NON-HODGKIN LYMPHOMA TREATMENT REGIMENS: Diffuse Large B-cell Lymphoma (Part 1 of 5)

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 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.

Systemic Therapy for Diffuse Large B-cell Lymphoma[1]

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

First-line Therapy

REGIMEN	DOSING
R-CHOP (Category 1)[2–7]	**Days 1, 22, and 43:** Rituximab 375mg/m² IV 7 days prior to beginning CHOP regimen **Day 1:** Cyclophosphamide 750mg/m² IV + doxorubicin 50mg/m² IV bolus + vincristine 1.4mg/m² IV bolus (max dose 2mg) **Days 3, 24, and 45:** Prednisone 100mg orally 5 days. Repeat each cycle every 3 weeks for 3 cycles. Radiotherapy begins 3 weeks after last cycle of R-CHOP.
Dose-dense R-CHOP 14 (Category 3)[8–10]	**Day 1:** Cyclophosphamide 750mg/m² IV + doxorubicin 50mg/m² IV + vincristine 2mg IV **Days 1-5:** Prednisone 100mg orally. Repeat every 2 weeks for 6 cycles. Granulocyte colony-stimulating factor (G-CSF) was given on day 4 or 6.
Dose-adjusted EPOCH + rituximab[11–13]	**Day 1:** Rituximab 375mg/m² IV **Days 1–4:** Etoposide 50mg/m² IV + doxorubicin 10mg/m² IV + vincristine 0.4mg/m² IV **Day 5:** Cyclophosphamide 750mg/m² IV **Days 1–5:** Prednisone 60mg/m² orally twice daily. Administer G-CSF 5 mcg/kg SQ daily until an ANC >5 × 10^9/L above nadir level starting day 6. Repeat cycle every 3 weeks for 6 cycles.

First-line Therapy for Patients With Poor Left Ventricular Function[a,b]

RCEPP[14]	**Days 1 and 8:** Cyclophosphamide 600mg/m² IV **Day 1 OR 8:** Rituximab 375mg/m² IV **Day 1:** Etoposide IV 70mg/m² IV (or days 1–3 if not giving oral etoposide) **Days 2 and 3:** Etoposide 140 mg/m² orally (rounded to the nearest 50mg capsule) **Days 1–10:** Procarbazine 60mg/m² orally + prednisone 60mg/m² orally. Repeat every 4 weeks until disease progression, or unacceptable toxicity.
RCDOP[15,16]	**Day 1:** Cyclophosphamide 750mg/m² IV + liposomal doxorubicin 30mg/m² IV + vincristine 2mg IV **Days 1–5:** Prednisone 60mg/m² IV **Day 8:** Rituximab 375mg/m² IV for cycle 1; administer on day 0 in subsequent cycles. Repeat cycle every 3 weeks for 6–8 cycles.
RGCVP[17]	**Day 1:** Rituximab 375mg/m² IV + cyclophosphamide 750mg/m² IV + vincristine 1.4mg/m² (maximum dose 2mg) IV **Days 1 and 8:** Gemcitabine 750-1000mg/m² IV **Days 1–5:** Prednisolone 100mg orally per day. **Day 9:** Pegfilgrastim 6mg SC. Repeat every 3 weeks for 6 cycles (Patients considered high risk for CNS relapse can receive methotrexate 12.5mg IT for 3 cycles).
DA-EPOCH + rituximab[18]	**Day 1:** Rituximab 275mg/m² **Days 1–4:** Doxorubicin 10mg/m² IV + etoposide 50mg/m² IV + vincristine 0.4mg/m² IV **Day 5:** Cyclophosphamide 750mg/m² IV **Days 1–5:** Prednisone 60mg/m² orally. Administer G-SCF on day 6 until ANC exceeds nadir. Repeat cycle every 3 weeks.
RCEOP[19]	**Day 1:** Rituximab 375mg/m² IV **Day 1:** Cyclophosphamide 750mg/m² IV + etoposide 50mg/m² IV + vincristine 1.4mg/m² IV (max dose 2mg) **Days 1–5:** Prednisone 100mg orally **Days 2–3:** Etoposide 100mg/m² orally. For limited-stage disease, repeat cycle every 3 weeks for 3–4 cycles; for advanced-stage disease, repeat cycle every 3 weeks for 6 cycles.

continued

NON-HODGKIN LYMPHOMA TREATMENT REGIMENS: Diffuse Large B-cell Lymphoma (Part 2 of 5)

Systemic Therapy for Diffuse Large B-cell Lymphoma[1] (continued)

First-Line Therapy for Very Frail Patients and Patients >80 Years of Age With Comorbidities

REGIMEN	DOSING
R-mini-CHOP[20]	**Day 1:** Rituximab 375mg/m^2 IV **Day 1:** Cyclophosphamide 400mg/m^2 IV + doxorubicin 25mg/m^2 IV + vincristine 1mg IV **Days 1–5:** Prednisone 40mg/m^2 orally. Repeat every 3 weeks for 6 cycles.
RGCVP[17]	**Day 1:** Rituximab 375mg/m^2 IV + cyclophosphamide 750mg/m^2 IV + vincristine 1.4mg/m^2 (maximum dose 2mg) IV **Days 1 and 8:** Gemcitabine 750-1000mg/m^2 IV **Days 1-5:** Prednisolone 100mg orally per day. **Day 9:** Pegfilgrastim 6mg SC. Repeat every 3 weeks for 6 cycles (Patients considered high risk for CNS relapse can receive methotrexate 12.5mg IT for 3 cycles).
RCEPP[14]	**Days 1 and 8:** Cyclophosphamide 600mg/m^2 IV **Day 1:** Etoposide IV 70mg/m^2 IV (or days 1–3 if not giving oral etoposide) **Days 2 and 3:** Etoposide 140 mg/m^2 orally (rounded to the nearest 50mg capsule) **Days 1–10:** Procarbazine 60mg/m^2 orally + prednisone 60mg/m^2 orally. Repeat every 4 weeks until disease progression, or unacceptable toxicity.
RCDOP[15,16]	**Day 1:** Cyclophosphamide 750mg/m^2 IV + liposomal doxorubicin 30mg/m^2 IV + vincristine 2mg IV **Days 1–5:** Prednisone 60mg/m^2 IV **Day 8:** Rituximab 375mg/m^2 IV for cycle 1; administer on day 0 in subsequent cycles. Repeat cycle every 3 weeks for 6–8 cycles.

First-line Consolidation (optional)

High-dose therapy with autologous stem cell rescue in patients with age-adjusted IPI high-risk disease (Category 2B)[21]	Induced with 5 cycles of CHOP or R-CHOP **followed by** autotransplantation at the first response to induction therapy with CHOP with or without rituximab for 3 cycles.
Lenalidomide maintenance for patients 60 - 80 years of age (Category 2B)[22]	**Days 1 to 21:** Lenalidomide 25mg daily. Repeat every 4 weeks for 24 months.

Concurrent Presentation With CNS Disease

Parenchymal[1]	Systemic methotrexate 3g/m^2 or more on day 15 of a 21-day R-CHOP cycle that has been supported by growth factors.
Leptomeningeal[1]	Methotrexate/cytarabine IT. Consider Ommaya reservoir placement and/or systemic methotrexate 3–3.5g/m^2.

Second-line and Subsequent Therapy (for patients with intention to proceed to high-dose therapy)[1,c,d]

DHAP ± rituximab[23–25]	**Days 1–4:** Cisplatin 100mg/m^2 IV via 24-hour infusion + cytosine 2g/m^2 in 2 pulses each given 12 hours apart IV + dexamethasone 40mg orally or IV **±** rituximab 375mg/m^2 IV prior to DHAP. Repeat in 3–4 weeks for 6-10 cycles.
ESHAP ± rituximab[26,27]	**Days 1–4:** Etoposide 40–60mg/m^2 **Days 1–5:** Methylprednisolone 250–500mg IV **Day 5:** Cytarabine 2g/m^2 IV over 2–3 hours **Days 1–4:** Cisplatin 25mg/m^2 IV via 24-hour infusion, **±** **Day 1 or 5:** Rituximab 375mg/m^2 IV. Repeat every 3–4 weeks for 3 cycles.
GDP ± rituximab[28,29]	**Days 1 and 8:** Gemcitabine 1000mg/m^2 IV over 30 minutes **Days 1–4:** Dexamethasone 40mg orally **Day 1:** Cisplatin 75mg/m^2 IV **OR** carboplatin at AUC 5mg·min/mL IV over 30 minutes, **±** **Day 8:** Rituximab 375mg/m^2 slow IV infusion for CD20-positive disease. Repeat every 3 weeks for up to 6 cycles.
GemOX ± rituximab[30]	**Day 1:** Gemcitabine 1000mg/m^2 and oxaliplatin 100mg/m^2 **±** rituximab 375mg/m^2 IV. Repeat every 15 days if ANC >1 × 10^9/L and platelet count >100 × 10^9/L; if not, then every 3 weeks.
ICE ± rituximab[31–33]	**Days 1–3:** Etoposide 100mg/m^2 IV bolus **Day 2:** Carboplatin AUC 5mg·min/mL (max dose 800mg) IV bolus and ifosfamide admixed with mesna both at a dose of 5g/m^2 via 24-hour continuous IV beginning day 2 **Days 5–12 (or days 7–14):** Filgrastim 5mcg/kg/day for cycles 1–2, increased to 10mcg/kg/day following cycle 3 until completion of peripheral blood stem cell collection, **±** **Days 1 and 3:** Rituximab 375mg/m^2 IV and on cycle 1, give additional dose rituximab 375mg/m^2 on Day 2. Repeat every 14 days or when ANC >1000 cells/mcL and platelet count >50000/mcL.

continued

NON-HODGKIN LYMPHOMA TREATMENT REGIMENS: Diffuse Large B-cell Lymphoma (Part 3 of 5)

Systemic Therapy for Diffuse Large B-cell Lymphoma[1] (continued)

Second-line and Subsequent Therapy (for patients with intention to proceed to high-dose therapy)[c,d] (continued)

REGIMEN	DOSING
MINE ± rituximab[34,35]	**Day 1:** Mitoxantrone 8mg/m² IV **Days 1-3:** Ifosfamide 2g/m² IV + mesna IV + etoposide 100mg/m² IV, **±** **Day 1:** Rituximab 375mg/m² IV. Repeat cycle every 4 weeks for 2 cycles, followed by high-dose chemotherapy and autologous stem cell transplantation (HDC-ASCT). Patients in remission after HDC-ASCT may receive rituximab 375mg/m² IV weekly for 4 weeks.

Second-line and Subsequent Therapy (non-candidates for high-dose therapy)[c,d]

Bendamustine ± rituximab[36-38]	**Days 1–2:** Bendamustine 120mg/m² IV, **±** **Day 1:** Rituximab 375mg/m² IV. Repeat every 4 weeks for up to 6 cycles.
Brentuximab vedotin for CD30+ disease (Category 2B)[39]	Brentuximab vedotin 1.8mg/kg IV over 30 minutes every 3 weeks. Repeat cycle until a maximum of 16 cycles, disease progression, or unacceptable toxicity.
CEPP ± rituximab (PO and IV)[40]	**Days 1 and 8:** Cyclophosphamide 600mg/m² IV **Day 1:** Etoposide IV 70mg/m² IV (or on days 1–3 if not giving oral etoposide) **Days 2 and 3:** Etoposide 140mg/m² orally (rounded to the nearest 50 mg capsule) **Days 1–10:** Procarbazine 60mg/m² orally + prednisone 60mg/m² orally, **±** **Day 1:** Rituximab 375mg/m² IV. Repeat every 4 weeks until disease progression or unacceptable toxicity.
CEOP ± rituximab[41]	**Day 1:** Cyclophosphamide 750mg/m² IV, vincristine 1.4mg/m² IV, and epirubicin 60mg/m² IV **Days 1–5:** Prednisone 100mg/day orally, **±** **Day 0:** Rituximab 375mg/m² IV. Repeat every 3 weeks for at least 6 cycles.
DA-EPOCH ± rituximab[42,43]	**Days 2–4:** Doxorubicin 15mg/m² via continuous IV infusion + etoposide 65mg/m² via continuous IV infusion + vincristine 0.5mg via continuous IV infusion **Day 5:** Cyclophosphamide 750mg/m² IV **Days 1–14:** Prednisone 60mg/m² orally, **±** **Day 1:** Rituximab 375mg/m² IV. Repeat every 3 weeks for 4-6 cycles.
GDP ± rituximab[28,29]	**Days 1 and 8:** Gemcitabine 1000mg/m² IV **Days 1–4:** Dexamethasone 40mg IV **Days 1–3:** Cisplatin 25mg/m² IV **OR** carboplatin AUC 5mg·min/mL on day 1, **±** **Day 1:** Rituximab 375mg/m² IV. Repeat every 3 weeks for 2–6 cycles (max of 4 cycles if using carboplatin).
GemOx ± rituximab[44,45]	**Days 1 and 8:** Gemcitabine 1200mg/m² 30-minute IV infusion **Day 2:** Oxaliplatin 120mg/m² 2-hour IV infusion, **±** **Day 1:** Rituximab 375mg/m² IV. Repeat every 3 weeks for 6 cycles.
Lenalidomide ± rituximab (non-GCB DLBCL)[46-48]	**Days 1–21:** Lenalidomide 20mg orally ± rituximab 375mg/m² IV weekly during cycle 1. Repeat every 4 weeks until complete response.
Rituximab[49]	**Day 1:** Rituximab 375mg/m² IV during each cycle of chemotherapy for up to 8 infusions.
Gemcitabine + vinorelbine ± rituximab (Category 3)[50,51]	**Days 1 and 8:** Gemcitabine 1000mg/m² + vinorelbine 30mg/m² **OR** **Days 1 and 8:** Gemcitabine 880mg/m² + vinorelbine 25mg/m² + rituximab 375mg/m². Repeat every 3 weeks for up to 6 cycles.
Ibrutinib (non-GCB DLBCL)[52]	Ibrutinib 560mg orally daily. Repeat every 4 weeks until disease progression or unacceptable toxicity.

[a] Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.
[b] There are limited published data regarding the use of these regimens; however, they are used at NCCN Member Institutions for the first-line treatment of DLBCL for patients with poor left ventricular function.
[c] If additional anthracycline is administered after a full course of therapy, careful cardiac monitoring is essential. Dexrazoxane may be added as a cardioprotectant.
[d] Rituximab should be included in second-line therapy if there is a relapse after a reasonable remission (>6 mo); however, rituximab should often be omitted in patients with primary refractory disease.

References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell Lymphomas. V4.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed May 24, 2018.
2. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-hodgkin's lymphoma. *N Engl J Med*. 1998;339:21-26.
3. Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage di use aggressive non-hodgkin's lymphoma: Eastern Cooperative Oncology Group Study 1484. *J Clin Oncol*. 2004;22:3032-3038.
4. Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved- eld radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group Study 0014. *J Clin Oncol*. 2008;26:2258-2263.

continued

References (continued)

5. Coiffer B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood*. 2010;116:2040-2045.
6. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 2005;23:4117-4126.
7. Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2006;7:379-391.
8. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol*. 2008;9:105-116.
9. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet*. 2013;381:1817-1826.
10. Lamy T, Damaj G, Soubeyran P, et al. R-CHOP 14 with or without radiotherapy in nonbulky limited- stage diffuse large B-cell lymphoma. *Blood*. 2018;131:174-181.
11. Purroy N, Bergua J, Gallur L, et al. Long-term follow-up of dose-adjusted EPOCH plus rituximab (DA-EPOCH-R) in untreated patients with poor prognosis large B-cell lymphoma. A phase II study conducted by the Spanish PETHEMA Group. *Br J Haematol*. 2015;169:188-198.
12. Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. *J Clin Oncol*. 2008;26:2717-2724.
13. Wilson WH, Jung SH, Porcu P, et al. A Cancer and Leukemia Group B multi-center study of DA- EPOCH-rituximab in untreated di use large B-cell lymphoma with analysis of outcome by molecular subtype. *Haematologica*. 2012;97:758-765.
14. Chao NJ, Rosenberg SA, Horning SJ. CEPP(B): An effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma. *Blood*. 1990;76:1293–1298.
15. Martino R, Perea G, Caballero MD, et al. Cyclophosphamide, pegylated liposomal doxorubicin (Caelyx), vincristine and prednisone (CCOP) in elderly patients with diffuse large B-cell lymphoma: Results from a prospective phase II study. *Haematologica*. 2002;87:822-827.
16. Zaja F, Tomadini V, Zaccaria A, et al. CHOP-rituximab with pegylated liposomal doxorubicin for the treatment of elderly patients with diffuse large B-cell lymphoma. *Leuk Lymphoma*. 2006;47:2174-2180.
17. Fields PA, Townsend W, Webb A, et al. De novo treatment of diffuse large B-cell lymphoma with rituximab, cyclophosphamide, vincristine, gemcitabine, and prednisolone in patients with cardiac comorbidity: a United Kingdom National Cancer Research Institute trial. *J Clin Oncol*. 2014;32:282-287.
18. Garcia-Suarez J, Banas H, Arribas I, et al. Dose-adjusted EPOCH plus rituximab is an effective regimen in patients with poor-prognostic untreated diffuse large B-cell lymphoma: results from a prospective observational study. *Br J Haematol*. 2006;126:276–285.
19. Moccia A, Scha K, Hoskins P, et al. R-CHOP with etoposide substituted for doxorubicin (R-CEOP): Excellent outcome in diffuse large B cell lymphoma for patients with a contraindication to anthracyclines [abstract]. *Blood*. 2009;114:Abstract 408.
20. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2011;12:460-468.
21. Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non- Hodgkin's lymphoma. *N Engl J Med*. 2013;369:1681-1690.
22. Thieblemont C, Tilly H, Gomes da Silva M, et al. Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol*. 2018;35:2473-2481.
23. Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). *Blood*. 1988;71: 117-122.
24. Mey UJ, Orlopp KS, Flieger D, et al. Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. *Cancer Invest*. 2006;24:593-600.
25. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28:4184-4190.
26. Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP - an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. *J Clin Oncol*. 1994;12:1169-1176.
27. Martin A, Conde E, Arnan M, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. *Haematologica*. 2008;93: 1829-1836.
28. Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma: a Phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). *Cancer*. 2004;101:1835-1842.
29. Gopal AK, Press OW, Shustov AR, et al. Efficacy and safety of gemcitabine, carboplatin, dexamethasone, and rituximab in patients with relapsed/refractory lymphoma: a prospective multi- center phase II study by the Puget Sound Oncology Consortium. *Leuk Lymphoma*. 2010;51:1523-1529.
30. Lopez A, Gutierrez A, Palacios A, et al. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: a phase II study. *Eur J Haematol*. 2008;80:127-132.
31. Zelenetz AD, Hamlin P, Kewalramani T, et al. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. *Ann Oncol*. 2003;14[suppl 1]:i5-10.
32. Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE (RICE) as second-line therapy prior to autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood. 2004;103:3684-3688.
33. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28:4184-4190.
34. Joyce RM, Regan M, Ottaway J, et al. A phase I–II study of rituximab, ifosfamide, mitoxantrone and etoposide (R-IME) for B cell non-Hodgkin's lymphoma prior to and after high-dose chemotherapy and autologous stem cell transplantation (HDC-ASCT). *Ann Oncol*. 2003; 14 (suppl 1):i21-i27.
35. Emmanouilides C, Lill M, Telatar M, et al. Mitoxantrone/ifosfamide/etoposide salvage regimen with rituximab for in vivo purging in patients with relapsed lymphoma. *Clin Lymphoma*. 2002;3:111–116.
36. Weidmann E, Kim SZ, Rost A, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. *Ann Oncol*. 2002;13:1285-1289.
37. Vacirca JL, Acs PI, Tabbara IA, et al. Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. *Ann Hematol*. 2014;93:403-409.
38. Ohmachi K, Niitsu N, Uchida T, et al. Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol*. 2013;31:2103-2109.
39. Jacobsen ED, Sharman JP, Oki Y, et al. Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/refractory DLBCL with variable CD30 expression. *Blood*. 2015;125:1394-1402.
40. Chao NJ, Rosenberg SA, and Horning SJ. CEPP(B): An effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma. *Blood*. 1990;76:1293-1298.
41. Yan L, Yimamu M, Wang X, et al. Addition of rituximab to a CEOP regimen improved the outcome in the treatment of non-germinal center immunophenotype diffuse large B cell lymphoma cells with high Bcl-2 expression. *Int J Hematol*. 2014:99:79-86.
42. Gutierrez M, Chabner BA, Pearson D, et al. Role of a doxorubicin-containing regimen in relapsed and resistant lymphomas: An 8-year follow-up study of EPOCH. *J Clin Oncol*. 2000; 18:3633-3642.

continued

References (continued)

43. Jermann M, Jost LM, Taverna C, et al. Rituximab-EPOCH, an effective salvage therapy for relapsed, refractory or transformed B-cell lymphomas: Results of a phase II study. *Ann Oncol*. 2004;15:511-516.
44. Corazzelli G, Capobianco G, Arcamone M, et al. Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma. *Cancer Chemother Pharmacol*. 2009;64:907-916.
45. El Gnaoui T, Dupuis J, Belhadj K, et al. Rituximab, gemcitabine and oxaliplatin: An effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. *Ann Oncol*. 2007;18:1363-1368.
46. Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. *Ann Oncol*. 2011;22:1622-1627.
47. Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive Non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26:4952-4957.
48. Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular, and transformed lymphoma: a phase II clinical trial. *Leukemia*. 2013;27:1902-1909.
49. Rituxan® (rituximab) [package insert]. Genentech, Inc. South San Francisco, CA.
50. Papageorgiou ES, Tsirigotis P, Dimopoulos M, et al. Combination chemotherapy with gemcitabine and vinorelbine in the treatment of relapsed or refractory diffuse large B-cell lymphoma: a phase-II trial by the Hellenic Cooperative Oncology Group. *Eur J Hematol*. 2005;75:124-129.
51. Xiros N, Economopoulos T, Valsami S, et al. Rituximab in combination with vinorelbine/gemcitabine chemotherapy in patients with primary refractory or early relapsed T cell rich B cell lymphoma. A pilot study. *Leuk Res*. 2003;27:1097-1099.
52. Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nat Med*. 2015;21:922-926.

(Revised 6/2018)
© 2018 by Haymarket Media, Inc.