

Lymphoma, Diffuse Large B-Cell Pathways**

Patient Name: _____ Date of Birth: _____
 Member ID: _____ Treatment Start Date: _____
 Stage: _____ Pathology: _____
 ECOG Status: 1 2 3 4 ICD-10 Code: _____
 Line of Therapy: 1st Line 2nd Line 3rd Line /+ Maint.

Biomarkers/Attributes: (select all that apply)

CD20 Status: <input type="checkbox"/> Negative <input type="checkbox"/> Positive	Hepatitis B Status: <input type="checkbox"/> Positive <input type="checkbox"/> Negative
HIV Associated Lymphoma: <input type="checkbox"/> Yes <input type="checkbox"/> No	CD30+: <input type="checkbox"/> Positive <input type="checkbox"/> Negative
Transplant Candidate: <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Unknown
Double or Triple HIT: <input type="checkbox"/> Yes <input type="checkbox"/> No	PMBCL: <input type="checkbox"/> Yes <input type="checkbox"/> No
<input type="checkbox"/> Unknown	<input type="checkbox"/> Unknown

First Line of Therapy

- Rituximab*+ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
- Rituximab* + mini-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)

Primary Mediastinal B-Cell Lymphoma (PMBCL), high-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6 (Double/Triple Hit Lymphoma), or high-grade B-cell lymphomas, NOS

- Rituximab* + DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
- Rituximab*+ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
- Rituximab*+ mini-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)

Frail patients, patients > 80 years of age with comorbidities, and/or patients with poor left ventricular function

- Rituximab*+ mini-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
- Rituximab* + CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)
- Rituximab* + CEOP (cyclophosphamide, etoposide, vincristine, prednisone)

Second and Subsequent Lines of Therapy

Intention to proceed to transplant

- Rituximab* +/- ICE (ifosfamide, carboplatin, etoposide)
- Rituximab* +/- DHAP (dexamethasone, cisplatin, cytarabine)
- Rituximab* +/- GDP (gemcitabine, dexamethasone, cisplatin or carboplatin)

Non-candidates for transplant

- Rituximab* +/- GDP (gemcitabine, dexamethasone, cisplatin or carboplatin)
- Rituximab* +/- GemOX (gemcitabine, oxaliplatin)
- Rituximab* +/- CEOP (cyclophosphamide, etoposide, vincristine, prednisone)

*a biosimilar agent may be preferred under the patient's specific health plan

**Therapies that are administered at Centers of Excellence, including stem cell transplant or CAR T-cell therapy, are not included in pathways. Patients eligible for transplant or CAR T-cell therapy should be referred appropriately for evaluation.

Note: Pathways are independent of specific Optum Care/health plan medical policy coverage criteria. Optum Care/health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered. Biosimilars or alternate formulations (along with the reference products) are considered on pathway unless otherwise specified by health plan formularies, medical policies, or preferred product rules.

References:

- Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2015;26 Suppl 5:v116-v125. doi:10.1093/annonc/mdv304
- National Comprehensive Cancer Network. B-Cell Lymphoma NCCN Evidence Blocks (Version 1.2022)
https://www.nccn.org/professionals/physician_gls/pdf/b-cell__blocks.pdf
- National Comprehensive Cancer Network. Hematopoietic Growth Factors (Version 1.2022)
https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf
- Abramson JS, Hellmann M, Barnes JA, et al. Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. *Cancer.* 2010;116(18):4283-4290. doi:10.1002/cncr.25278
- Arkenau HT, Chong G, Cunningham D, et al. The role of intrathecal chemotherapy prophylaxis in patients with diffuse large B-cell lymphoma. *Ann Oncol.* 2007;18(3):541-545. doi:10.1093/annonc/mdl434
- Bartlett NL, Wilson WH, Jung SH, et al. Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. *J Clin Oncol.* 2019;37(21):1790-1799. doi:10.1200/JCO.18.01994
- Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol.* 2021;22(6):790-800. doi:10.1016/S1470-2045(21)00139-X
- 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(7):1293-1298.
- Coiffier B, Haioun C, Ketterer N, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. *Blood.* 1998;92(6):1927-1932.
- Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med.* 2002;346(4):235-242. doi:10.1056/NEJMoa011795
- Coiffier 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(12):2040-2045. doi:10.1182/blood-2010-03-276246
- 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(5):907-916. doi:10.1007/s00280-009-0941-9
- Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. *J Clin Oncol.* 2014;32(31):3490-3496. doi:10.1200/JCO.2013.53.9593
- Davies A, Merli F, Mihaljević B, et al. Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase 3 trial. *Lancet Haematol.* 2017;4(6):e272-e282. doi:10.1016/S2352-3026(17)30078-9
- Dunleavy K, Fanale MA, Abramson JS, et al. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study. *Lancet Haematol.* 2018;5(12):e609-e617. doi:10.1016/S2352-3026(18)30177-7
- Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *N Engl J Med.* 2013;368(15):1408-1416. doi:10.1056/NEJMoa1214561

Note: Pathways are independent of specific Optum Care/health plan medical policy coverage criteria. Optum Care/health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered. Biosimilars or alternate formulations (along with the reference products) are considered on pathway unless otherwise specified by health plan formularies, medical policies, or preferred product rules.

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 [published correction appears in *J Clin Oncol*. 2014 Oct 20;32(30):3461]. *J Clin Oncol*. 2014;32(4):282-287. doi:10.1200/JCO.2013.49.7586

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(8):1523-1529. doi:10.3109/10428194.2010.491137

Hou Y, Wang HQ, Ba Y. Rituximab, gemcitabine, cisplatin, and dexamethasone in patients with refractory or relapsed aggressive B-cell lymphoma. *Med Oncol*. 2012;29(4):2409-2416. doi:10.1007/s12032-012-0211-2

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(9):1394-1402. doi:10.1182/blood-2014-09-598763

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. doi:10.1093/annonc/mdg705

Kalakonda N, Maerevoet M, Cavallo F, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. *Lancet Haematol*. 2020;7(7):e511-e522. doi:10.1016/S2352-3026(20)30120-4

Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. *Blood*. 2004;103(10):3684-3688. doi:10.1182/blood-2003-11-3911

Kovacs CS, William J; et al; Intrathecal Chemotherapy Prophylaxis for CNS Relapse of DLBCL In the RCHOP Era: A Single Center Analysis.. *Blood* 2010; 116 (21): 2804. doi: <https://doi.org/10.1182/blood.V116.21.2804.2804>

Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. *J Clin Oncol*. 2016;34(23):2698-2704. doi:10.1200/JCO.2015.65.9789

López A, Gutiérrez 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(2):127-132. doi:10.1111/j.1600-0609.2007.00996.x

Martín 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(12):1829-1836. doi:10.3324/haematol.13440

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(8):822-827.

Mey UJ, Orloff 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(6):593-600. doi:10.1080/07357900600814490

Moccia A, Schaff K, et al. R-CHOP with Etoposide Substituted for Doxorubicin (R-CEOP): Excellent Outcome in DLBCL for patients with a Contraindication to Anthracyclines. *Blood*. 2009; 114 (22);408. doi.org/10.1182/blood.V114.22.408.408

Morschhauser F, Flinn IW, Advani R, et al. Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS). *Lancet Haematol*. 2019;6(5):e254-e265. doi:10.1016/S2352-3026(19)30026-2

Moskowitz C, Hamlin P, et al.; Sequential Dose-Dense RCHOP Followed by ICE Consolidation (MSKCC protocol 01-142) without Radiotherapy for Patients with Primary Mediastinal Large B Cell Lymphoma. *Blood* 2010; 116 (21): 420. doi: <https://doi.org/10.1182/blood.V116.21.420.420>

Note: Pathways are independent of specific Optum Care/health plan medical policy coverage criteria. Optum Care/health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered. Biosimilars or alternate formulations (along with the reference products) are considered on pathway unless otherwise specified by health plan formularies, medical policies, or preferred product rules.

Mounier N, El Gnaoui T, Tilly H, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. *Haematologica*. 2013;98(11):1726-1731. doi:10.3324/haematol.2013.090597

Oki Y, Westin JR, Vega F, et al. Prospective phase II study of rituximab with alternating cycles of hyper-CVAD and high-dose methotrexate with cytarabine for young patients with high-risk diffuse large B-cell lymphoma. *Br J Haematol*. 2013;163(5):611-620. doi:10.1111/bjh.12585

Palanca-Wessels MC, Czuczman M, Salles G, et al. Safety and activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: a phase 1 study. *Lancet Oncol*. 2015;16(6):704-715. doi:10.1016/S1470-2045(15)70128-2

Papageorgiou ES, Tsigotis 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 Haematol*. 2005;75(2):124-129. doi:10.1111/j.1600-0609.2005.00482.x

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(5):460-468. doi:10.1016/S1470-2045(11)70069-9

Philippe Armand, Scott J Rodig, et al; Pembrolizumab in Patients with Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma (PMBCL): Data from the Keynote-013 and Keynote-170 Studies. *Blood* 2018; 132 (Supplement 1): 228. doi: <https://doi.org/10.1182/blood-2018-99-110220>

Pier Luigi Zinzani, Vladimir Melnichenko, et al; Pembrolizumab Monotherapy in Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma (PMBCL): 3-Year Follow-up of the Keynote-170 Study. *Blood* 2020; 136 (Supplement 1): 42–43. doi: <https://doi.org/10.1182/blood-2020-137080>

Poeschel V, Held G, Ziepert M, et al. Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial. *Lancet*. 2019;394(10216):2271-2281. doi:10.1016/S0140-6736(19)33008-9

Rigacci L, Fabbri A, Puccini B, et al. Oxaliplatin-based chemotherapy (dexamethasone, high-dose cytarabine, and oxaliplatin)±rituximab is an effective salvage regimen in patients with relapsed or refractory lymphoma. *Cancer*. 2010;116(19):4573-4579. doi:10.1002/cncr.25216

Salles G, Duell J, González Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. *Lancet Oncol*. 2020;21(7):978-988. doi:10.1016/S1470-2045(20)30225-4

Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *J Clin Oncol*. 2020;38(2):155-165. doi:10.1200/JCO.19.00172

Shah N, Szabo A, Huntington SF, et al. R-CHOP versus dose-adjusted R-EPOCH in frontline management of primary mediastinal B-cell lymphoma: a multi-centre analysis [published correction appears in *Br J Haematol*. 2018 Apr;181(1):152]. *Br J Haematol*. 2018;180(4):534-544. doi:10.1111/bjh.15051

Sun H, Savage KJ, Karsan A, et al. Outcome of Patients With Non-Hodgkin Lymphomas With Concurrent MYC and BCL2 Rearrangements Treated With CODOX-M/IVAC With Rituximab Followed by Hematopoietic Stem Cell Transplantation. *Clin Lymphoma Myeloma Leuk*. 2015;15(6):341-348. doi:10.1016/j.clml.2014.12.015

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*. 2017;35(22):2473-2481. doi:10.1200/JCO.2017.72.6984

Tsai J, Greer JP; Role Of Aggressive Chemotherapeutic Regimens In Double Hit Lymphoma- Can Alternate Aggressive Induction Regimens Overcome The Poor Prognosis Of Diffuse Large B Cell Lymphoma?. *Blood* 2013; 122 (21): 4361. doi: <https://doi.org/10.1182/blood.V122.21.4361.4361>

Vacirca JL, Acs PI, Tabbara IA, Rosen PJ, Lee P, Lynam E. Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. *Ann Hematol*. 2014;93(3):403-409. doi:10.1007/s00277-013-1879-x

Note: Pathways are independent of specific Optum Care/health plan medical policy coverage criteria. Optum Care/health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered. Biosimilars or alternate formulations (along with the reference products) are considered on pathway unless otherwise specified by health plan formularies, medical policies, or preferred product rules.

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(1):117-122.

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(6):1169-1176. doi:10.1200/JCO.1994.12.6.1169

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(9):1902-1909. doi:10.1038/leu.2013.95

Weidmann E, Kim SZ, Rost A, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. *Ann Oncol*. 2002;13(8):1285-1289. doi:10.1093/annonc/mdf189

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(8):922-926. doi:10.1038/nm.3884

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(7):1622-1627. doi:10.1093/annonc/mdq626

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(10):2174-2180. doi:10.1080/10428190600799946

Zelenetz AD, Hamlin P, Kewalramani T, Yahalom J, Nimer S, Moskowitz CH. 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-i10. doi:10.1093/annonc/mdg702

Zinzani PL, Ribrag V, Moskowitz CH, et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. *Blood*. 2017;130(3):267-270. doi:10.1182/blood-2016-12-758383

Zinzani PL, Santoro A, Gritti G, et al. Nivolumab Combined With Brentuximab Vedotin for Relapsed/Refractory Primary Mediastinal Large B-Cell Lymphoma: Efficacy and Safety From the Phase II CheckMate 436 Study. *J Clin Oncol*. 2019;37(33):3081-3089. doi:10.1200/JCO.19.01492

Chihara D, Westin JR, Oki Y, et al. Management strategies and outcomes for very elderly patients with diffuse large B-cell lymphoma. *Cancer*. 2016;122(20):3145-3151. doi:10.1002/cncr.30173

García-Suárez J, Bañas H, Arribas I, De Miguel D, Pascual T, Burgaleta C. 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*. 2007;136(2):276-285. doi:10.1111/j.1365-2141.2006.06438.x

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(21):3633-3642. doi:10.1200/JCO.2000.18.21.3633

Wilson WH, Bryant G, Bates S, et al. EPOCH chemotherapy: toxicity and efficacy in relapsed and refractory non-Hodgkin's lymphoma. *J Clin Oncol*. 1993;11(8):1573-1582. doi:10.1200/JCO.1993.11.8.1573

Note: Pathways are independent of specific Optum Care/health plan medical policy coverage criteria. Optum Care/health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered. Biosimilars or alternate formulations (along with the reference products) are considered on pathway unless otherwise specified by health plan formularies, medical policies, or preferred product rules.