarabine 25mg/m² IV + mitoxantrone 10mg/m² IV for cycles 2-5 Days 1-5: Dexamethasone 20g/m² IV or orally. Repeat every 28 days for 5 cycles.
Idelalisib ²⁶	Idelalisib 150mg orally twice daily.
I	continued

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

Second-line Consolidation or Extended Dosing¹

REGIMEN

DOSING

High-dose therapy with autologous stem cell rescue

Allogeneic stem cell transplant for highly selected patients

Rituximab maintenance (Category 1; optional)^{27,28}

Rituximab 375mg/m² IV one dose every 12 weeks for 2 years.

Obinutuzumab maintenance for rituximab-refractory disease (Category 2B)²⁹

Obinutuzumab 1g IV every 8 weeks for a total of 12 doses.

References

- Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Hodgkin's Lymphomas V3.2016. Available at: http://www.nccn.org/ Accessed August 30, 2015.
- 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 noninferiority trial. *Lancet*. 2013;381:1203–1210.
- 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.
- 4. 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.
- 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.
- Marcus R, Imrie K, Belch A et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood*. 2005;105:1417–1423.
- 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.
- 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.
- 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.
- Fowler N, Davis R, Rawal S, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 tial. *Lancet Oncol.* 2014;15: 1311–1318.
- Scholz CW, Pinto A, Linkesch W, et al. 90Yttrium ibritumomab tiuxetan as first line treatment for follicular lymphoma. first results from an international phase II clinical trial [abstract]. Blood. 2010:116:Abstract 593.
- Rigacci L, Nassi L, Puccioni M, et al. Rituximab and chlorambucil as first-line treatment for low-grade ocular adnexal lymphomas. Ann Hematol. 2007;86:565–568.
- Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with Yttrium-90-libriumomab Tiuwetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol. 2008;26: 5156–5164.
- 14. Hagenbeek A, Radford J, Van Hoof A, et al. 90Y-lbritumomab tiuxetan (Zevalin®) consolidation of first remission in advanced-stage follicular non-hodgkin's lymphoma: Updated results after a median follow-up of 66.2 months from the international, randomized, phase III First-Line Indolent Trial (FIT) in 414 Patients [abstract]. Blood. 2010;116:Abstract 594.
- 14. 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.

- 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.
- 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 × 4 schedule. *Blood*. 2004;103:4416–4423.
- 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.
- Leonard J, Jung S-H, Johnson JL, et al. CALGB 50401: A randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma [abstract]. J Clin Oncol. 2012;30:Abstract 8000.
- 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.
- 21 Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximabrefractory follicular non-Hodgkin's lymphoma. J Clin Oncol. 2002;20: 3262–3269.
- Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan 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.
- 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.
- 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 x 4 schedule. *Blood*. 2004:103:4416-4423.
- 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.
- Gopal A, Kahl B, De Vos S, et al. PI3Kô inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014;370:1008–1018
- van Oers MHJ, Van Glabbeke M, Giurgea 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.
- 28. 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.
- Sehn LH, Chua NS, Mayer J, et al. GADOLIN: Primary results from a phase III study of obinutuzumab plus bendamustine compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma [abstract]. J Clin Oncol. 2015;33(15_suppl):Abstr LBA8502.