Arzerra® (ofatumumab)
(Intravenous)

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I. Length of Authorization[1,5,8,10]

Coverage will be provided for 6 months with renewal subject to the following:

- CLL/SLL (first-line) may be renewed to allow for a total of 12 cycles
- CLL/SLL (relapsed or refractory) may not be renewed (unless the provisions for extended treatment have been met)
- CLL/SLL (extended treatment) may be renewed to provide for a total of 2 years of therapy
- NHL/FL may be renewed to provide up to a total of 8 doses
- Waldenström's Macroglobulinemia/Lymphoplasmacytic lymphoma may be renewed to allow for up to a total of 3 cycles

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Arzerra 100 mg/5 mL: 3 vials Day 1
- Arzerra 1000 mg/50 mL: 2 vials weekly x 7 doses, then 2 vials every 4 weeks, then 1 vial every 8 weeks for up to 24 months

B. Max Units (per dose and over time) [HCPCS Unit]:

CLL/SLL	**First- Line** ▪ 30 billable units on day 1 and 100 billable units on day 8; then ▪ 100 billable units every 28 days for up to 11 doses **Refractory** ▪ 30 billable units on day 1; then ▪ 200 billable units weekly x 7 doses; then ▪ 200 billable units every 28 days x 4 doses **Relapsed** ▪ 30 billable units on day 1 and 100 billable units on day 8; then ▪ 100 billable units every 28 days for up to 5 doses **Extended Treatment** ▪ 30 billable units on day 1 and 100 billable units on day 8; then ▪ 100 billable units 7 weeks later and every 8 weeks thereafter
NHL/FL	▪ 100 billable units every 7 days x 4 doses

	▪ 100 billable units every 8 weeks thereafter
Waldenström's Macroglobulinemia / Lymphoplasmacytic Lymphoma	▪ 30 billable units on day 1; then ▪ 200 billable units every 7 days x 4 doses

III. Initial Approval Criteria[1-7,10-14]

Coverage is provided in the following conditions:

- Patient is at least 18 years old; **AND**

Universal Criteria

- Patient must be screened for HBV infection (i.e., HBsAg and anti-HBc) prior to initiating therapy; **AND**
- Must not be administered concurrently with live vaccines; **AND**

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) † Φ [6,12,22,27]

- Used as first-line therapy in combination with chlorambucil in patients considered inappropriate for fludarabine-based therapy; **OR**
- Used as first-line therapy in combination with bendamustine ‡; **AND**
  - Patient does not have del(17p)/TP53 mutation; **AND**
  - Patient is not considered to be frail with significant comorbidities; **OR**
- Used for relapsed or refractory disease; **AND**
  - Used as a single agent; **AND**
    - Patient is refractory to both fludarabine- and alemtuzumab-containing regimens; **OR**
    - Patient is refractory to fludarabine and unable to receive treatment with alemtuzumab as a result of bulky (> 5 cm) lymphadenopathy; **OR**
  - Used in combination with fludarabine and cyclophosphamide (FC); **OR**
- Used as extended treatment in patients with complete or partial response after 2 or more lines of therapy; **AND**
  - Used as a single agent

B-Cell Lymphomas ‡

- Used as a substitute for rituximab or obinutuzumab in patients experiencing rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis; **AND**
- Patient has any of the following:
  - Follicular Lymphoma (low grade 1-2)
  - MALT Lymphoma (Gastric or Non-Gastric)
  - Marginal Zone Lymphoma (Splenic or Nodal)
  - Diffuse Large B-Cell Lymphoma (DLBCL)
  - Histologic Transformation of Nodal Marginal Zone Lymphoma to DLBCL

- Mantle Cell Lymphoma
- High-Grade B-Cell Lymphomas with Translocations of MYC and BCL2 and/or BCL6 (Double/Triple Hit Lymphoma)

Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma ‡ [5,96]

- Used as a single agent; **AND**
- Patient is intolerant to rituximab; **AND**
  - Patient has previously failed or was intolerant to primary therapy; **OR**
  - Patient has progressive or relapsed disease

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria[1-4,7]

Authorizations can be renewed based on the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: Hepatitis B virus reactivation/infection, progressive multifocal leukoencephalopathy, severe infusion reactions, tumor lysis syndrome, cytopenias (neutropenia, anemia, and thrombocytopenia), etc.

V. Dosage/Administration[1-5,7,8,10-14]

Indication	Dose
CLL/SLL (First-line)	300 mg on Day 1, then 1,000 mg on Day 8, followed by 1,000 mg on Day 1 of subsequent 28-day cycles for a minimum of 3 cycles until best response or a maximum of 12 cycles
CLL/SLL (Refractory)	300 mg on Day 1, followed 1 week later by 2,000 mg given weekly x 7 doses (infusions 2 through 8), followed 4 weeks later by 2,000 mg every 4 weeks for 4 doses (infusions 9 through 12) for a total of 12 doses
CLL/SLL (Relapsed)	300 mg on Day 1, then 1,000 mg on Day 8, followed by 1,000 mg on Day 1 of subsequent 28-day cycles for a maximum of 6 cycles
CLL/SLL (Extended treatment)	300 mg on Day 1, then 1,000 mg on Day 8, followed by 1,000 mg 7 weeks later and every 8 weeks thereafter for up to a maximum of 2 years

NHL/FL	1,000 mg weekly for 4 doses, then 1,000 mg every 8 weeks for 4 doses
Waldenström's/ Lymphoplasmacytic lymphoma	**Cycle 1:** 300 mg on day 1, then 1,000 mg weekly for weeks 2 through 4; **OR** 300 mg on day 1, then 2,000 mg weekly for weeks 2 through 5 **Cycle 2-3:** • Patients with stable disease or a minor response at week 16 of cycle 1 are eligible to receive a re-treatment cycle of 300 mg on day 1, then 2,000 mg for weeks 2 through 5. Patients responding to cycle 1 or the redosing cycle who developed disease progression within 36 months can receive treatment with 300 mg on day 1, then 2,000 mg for weeks 2 through 5.

VI. Billing Code/Availability Information

HCPCS Code:

- J9302 - injection, ofatumumab, 10 mg; 1 billable unit = 10 mg

NDC:

- Arzerra 1000 mg/50 mL single-use vial: 00078-0690-xx
- Arzerra 100 mg/5 mL single-use vial: 00078-0669-xx

VII. References (STANDARD)

1. Arzerra [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corporation, August 2016. Accessed April 2021.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) ofatumumab. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2021.
3. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 3.2021. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2021.
4. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Version 1.2021. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER

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5. Furman RR, Eradat H, DiRienzo CG, et al. A phase II trial of ofatumumab in subjects with Waldenstrom's macroglobulinemia. Blood. 2011;118:3701
6. Wierda WG, Kipps TJ, Mayer J, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2010;28:1749-1755
7. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) B-Cell Lymphomas. Version 3.2021. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2021.
8. Rosenbaum CA, Jung SH, Pitcher B, et al. Phase 2 multicentre study of single-agent ofatumumab in previously untreated follicular lymphoma: CALGB 50901 (Alliance). Br J Haematol. 2019 Feb 5.
9. Van Imhoff GW, McMillan A, Matasar MJ et al. Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The ORCHARRD Study. J Clin Oncol 2017;35 (5):544-551.
10. Furman RR, Eradat HA, DiRienzo CG, et al. Once-weekly ofatumumab in untreated or relapsed Waldenström's macroglobulinaemia: an open-label, single-arm, phase 2 study. Lancet Haematol. 2017 Jan;4(1):e24-e34. doi: 10.1016/S2352-3026(16)30166-1. Epub 2016 Dec 1.
11. Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. Lancet. 2015 May 9;385(9980):1873-83. doi: 10.1016/S0140-6736(15)60027-7. Epub 2015 Apr 14.
12. Robak T, Warzocha K, Govind Babu K, et al. Ofatumumab plus fludarabine and cyclophosphamide in relapsed chronic lymphocytic leukemia: results from the COMPLEMENT 2 trial. Leuk Lymphoma. 2017 May;58(5):1084-1093. doi: 10.1080/10428194.2016.1233536. Epub 2016 Oct 12.
13. van Oers MH, Kuliczkowski K, Smolej L, et al. Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase 3 study. Lancet Oncol. 2015 Oct;16(13):1370-9. doi: 10.1016/S1470-2045(15)00143-6. Epub 2015 Sep 13.
14. Lemery SJ, Zhang J, Rothmann MD, et al. U.S. Food and Drug Administration Approval: Ofatumumab for the Treatment of Patients with Chronic Lymphocytic Leukemia Refractory to Fludarabine and Alemtuzumab. 10.1158/1078-0432.CCR-10-0570 Published September 2010.

VIII. References (ENHANCED)

1e. Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol. 2016 Jun 23. pii: S1470-2045(16)30097-3.

2e. Cheson BD, Chua N, Mayer J, et al. Overall Survival Benefit in Patients With Rituximab-Refractory Indolent Non-Hodgkin Lymphoma Who Received Obinutuzumab Plus Bendamustine Induction and Obinutuzumab Maintenance in the GADOLIN Study. J Clin Oncol. 2018 36:22, 2259-2266.

3e. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med. 2015;373(25):2425–2437.

4e. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018 Dec 27;379(26):2517-2528.

5e. Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2012 Sep 10;30(26):3209-16.

6e. Michallet AS, Aktan M, Hiddemann W, et al. Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study. Haematologica. 2018;103(4):698–706.

7e. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014 Mar 20;370(12):1101-10.

8e. Shanafelt TD, Wang V, Kay NE, et al. A Randomized Phase III Study of Ibrutinib (PCI-32765)-Based Therapy Vs. Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL): A Trial of the ECOG-ACRIN Cancer Research Group (E1912). Blood. 2018;132:LBA-4.

9e. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood. 2016 Jan 14;127(2):208-15.

10e. Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016 Jul;17(7):928-942.

11e. Woyach JA, Ruppert AS, Heerema NA, et al. Chemoimmunotherapy with fludarabine and rituximab produces extended overall survival and progression-free survival in chronic lymphocytic leukemia: long-term follow-up of CALGB study 9712. J Clin Oncol. 2011;29(10):1349–1355.

12e. Flinn IW, Panayiotidis P, Afanasyev B, et al. A phase 2, multicenter study investigating ofatumumab and bendamustine combination in patients with untreated or relapsed CLL. Am J Hematol. 2016 Sep;91(9):900-6.

13e. Sharman JP, Yimer HA, Boxer M, et al. Results of a phase II multicenter study of obinutuzumab plus bendamustine in pts with previously untreated chronic lymphocytic leukemia (CLL). J Clin Oncol. 2017;35(15_suppl):7523-7523.

14e. Ahn IE, Farooqui MZH, Tian X, et al. Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. Blood. 2018 May 24;131(21):2357-2366.

15e. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol. 2007 Dec 10;25(35):5616-23.

16e. Castro JE, James DF, Sandoval-Sus JD, et al. Rituximab in combination with high-dose methylprednisolone for the treatment of chronic lymphocytic leukemia [published correction appears in Leukemia. 2009 Dec;23(12):2326]. Leukemia. 2009;23(10):1779–1789.

17e. Byrd JC, Flynn JM, Kipps TJ, et al. Randomized phase 2 study of obinutuzumab monotherapy in symptomatic, previously untreated chronic lymphocytic leukemia. Blood. 2016;127(1):79–86.

18e. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. N Engl J Med 2018; 378:1107-1120.

19e. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371(3):213–223.

20e. Byrd JC, Hillmen P, O'Brien SM, et al. Long-term efficacy and safety with ibrutinib (ibr) in previously treated chronic lymphocytic leukemia (CLL): Up to four years follow-up of the RESONATE study. J Clin Oncol. 2017;35(15_suppl):7510-7510.

21e. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014;370(11):997–1007.

22e. Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. Blood. 2018;132(23):2446–2455.

23e. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. Blood. 2002 May 15;99(10):3554-61.

24e. Faderl S, Ferrajoli A, Wierda W, O'Brien S, Lerner S, Keating MJ. Alemtuzumab by continuous intravenous infusion followed by subcutaneous injection plus rituximab in the treatment of patients with chronic lymphocytic leukemia recurrence [published correction appears in Cancer. 2010 Aug 15;116(16):3982. Dosage error in article text]. Cancer. 2010;116(10):2360–2365.

25e. Robak T, Dmoszynska A, Solal-Céligny P, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol. 2010 Apr 1;28(10):1756-65.

26e. Castro JE, Sandoval-Sus JD, Bole J, Rassenti L, Kipps TJ. Rituximab in combination with high-dose methylprednisolone for the treatment of fludarabine refractory high-risk chronic lymphocytic leukemia. Leukemia. 2008;22(11):2048–2053.

27e. Badoux XC, Keating MJ, Wen S, et al. Phase II study of lenalidomide and rituximab as salvage therapy for patients with relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol. 2012;31(5):584–591.

28e. Bühler A, Wendtner CM, Kipps TJ, et al. Lenalidomide treatment and prognostic markers in relapsed or refractory chronic lymphocytic leukemia: data from the prospective, multicenter phase-II CLL-009 trial. Blood Cancer J. 2016;6(3):e404. Published 2016 Mar 11.

29e. Byrd JC, Wierda WG, Schuh A, et al. Acalabrutinib Monotherapy in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Updated Results from the Phase 1/2 ACE-CL-001 Study. Blood. 2017;130:498.

30e. Gopal AK, Davies AJ, Flinn IW, et al. Idelalisib Monotherapy and Durable Responses in Patients with Relapsed or Refractory Small Lymphocytic Lymphoma (SLL). Blood. 2015;126:2743.

31e. Cartron G, de Guibert S, Dilhuydy MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. Blood. 2014: 2196-2202.

32e. Österborg A, Jewell RC, Padmanabhan-Iyer S, et al. Ofatumumab monotherapy in fludarabine-refractory chronic lymphocytic leukemia: final results from a pivotal study. Haematologica. 2015;100(8):e311–e314.

33e. Lamanna N, Kalaycio M, Maslak P, et al. Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia. J Clin Oncol. 2006 Apr 1;24(10):1575-81.

34e. Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. Lancet Oncol. 2017;19(1):65–75.

35e. Zelenetz AD, Barrientos JC, Brown JR, et al. Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2017;18(3):297–311.

36e. Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. Lancet Oncol. 2016 Feb;17(2):200-211.

37e. O'Brien S, Jones JA2, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol. 2016 Oct;17(10):1409-1418.

38e. Brown JR, Hillmen P, O'Brien S, et al. Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously treated CLL/SLL. Leukemia. 2017;32(1):83–91.

39e. Sharman JP, Coutre SE, Furman RR, et al. Second Interim Analysis of a Phase 3 Study of Idelalisib (ZYDELIG®) Plus Rituximab (R) for Relapsed Chronic Lymphocytic Leukemia (CLL): Efficacy Analysis in Patient Subpopulations with Del(17p) and Other Adverse Prognostic Factors. Blood. 2014;124:330.

40e. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol. 2016 Jun;17(6):768-778.

41e. Stilgenbauer S, Zenz T, Winkler D, et al. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2009 Aug 20;27(24):3994-4001.

42e. Bowen DA, Call TG, Jenkins GD, et al. Methylprednisolone-rituximab is an effective salvage therapy for patients with relapsed chronic lymphocytic leukemia including those with unfavorable cytogenetic features. Leuk Lymphoma. 2007 Dec;48(12):2412-7.

43e. Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110δ, for relapsed/refractory chronic lymphocytic leukemia. Blood. 2014;123(22):3390–3397.

44e. 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 Oct 1;26(28):4579-86.

45e. Federico M, Luminari S, Dondi A, Tucci, et al. R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. J Clin Oncol. 2013 Apr 20;31(12):1506-13.

46e. Rummel MJ, 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 Apr 6;381(9873):1203-10.

47e. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med 2017; 377:1331-1344.

48e. Schulz H, Bohlius JF, Trelle S, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst. 2007 May 2;99(9):706-14.

49e. McLaughlin P, Grillo-López 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 Aug;16(8):2825-33.

50e. Dreyling M, Santoro A, Mollica L, et al. Long-Term Efficacy and Safety from the Copanlisib CHRONOS-1 Study in Patients with Relapsed or Refractory Indolent B-Cell Lymphoma. Blood. 2018; 132;1595.

51e. Czuczman MS, Fayad L, Delwail V, et al. Ofatumumab monotherapy in rituximab-refractory follicular lymphoma: results from a multicenter study. Blood. 2012 Apr 19;119(16):3698-704.

52e. Sehn LH, Goy A, Offner FC, et al. Randomized Phase II Trial Comparing Obinutuzumab (GA101) With Rituximab in Patients With Relapsed CD20+ Indolent B-Cell Non-Hodgkin Lymphoma: Final Analysis of the GAUSS Study. J Clin Oncol. 2015;33(30):3467–3474.

53e. Salles G, 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, randomised controlled trial. Lancet. 2011 Jan 1;377(9759):42-51.

54e. Martinelli G, Laszlo D, Ferreri AJ, et al. Clinical activity of rituximab in gastric marginal zone non-Hodgkin's lymphoma resistant to or not eligible for anti-Helicobacter pylori therapy. J Clin Oncol. 2005 Mar 20;23(9):1979-83.

55e. Conconi A, Martinelli G, Thiéblemont C, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. Blood. 2003 Oct 15;102(8):2741-5.

56e. Raderer M, Wohrer S, Streubel B, et al. Activity of rituximab plus cyclophosphamide, doxorubicin/mitoxantrone, vincristine and prednisone in patients with relapsed MALT lymphoma. Oncology. 2006;70(6):411-7.

57e. Salar A, Domingo-Domenech E, Estany C, et al. Combination therapy with rituximab and intravenous or oral fludarabine in the first-line, systemic treatment of patients with extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type. Cancer. 2009 Nov 15;115(22):5210-7.

58e. Zucca E, Conconi A, Laszlo D, et al. Addition of rituximab to chlorambucil produces superior event-free survival in the treatment of patients with extranodal marginal-zone B-cell lymphoma: 5-year analysis of the IELSG-19 Randomized Study. J Clin Oncol. 2013 Feb 10;31(5):565-72.

59e. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014;123(19):2944–2952.

60e. Salar A, Domingo-Domenech E, Panizo C, et al. Final Results of a Multicenter Phase II Trial with Bendamustine and Rituximab As First Line Treatment for Patients with MALT Lymphoma (MALT-2008–01). Blood. 2012;120:3691.

61e. Conconi A, Martinelli G, Thiéblemont C, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. Blood. 2003 Oct 15;102(8):2741-5.

62e. Kiesewetter B, Neuper O1, Mayerhoefer ME, et al. A pilot phase II study of ofatumumab monotherapy for extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) lymphoma. Hematol Oncol. 2018 Feb;36(1):49-55.

63e. Noy A, de Vos S, Thieblemont C, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Blood. 2017;129(16):2224–2232.

64e. Leonard JP, Trněný M, Izutsu K, et al. AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R2) Vs Rituximab/Placebo in Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma. Blood. 2018;132:445.

65e. Tsimberidou AM, Catovsky D, Schlette E, et al. Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone. Cancer. 2006 Jul 1;107(1):125-35.

66e. Else M, Marín-Niebla A, de la Cruz F, et al. Rituximab, used alone or in combination, is superior to other treatment modalities in splenic marginal zone lymphoma. Br J Haematol. 2012 Nov;159(3):322-8.

67e. 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.

68e. Pfreundschuh M, Kuhnt E, Trümper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol. 2011 Oct;12(11):1013-22.

69e. Gisselbrecht C, Schmitz N, Mounier N, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. J Clin Oncol. 2012;30(36):4462–4469.

70e. 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 Jun 10;31(17):2103-9.

71e. 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 Feb 26;125(9):1394-402.

72e. Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol. 2005 Oct 1;23(28):7013-23.

73e. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol. 2005 Mar 20;23(9):1984-92.

74e. Schulz H, Bohlius JF, Trelle S, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst. 2007 May 2;99(9):706-14.

75e. Casulo C, Iannotta A, Walkley J, et al. Ofatumumab-Bendamustine As First Line Treatment for Elderly Patients with Mantle Cell Lymphoma: A Phase II Risk Adapted Design with Comprehensive Geriatric Assessment. Blood. 2014;124:1751.

76e. Cavalli F, Rooney B, Pei L, et al. Randomized phase 3 study of rituximab, cyclophosphamide, doxorubicin, and prednisone plus vincristine (R-CHOP) or bortezomib (VR-CAP) in newly diagnosed mantle cell lymphoma (MCL) patients (pts) ineligible for bone marrow transplantation (BMT). J Clin Oncol. 2014;32(15_suppl):8500-8500.

77e. Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Ann Oncol. 2008;20(3):520–525.

78e. Furtado M, Dyer MJ, Johnson R, et al. Ofatumumab monotherapy in relapsed/refractory mantle cell lymphoma--a phase II trial. Br J Haematol. 2014 May;165(4):575-8.

79e. Dimopoulos MA, García-Sanz R, Gavriatopoulou M, et al. Primary therapy of Waldenstrom macroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). Blood. 2013 Nov 7;122(19):3276-82.

80e. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. J Clin Oncol. 2007 Aug 1;25(22):3344-9.

81e. Treon SP, Hanzis C, Tripsas C, et al. Bendamustine therapy in patients with relapsed or refractory Waldenström's macroglobulinemia. Clin Lymphoma Myeloma Leuk. 2011 Feb;11(1):133-5.

82e. Paludo J, Abeykoon JP, Shreders A, et al. Bendamustine and rituximab (BR) versus dexamethasone, rituximab, and cyclophosphamide (DRC) in patients with Waldenström macroglobulinemia. Ann Hematol. 2018 Aug;97(8):1417-1425.

83e. Treon SP, Hunter ZR, Matous J, et al. Multicenter clinical trial of bortezomib in relapsed/refractory Waldenstrom's macroglobulinemia: results of WMCTG Trial 03-248. Clin Cancer Res. 2007 Jun 1;13(11):3320-5.

84e. Ghobrial IM, Witzig TE, Gertz M, et al. Long-term results of the phase II trial of the oral mTOR inhibitor everolimus (RAD001) in relapsed or refractory Waldenstrom Macroglobulinemia. Am J Hematol. 2014 Mar;89(3):237-42.

85e. Österborg A, Jewell RC, Padmanabhan-Iyer S, et al. Ofatumumab monotherapy in fludarabine-refractory chronic lymphocytic leukemia: final results from a pivotal study. Haematologica. 2015;100(8):e311–e314. doi:10.3324/haematol.2014.121459.

86e. Magellan Health, Magellan Rx Management. Arzerra Clinical Literature Review Analysis. Last updated April 2021. Accessed April 2021.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C82.00	Follicular lymphoma grade I unspecified site
C82.01	Follicular lymphoma grade I lymph nodes of head, face, and neck
C82.02	Follicular lymphoma grade I intrathoracic lymph nodes
C82.03	Follicular lymphoma grade I intra-abdominal lymph nodes
C82.04	Follicular lymphoma grade I lymph nodes of axilla and upper limb
C82.05	Follicular lymphoma grade I lymph nodes of inguinal region and lower limb
C82.06	Follicular lymphoma grade I intrapelvic lymph nodes
C82.07	Follicular lymphoma grade I spleen
C82.08	Follicular lymphoma grade I lymph nodes of multiple sites
C82.09	Follicular lymphoma grade I extranodal and solid organ sites
C82.10	Follicular lymphoma grade II unspecified site
C82.11	Follicular lymphoma grade II lymph nodes of head, face, and neck
C82.12	Follicular lymphoma grade II intrathoracic lymph nodes
C82.13	Follicular lymphoma grade II intra-abdominal lymph nodes
C82.14	Follicular lymphoma grade II lymph nodes of axilla and upper limb
C82.15	Follicular lymphoma grade II lymph nodes of inguinal region and lower limb
C82.16	Follicular lymphoma grade II intrapelvic lymph nodes
C82.17	Follicular lymphoma grade II spleen
C82.18	Follicular lymphoma grade II lymph nodes of multiple sites
C82.19	Follicular lymphoma grade II extranodal and solid organ sites
C82.20	Follicular lymphoma grade III unspecified site
C82.21	Follicular lymphoma grade III lymph nodes of head, face, and neck
C82.22	Follicular lymphoma grade III intrathoracic lymph nodes
C82.23	Follicular lymphoma grade III intra-abdominal lymph nodes
C82.24	Follicular lymphoma grade III lymph nodes of axilla and upper limb
C82.25	Follicular lymphoma grade III lymph nodes of inguinal region and lower limb
C82.26	Follicular lymphoma grade III intrapelvic lymph nodes
C82.27	Follicular lymphoma grade III spleen
C82.28	Follicular lymphoma grade III lymph nodes of multiple sites
C82.29	Follicular lymphoma grade III extranodal and solid organ sites
C82.30	Follicular lymphoma grade IIIa unspecified site
C82.31	Follicular lymphoma grade IIIa lymph nodes of head, face, and neck

ICD-10	ICD-10 Description
C82.32	Follicular lymphoma grade IIIa intrathoracic lymph nodes
C82.33	Follicular lymphoma grade IIIa intra-abdominal lymph nodes
C82.34	Follicular lymphoma grade IIIa lymph nodes of axilla and upper limb
C82.35	Follicular lymphoma grade IIIa lymph nodes of inguinal region and lower limb
C82.36	Follicular lymphoma grade IIIa intrapelvic lymph nodes
C82.37	Follicular lymphoma grade IIIa spleen
C82.38	Follicular lymphoma grade IIIa lymph nodes of multiple sites
C82.39	Follicular lymphoma grade IIIa extranodal and solid organ sites
C82.40	Follicular lymphoma grade IIIb unspecified site
C82.41	Follicular lymphoma grade IIIb lymph nodes of head, face, and neck
C82.42	Follicular lymphoma grade IIIb intrathoracic lymph nodes
C82.43	Follicular lymphoma grade IIIb intra-abdominal lymph nodes
C82.44	Follicular lymphoma grade IIIb lymph nodes of axilla and upper limb
C82.45	Follicular lymphoma grade IIIb lymph nodes of inguinal region and lower limb
C82.46	Follicular lymphoma grade IIIb intrapelvic lymph nodes
C82.47	Follicular lymphoma grade IIIb spleen
C82.48	Follicular lymphoma grade IIIb lymph nodes of multiple sites
C82.49	Follicular lymphoma grade IIIb extranodal and solid organ sites
C82.50	Diffuse follicle center lymphoma unspecified site
C82.51	Diffuse follicle center lymphoma lymph nodes of head, face, and neck
C82.52	Diffuse follicle center lymphoma intrathoracic lymph nodes
C82.53	Diffuse follicle center lymphoma intra-abdominal lymph nodes
C82.54	Diffuse follicle center lymphoma lymph nodes of axilla and upper limb
C82.55	Diffuse follicle center lymphoma lymph nodes of inguinal region and lower limb
C82.56	Diffuse follicle center lymphoma intrapelvic lymph nodes
C82.57	Diffuse follicle center lymphoma spleen
C82.58	Diffuse follicle center lymphoma lymph nodes of multiple sites
C82.59	Diffuse follicle center lymphoma extranodal and solid organ sites
C82.60	Cutaneous follicle center lymphoma unspecified site
C82.61	Cutaneous follicle center lymphoma lymph nodes of head, face, and neck
C82.62	Cutaneous follicle center lymphoma intrathoracic lymph nodes
C82.63	Cutaneous follicle center lymphoma intra-abdominal lymph nodes
C82.64	Cutaneous follicle center lymphoma lymph nodes of axilla and upper limb

ICD-10	ICD-10 Description
C82.65	Cutaneous follicle center lymphoma lymph nodes of inguinal region and lower limb
C82.66	Cutaneous follicle center lymphoma intrapelvic lymph nodes
C82.67	Cutaneous follicle center lymphoma spleen
C82.68	Cutaneous follicle center lymphoma lymph nodes of multiple sites
C82.69	Cutaneous follicle center lymphoma extranodal and solid organ sites
C82.80	Other types of follicular lymphoma unspecified site
C82.81	Other types of follicular lymphoma lymph nodes of head, face, and neck
C82.82	Other types of follicular lymphoma intrathoracic lymph nodes
C82.83	Other types of follicular lymphoma intra-abdominal lymph nodes
C82.84	Other types of follicular lymphoma lymph nodes of axilla and upper limb
C82.85	Other types of follicular lymphoma lymph nodes of inguinal region and lower limb
C82.86	Other types of follicular lymphoma intrapelvic lymph nodes
C82.87	Other types of follicular lymphoma spleen lymph nodes of multiple sites
C82.88	Other types of follicular lymphoma lymph nodes of multiple sites
C82.89	Other types of follicular lymphoma extranodal and solid organ sites
C82.90	Follicular lymphoma, unspecified site
C82.91	Follicular lymphoma, unspecified lymph nodes of head, face, and neck
C82.92	Follicular lymphoma, unspecified intrathoracic lymph nodes
C82.93	Follicular lymphoma, unspecified intra-abdominal lymph nodes
C82.94	Follicular lymphoma, unspecified lymph nodes of axilla and upper limb
C82.95	Follicular lymphoma, unspecified lymph nodes of inguinal region and lower limb
C82.96	Follicular lymphoma, unspecified intrapelvic lymph nodes
C82.97	Follicular lymphoma, unspecified spleen
C82.98	Follicular lymphoma, unspecified lymph nodes of multiple sites
C82.99	Follicular lymphoma, unspecified extranodal and solid organ sites
C83.00	Small cell B-cell lymphoma, unspecified site
C83.01	Small cell B-cell lymphoma, lymph nodes of head, face and neck
C83.02	Small cell B-cell lymphoma, intrathoracic lymph nodes
C83.03	Small cell B-cell lymphoma, intra-abdominal lymph nodes
C83.04	Small cell B-cell lymphoma, lymph nodes of axilla and upper limb
C83.05	Small cell B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.06	Small cell B-cell lymphoma, intrapelvic lymph nodes
C83.07	Small cell B-cell lymphoma, spleen

ICD-10	ICD-10 Description
C83.08	Small cell B-cell lymphoma, lymph nodes of multiple sites
C83.09	Small cell B-cell lymphoma, extranodal and solid organ sites
C83.10	Mantle cell lymphoma, unspecified site
C83.11	Mantle cell lymphoma, lymph nodes of head, face, and neck
C83.12	Mantle cell lymphoma, intrathoracic lymph nodes
C83.13	Mantle cell lymphoma, intra-abdominal lymph nodes
C83.14	Mantle cell lymphoma, lymph nodes of axilla and upper limb
C83.15	Mantle cell lymphoma, lymph nodes of inguinal region and lower limb
C83.16	Mantle cell lymphoma, intrapelvic lymph nodes
C83.17	Mantle cell lymphoma, spleen
C83.18	Mantle cell lymphoma, lymph nodes of multiple sites
C83.19	Mantle cell lymphoma, extranodal and solid organ sites
C83.30	Diffuse large B-cell lymphoma, unspecified site
C83.31	Diffuse large B-cell lymphoma, lymph nodes of head, face, and neck
C83.32	Diffuse large B-cell lymphoma, intrathoracic lymph nodes
C83.33	Diffuse large B-cell lymphoma, intra-abdominal lymph nodes
C83.34	Diffuse large B-cell lymphoma, lymph nodes of axilla and upper limb
C83.35	Diffuse large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.36	Diffuse large B-cell lymphoma, intrapelvic lymph nodes
C83.37	Diffuse large B-cell lymphoma, spleen
C83.38	Diffuse large B-cell lymphoma, lymph nodes of multiple sites
C83.39	Diffuse large B-cell lymphoma, extranodal and solid organ sites
C83.70	Burkitt lymphoma, unspecified site
C83.71	Burkitt lymphoma, lymph nodes of head, face, and neck
C83.72	Burkitt lymphoma, intrathoracic lymph nodes
C83.73	Burkitt lymphoma, intra-abdominal lymph nodes
C83.74	Burkitt lymphoma, lymph nodes of axilla and upper limb
C83.75	Burkitt lymphoma, lymph nodes of inguinal region and lower limb
C83.76	Burkitt lymphoma, intrapelvic lymph nodes
C83.77	Burkitt lymphoma, spleen
C83.78	Burkitt lymphoma, lymph nodes of multiple sites
C83.79	Burkitt lymphoma, extranodal and solid organ sites
C83.80	Other non-follicular lymphoma unspecified site

ICD-10	ICD-10 Description
C83.81	Other non-follicular lymphoma lymph nodes of head, face, and neck
C83.82	Other non-follicular lymphoma intrathoracic lymph nodes
C83.83	Other non-follicular lymphoma intra-abdominal lymph nodes
C83.84	Other non-follicular lymphoma lymph nodes of axilla and upper limb
C83.85	Other non-follicular lymphoma lymph nodes of inguinal region and lower limb
C83.86	Other non-follicular lymphoma intrapelvic lymph nodes
C83.87	Other non-follicular lymphoma spleen
C83.88	Other non-follicular lymphoma lymph nodes of multiple sites
C83.89	Other non-follicular lymphoma extranodal and solid organ sites
C83.90	Non-follicular (diffuse) lymphoma, unspecified, unspecified site
C83.91	Non-follicular (diffuse) lymphoma, unspecified, lymph nodes of head, face, and neck
C83.92	Non-follicular (diffuse) lymphoma, unspecified, intrathoracic lymph nodes
C83.93	Non-follicular (diffuse) lymphoma, unspecified, intra-abdominal lymph nodes
C83.94	Non-follicular (diffuse) lymphoma, unspecified, lymph nodes of axilla and upper limb
C83.95	Non-follicular (diffuse) lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C83.96	Non-follicular (diffuse) lymphoma, unspecified, intrapelvic lymph nodes
C83.97	Non-follicular (diffuse) lymphoma, unspecified, spleen
C83.98	Non-follicular (diffuse) lymphoma, unspecified, lymph nodes of multiple sites
C83.99	Non-follicular (diffuse) lymphoma, unspecified, extranodal and solid organ sites
C85.10	Unspecified B-cell lymphoma, unspecified site
C85.11	Unspecified B-cell lymphoma, lymph nodes of head, face, and neck
C85.12	Unspecified B-cell lymphoma, intrathoracic lymph nodes
C85.13	Unspecified B-cell lymphoma, intra-abdominal lymph nodes
C85.14	Unspecified B-cell lymphoma, lymph nodes of axilla and upper limb
C85.15	Unspecified B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.16	Unspecified B-cell lymphoma, intrapelvic lymph nodes
C85.17	Unspecified B-cell lymphoma, spleen
C85.18	Unspecified B-cell lymphoma, lymph nodes of multiple sites
C85.19	Unspecified B-cell lymphoma, extranodal and solid organ sites
C85.20	Mediastinal (thymic) large B-cell lymphoma, unspecified site
C85.21	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of head, face, and neck
C85.22	Mediastinal (thymic) large B-cell lymphoma, intrathoracic lymph nodes
C85.23	Mediastinal (thymic) large B-cell lymphoma, intra-abdominal lymph nodes

ICD-10	ICD-10 Description
C85.24	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of axilla and upper limb
C85.25	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.26	Mediastinal (thymic) large B-cell lymphoma, intrapelvic lymph nodes
C85.27	Mediastinal (thymic) large B-cell lymphoma, spleen
C85.28	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of multiple sites
C85.29	Mediastinal (thymic) large B-cell lymphoma, extranodal and solid organ sites
C85.80	Other specified types of non-Hodgkin lymphoma, unspecified site
C85.81	Other specified types of non-Hodgkin lymphoma, lymph nodes of head, face, and neck
C85.82	Other specified types of non-Hodgkin lymphoma, intrathoracic lymph nodes
C85.83	Other specified types of non-Hodgkin lymphoma, intra-abdominal lymph nodes
C85.84	Other specified types of non-Hodgkin lymphoma, lymph nodes of axilla and upper limb
C85.85	Other specified types of non-Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C85.86	Other specified types of non-Hodgkin lymphoma, intrapelvic lymph nodes
C85.87	Other specified types of non-Hodgkin lymphoma, spleen
C85.88	Other specified types of non-Hodgkin lymphoma, lymph nodes of multiple sites
C85.89	Other specified types of non-Hodgkin lymphoma, extranodal and solid organ sites
C88.0	Waldenström macroglobulinemia
C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma]
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
D47.Z2	Castleman disease

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; DLBCL = diffuse large B-cell lymphoma; MRD = minimal residual disease; TLS = tumor lysis syndrome; IPI = International Prognostic Index; ASCT = autologous stem-cell transplantation; TTF = time to treatment failure; DFS = disease free survival

Chronic lymphocytic leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

Without del(17p) or TP53 Mutation – First line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Ibrutinib	1 preferred	Yes	Phase 3 (RESONATE-2), randomized, open-label	Chlorambucil	PFS	First line	• Ibrutinib was superior to chlorambucil in previously untreated patients with CLL or small lymphocytic lymphoma, as assessed by progression-free survival, overall survival, response rate, and improvement in hematologic variables.
Ibrutinib	1 preferred	Yes	Phase 3 (A041202)	Ibrutinib + rituximab vs. Bendamustine + rituximab (BR)	PFS	First line	• Among older patients with untreated CLL, treatment with ibrutinib was superior to treatment with bendamustine plus rituximab with regard to progression-free survival. There was no significant difference between ibrutinib and ibrutinib plus rituximab with regard to progression-free survival.
Bendamustine + rituximab (BR)	2A	No	Phase 2 (CLL2M), multi-center	N/A	ORR	First line	• Chemoimmunotherapy with BR is effective (ORR 88%) and safe in patients with previously untreated CLL
Bendamustine + rituximab (BR)	2A	No	Phase 3 (MABLE), randomized	Chlorambucil + rituximab	CR	First line	• Bendamustine plus rituximab demonstrated a complete response rate of 24% and was superior to chlorambucil plus rituximab in first-line therapy for CLL. Improvement in PFS

							was significant however there was no difference in ORR or OS.
Chlorambucil + ofatumumab	None	Yes (for whom fludarabine based therapy is considered inappropriate)	Phase 3 (COMPLEMENT 1), randomized, multi-center, open-label	Chlorambucil	PFS	First line	• Addition of ofatumumab to chlorambucil led to an improvement in PFS and ORR in treatment-naïve patients with CLL who were elderly or had comorbidities.
Chlorambucil + obinutuzumab	2A	Yes	Phase 3 (CLL11), randomized, open-label	Chlorambucil + rituximab vs. Chlorambucil	PFS	First line	• Combining an anti-CD20 antibody with chemotherapy improved outcomes in patients with CLL and coexisting conditions. In this patient population, obinutuzumab was superior to rituximab when each was combined with chlorambucil.
Ibrutinib + rituximab	2B	No	Phase 3 (ECOG-ACRIN E1912), randomized	Fludarabine + cyclophosphamide + rituximab (FCR)	PFS	First-line	• The combination of ibrutinib and rituximab provides superior PFS and OS relative to FCR for patients with previously untreated CLL age <70.
Fludarabine + cyclophosphamide + rituximab (FCR)	2A	Yes	Phase 3 (CLL8), randomized	Fludarabine + cyclophosphamide (FC)	PFS	First line	• First-line chemoimmunotherapy with FCR induces long-term remissions and highly relevant improvement in OS in specific genetic subgroups of fit patients with CLL, in particular those with IGHV MUT.
Fludarabine + cyclophosphamide + rituximab (FCR)	2A	Yes	Phase 3 (CLL10), randomized, open-label, international	Bendamustine + rituximab (BR)	PFS	First line	• The combination of fludarabine, cyclophosphamide, and rituximab demonstrated superiority over bendamustine plus rituximab in terms of PFS and MRD negativity in fit patients with CLL. However, bendamustine and rituximab is associated with less toxic effects.

Fludarabine + rituximab (FR) concurrently	2A [not recommended for CLL with del (11q)]	No	Phase 2 (CALGB 9712), randomized	Fludarabine + rituximab (FR) sequentially	PFS OS	First line	• Long-term follow-up of CALGB 9712 demonstrates extended OS (85 months) and PFS (42 months) with fludarabine plus rituximab.
Bendamustine + rituximab (BR)	2A	No	Phase 2 (CLL2M), multi-center	N/A	ORR	First line	• Chemoimmunotherapy with BR is effective (ORR 88%) and safe in patients with previously untreated CLL
Bendamustine + ofatumumab	2A	No	Phase 2, open-label, single-arm, multi-center	N/A	ORR	First line and relapsed disease	• The combination of ofatumumab and bendamustine was effective in these previously untreated or relapsed populations. ORR for previously untreated patients was 85% and 74% for patients with relapsed disease
Bendamustine + obinutuzumab	2A	No	Phase 2, multi-center	N/A	CR	First line	• Bendamustine plus obinutuzumab is an effective regimen with an ORR of 89% for first-line treatment of CLL patients inducing a complete response rate of 49% after 6 cycles of therapy.
With del(17p) or TP53 Mutation – First-line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Ibrutinib	1 preferred	Yes	Phase 2	N/A	ORR	First line	• Long-term administration of ibrutinib was associated with an ORR of 97% and 5-year OS of 85%.
Alemtuzumab	2A	No	Phase 3 (CAM307), randomized	Chlorambucil	PFS	First line	• As first-line treatment for patients with CLL, alemtuzumab demonstrated significantly improved PFS, ORR, and CR compared with chlorambucil.

HDMP + rituximab	2A	No	Single institution study	N/A	ORR	First line	• This study demonstrates that HDMP and rituximab is an effective nonmyelosuppressive treatment combination for patients with CLL however, only 1 out of 28 patients had a del(17p) genetic abnormality.
Obinutuzumab	2A	No	Phase 2	N/A	ORR	First line	• This study demonstrates significant efficacy of obinutuzumab monotherapy, for 1000 mg as well as for 2000 mg, in untreated CLL patients (ORR 49% and 67%, respectively).
Alemtuzumab + rituximab	2A		No clinical trial evidence				
Without del(17p) or TP53 Mutation – Relapsed/Refractory therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Venetoclax + rituximab (VenR)	1 preferred	Yes (after at least one prior therapy)	Phase 3 (MURANO), randomized	Bendamustine + rituximab (BR)	PFS	Relapsed or refractory disease	• Among patients with relapsed or refractory chronic lymphocytic leukemia, venetoclax plus rituximab resulted in significantly higher rates of progression-free survival than bendamustine plus rituximab.
Ibrutinib	1 preferred	Yes	Phase 3 (RESONATE), randomized, open-label 4-year follow-up study	Ofatumumab	PFS	Relapsed or refractory disease	• Ibrutinib, as compared with ofatumumab, significantly improved progression-free survival, overall survival, and response rate among patients with previously treated CLL or SLL.

Idelalisib + rituximab	2A preferred	Yes	Phase 3, randomized, multi-center, double-blind, placebo-controlled	Placebo + rituximab	PFS	Relapsed disease	• The combination of idelalisib and rituximab, as compared with placebo and rituximab, significantly improved progression-free survival, response rate, and overall survival among patients with relapsed CLL who were less able to undergo chemotherapy.
Duvelisib	2A preferred	Yes (after at least 2 prior therapies)	Phase 3 (DUO), randomized	Ofatumumab	PFS	Relapsed or refractory disease	• Duvelisib demonstrated to be a potentially effective treatment option for patients with relapsed or refractory CLL/SLL with an improvement in reduction in lymph node burden, ORR, and PFS.
Alemtuzumab	2A	Yes (for B-CLL)	Phase 2	N/A	ORR	Fludarabine-refractory disease	• Alemtuzumab induced an ORR of 33% in patients with relapsed or refractory CLL after fludarabine therapy.
Alemtuzumab + rituximab	2A	No	Exploration study	N/A	ORR	Relapsed or refractory disease	• The combination of alemtuzumab plus rituximab has an ORR of 53% in patients with relapsed or refractory CLL.
Fludarabine + cyclophosphamide + rituximab (FCR) – reduced dose	2A	No (first-line only)	Phase 3 (REACH), randomized	Fludarabine + cyclophosphamide (FC)	PFS	First relapse	• FCR significantly improved PFS in patients with previously treated CLL however, the difference is OS was not significantly different.
Fludarabine + cyclophosphamide + ofatumumab	2A	Yes	Phase 3 (COMPLEMENT 2), multi-center, open-label, randomized	Fludarabine + cyclophosphamide (FC)	PFS	Relapsed CLL	• Ofatumumab plus fludarabine and cyclophosphamide improved PFS with manageable safety for patients with relapsed CLL compared with FC alone.

High-dose methylprednisolone (HDMP) + rituximab	2A	No	Small study	N/A	ORR	Fludarabine-refractory disease	• HDMP combined with rituximab was effective in patients with heavily pretreated CLL (ORR 93%).
Lenalidomide + rituximab	2A	No	Phase 2	N/A	ORR	Relapsed or refractory disease	• The combination of lenalidomide and rituximab is active in patients with recurrent CLL with an ORR of 66%. ORR was lower for patients with fludarabine-refractory disease compared to fludarabine-sensitive CLL.
Lenalidomide	2A	No	Phase 2 (CLL-009 trial), randomized, multi-center	Lenalidomide (other regimens)	Adverse events ORR (secondary endpoint)	Relapsed or refractory disease	• Lenalidomide monotherapy is active in patients with relapsed or refractory CLL with an ORR of 40%.
Acalabrutinib	2A	No	Phase 2	N/A	Safety ORR (secondary endpoint)	Relapsed or refractory to at least 1 prior treatment	• Treatment with acalabrutinib was associated with high response rates (ORR 85%) and durable remissions in patients with relapsed or refractory CLL.
Idelalisib	2A	No	Phase 2	N/A	ORR	Relapsed or refractory disease	• Idelalisib monotherapy demonstrated clinical activity in patients with relapsed or refractory SLL with an ORR of 61%.
Obinutuzumab	2A	No	Phase 1/2 (GAUGUIN)	N/A	ORR	Relapsed or	• Obinutuzumab monotherapy is active in patients with heavily pretreated relapsed/ refractory CLL with an ORR of 30%.

						refractory disease	
Ofatumumab	2A	Yes	Phase 2 Final Analysis	N/A	ORR	Fludarabine- and alemtuzumab-refractory disease OR fludarabine-refractory with bulky lymphadenopathy (>5 cm)	• Ofatumumab demonstrated an ORR of 43%-49% in patients with difficult-to-treat relapsed or refractory CLL.
Pentostatin + cyclophosphamide + rituximab (PCR) – reduced dose	2A	No	Small series	N/A	ORR	Fludarabine-refractory disease	• The PCR regimen is safe and effective in patients with previously treated CLL (ORR 75%).
Venetoclax	2A	No	Phase 2, multi-center, open-label, non-randomized	N/A	ORR	Ibrutinib-refractory or relapsed disease	• Venetoclax demonstrated an ORR of 65% in patients with relapsed or refractory CLL whose disease progressed during or after discontinuation of ibrutinib therapy.
Bendamustine + rituximab (BR)	2A	No	Phase 2	N/A	Bendamustine + rituximab + placebo	Relapsed or refractory disease	• Chemoimmunotherapy with BR is effective and safe in patients with relapsed CLL and has notable activity in fludarabine-refractory disease.

Bendamustine + rituximab + idelalisib	2B/3	No	Phase 3, randomized	Bendamustine + rituximab + placebo	PFS	Relapsed or refractory disease	• Idelalisib in combination with bendamustine plus rituximab improved PFS compared with bendamustine plus rituximab alone in patients with relapsed or refractory chronic lymphocytic leukemia. However, careful attention needs to be paid to management of serious adverse events and infections associated with this regimen during treatment selection.
Bendamustine + rituximab + ibrutinib	2B/3	No	Phase 3 (HELIOS), randomized, double-blind	Bendamustine + rituximab + placebo	PFS	Relapsed or refractory disease following 1 or more lines of therapy	• The addition of ibrutinib to bendamustine and rituximab results in significant improvements in PFS.
Chlorambucil + rituximab	2A	No	No evidence in relapsed or refractory disease.				
With del(17p) or TP53 Mutation – Relapsed/Refractory therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Ibrutinib	1 preferred	Yes	Phase 2 (RESONATE-17), multi-center, open-label, single-arm, international	N/A	ORR	Relapsed or refractory disease	• 83% of patients with del17p relapsed or refractory CLL had a clinical response to ibrutinib.

Ibrutinib	1 preferred	Yes	Phase 3 (RESONATE) subgroup analysis	Ofatumumab	PFS	Relapsed or refractory disease	• The improved efficacy of ibrutinib vs ofatumumab continues in all prognostic subgroups including del17p and del11q. No significant difference within the ibrutinib arm was observed for PFS across most genomic subtypes, although a subset carrying both TP53 mutation and del17p had reduced PFS compared with patients with neither abnormality.
Venetoclax + rituximab	1 preferred	Yes (after at least one prior therapy)	Phase 3 (MURANO), randomized	Bendamustine + rituximab (BR)	PFS	Relapsed or refractory disease	• Among patients with relapsed or refractory chronic lymphocytic leukemia, venetoclax plus rituximab resulted in significantly higher rates of progression-free survival than bendamustine plus rituximab across all subgroups of patients, including those with del(17p) or TP53 mutation.
Idelalisib + rituximab	2A preferred	Yes	Phase 3 second interim analysis	Placebo + rituximab	PFS	Relapsed disease	• The combination of idelalisib and rituximab, as compared with placebo and rituximab, significantly improved progression-free survival, response rate, and overall survival among patients with relapsed CLL who were less able to undergo chemotherapy.
Duvelisib	2A preferred	Yes (after at least 2 prior therapies)	Phase 3 (DUO), randomized	Ofatumumab	PFS	Relapsed or refractory disease	• Duvelisib demonstrated to be a potentially effective treatment option for patients with relapsed or refractory CLL/SLL with an improvement in ORR and PFS compared to ofatumumab regardless of del17p and/or TP53 mutation.
Venetoclax	2A preferred	Yes	Phase 2	N/A	ORR	Relapsed or refractory disease	• Venetoclax monotherapy is active in patients with relapsed or refractory del(17p) CLL with an ORR of 79.4%.

Alemtuzumab + rituximab	2A	No	No clinical evidence to support use of alemtuzumab in combination with rituximab for relapsed or refractory CLL>				
Alemtuzumab subcutaneous	2A	No	Phase 2 (CLL2H)	N/A	ORR	Fludarabine-refractory	• Subcutaneous alemtuzumab was effective in the treatment of fludarabine-refractory CLL with an ORR of 34% including patients with those associated with poor-prognosis genetic abnormalities.
HDMP + rituximab	2A	No	Exploration study	N/A	------	Relapsed disease	• HDMP-rituximab is an active regimen in patients with relapsed and cytogenetically high-risk CLL with a 3-year survival rate of 41%.
Lenalidomide + rituximab	2A	No	Phase 2	N/A	ORR	Relapsed or refractory disease	• The combination of lenalidomide and rituximab is active in patients with recurrent del17p CLL with an ORR of 53%.
Idelalisib	2A	No	Phase 1	N/A	-----	Relapsed or refractory disease	• Idelalisib demonstrated an ORR of 54% in patients with del17p and/or TP53 mutated relapsed or refractory CLL.
Ofatumumab	2A	Yes	Phase 2 Final Analysis	N/A	ORR	Fludarabine- and alemtuzumab-refractory disease OR fludarabine-refractory with bulky	• Ofatumumab demonstrated an ORR of 43%-49% in patients with difficult-to-treat relapsed or refractory CLL.

						lymphadenopathy	
Ofatumumab	2B (Post second-line maintenance therapy following complete or partial response to treatment for relapsed or refractory disease	Yes	Phase 3 (PROLONG), randomized, open-label, multi-center	Observation	PFS	Maintenance for relapsed CLL in complete or partial remission after second-or third-line treatment	• Ofatumumab reduced a patient's risk of disease progression or death by 50% after they have achieved a complete or partial remission. However, a benefit in OS was not observed.

B-Cell Lymphomas

Low-grade or Follicular Lymphoma – First line							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab + cyclophosphamide + vincristine + prednisone (R-CVP)	2A	Yes	Phase 3 (MARCUS), multi-center, open-label	Cyclophosphamide + vincristine + prednisone (CVP)	TTF	First line	• The addition of rituximab to the CVP regimen significantly improves the clinical outcome including TTF, ORR, and 4-year OS rate in patients with previously untreated advanced follicular lymphoma
Rituximab + cyclophosphamide + vincristine +	2A	Yes	Phase 3 (FOLL05), randomized,	R-CHOP vs. rituximab + fludarabine +	TTF	First line	• In this study, R-CHOP and R-FM were superior to R-CVP in terms of 3-year TTF and PFS. In addition, R-CHOP had a better risk-benefit ratio compared with R-FM.

prednisone (R-CVP)			open-label, multi-center	mitoxantrone (R-FM)			
Bendamustine + rituximab (BR)	2A preferred	No	Phase 3 (StiL), open-label, multi-center, randomized	R-CHOP	PFS	First line	• The primary endpoint of PFS was significantly longer with BR compared with R-CHOP.
Obinutuzumab + bendamustine, CHOP, or CVP, followed by obinutuzumab maintenance	2A preferred	Yes	Phase 3 (GALLIUM), randomized, open-label, multi-center	Rituximab + bendamustine, CHOP, or CVP, followed by rituximab	PFS	First line	• Obinutuzumab-based immunochemotherapy and maintenance therapy resulted in longer progression-free survival than rituximab-based therapy. High-grade adverse events were more common with obinutuzumab-based chemotherapy.
Ofatumumab	2A (as a substitute for rituximab or obinutuzumab)	No	Phase 2 (CALGB 50901)	N/A	ORR	First line	• Ofatumumab monotherapy demonstrated clinical activity in patients with untreated low or intermediate risk follicular lymphoma with an ORR of 84%.
Rituximab + chemotherapy	2A	Yes	Meta-analysis	N/A	OS	Untreated and previously treated	• In patients with indolent or mantle cell lymphoma, R-chemo is superior to chemotherapy alone with respect to overall survival
Low-grade or Follicular Lymphoma – Second line or subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab (weekly x4)	2A	Yes	Single-arm, multi-center	N/A	-----	Relapsed disease	• The response rate of 48% with rituximab is comparable to results with single-agent

							cytotoxic chemotherapy. Toxicity was mild.
Bendamustine + obinutuzumab (BO), followed by maintenance obinutuzumab in non-progressing patients	2A preferred (in patients refractory to rituximab)	Yes	Phase 3 (GADOLIN), randomized, controlled, open-label, multi-center	Bendamustine (B)	PFS	Refractory to rituximab	• Obinutuzumab plus bendamustine followed by obinutuzumab maintenance has improved PFS over bendamustine monotherapy in rituximab-refractory patients with indolent non-Hodgkin lymphoma, with manageable toxicity
Copanlisib	2A	Yes	Phase 2 (CHRONOS-1)	N/A	ORR	Relapsed or refractory indolent B-cell NHL after ≥ 2 prior lines of therapy (including rituximab and an alkylating agent/ regimen)	• Copanlisib demonstrated significant efficacy with an ORR of 61% and a manageable safety profile in heavily pretreated patients with relapsed or refractory indolent lymphoma.
Ofatumumab	2A	No	Phase 2	N/A	ORR	Refractory to rituximab	• Ofatumumab is modestly active with an ORR of 22% in patients refractory to rituximab
Obinutuzumab	None	No	Phase 2 (GAUSS study), randomized	Rituximab	ORR	Relapsed or refractory	• Obinutuzumab failed to demonstrate a PFS or OS benefit when compared with rituximab.
Low-grade or Follicular Lymphoma – Maintenance Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Rituximab (2 years)		Yes	Phase 3 (PRIMA), randomized, open-label	Placebo	PFS	Maintenance after an initial response to rituximab (R-CHOP, R-CVP, R-FCM)	• 2 years of rituximab maintenance therapy after immunochemotherapy as first-line treatment for follicular lymphoma significantly improves PFS
Obinutuzumab + bendamustine, CHOP, or CVP, followed by obinutuzumab maintenance	2A	Yes	Phase 3 (GALLIUM), randomized, open-label, multi-center	Rituximab + bendamustine, CHOP, or CVP, followed by rituximab	PFS	First line	• Obinutuzumab-based immunochemotherapy and maintenance therapy resulted in longer progression-free survival than rituximab-based therapy. High-grade adverse events were more common with obinutuzumab-based chemotherapy.
Bendamustine + obinutuzumab (BO), followed by maintenance obinutuzumab in non-progressing patients	2A preferred (in patients refractory to rituximab)	Yes	Phase 3 (GADOLIN), randomized, controlled, open-label, multi-center Updated analysis	Bendamustine (B)	PFS	Refractory to rituximab (no response to or progressed within 6 months of therapy with a rituximab-containing regimen)	• Obinutuzumab plus bendamustine followed by obinutuzumab maintenance has improved efficacy (PFS and OS) over bendamustine monotherapy in rituximab-refractory patients with indolent non-Hodgkin lymphoma, with manageable toxicity
Gastric & Non-Gastric MALT Lymphoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab	2A preferred	No	Prospective study	N/A	-----	Resistant to or not eligible	• This study demonstrated the clinical activity of rituximab in gastric MALT NHL patients resistant/refractory to antibiotics treatment or not presenting

						for anti-H. pylori therapy	with clinical evidence of Helicobacter pylori infection. ORR was 77%.
Rituximab	2A preferred	No	Phase 2	N/A	-----	Untreated and relapsed MALT lymphomas	• Rituximab demonstrated clinical activity in patients with non-gastric MALT lymphomas with an ORR of 80%.
Rituximab + cyclophosphamide + doxorubicin/ mitoxantrone + vincristine + prednisone (R-CHOP or R-CNOP)	2A preferred	No	Retrospective analysis	N/A	-----	Relapsed disease	• Data demonstrated R-CHOP/R-CNOP activity with a CR of 77% in relapsing MALT lymphoma.
Rituximab + fludarabine	None	No	Phase 2	N/A	-----	First line	• Combination therapy with rituximab and fludarabine demonstrated a CR of 100% as first-line systemic treatment for patients with extranodal MALT lymphoma.
Rituximab + chlorambucil	2A	No	Phase 3 (IELSG-19), randomized	Chlorambucil	EFS	First line systemic therapy	• Both treatments were active; the better response rate and EFS obtained with the addition of rituximab did not translate into improved OS
Bendamustine + rituximab (BR)	2A	No	Phase 3 (StiL), open-label, multi-center, randomized	R-CHOP	PFS	First line	• Among the patients with marginal zone lymphoma, median PFS with BR was not significantly different from that with R-CHOP.
Bendamustine + rituximab (BR)	2A	No	Phase 3 (BRIGHT), randomized	R-CHOP or R-CVP	CR	First-line	• Among the patients with marginal zone lymphoma, BR resulted in similar CR (20 versus 24 percent) and overall (92 versus 71 percent) response rates.

Bendamustine + rituximab (BR)	2A	No	Phase 2 (MALT-2008-01)	N/A	-----	First-line	• The combination of bendamustine and rituximab in first line treatment of MALT lymphoma achieved an ORR of 100% after only 3 cycles. CR rate after completing treatment plan was 98%.
Rituximab	2A	No	Phase 2	N/A	-----	Untreated and relapsed MALT lymphomas	• Rituximab demonstrated clinical activity in patients with non-gastric MALT lymphomas with an ORR of 80%.
Ofatumumab	2A (as a substitute for rituximab or obinutuzumab)	No	Phase 2 (O-MA 1)	N/A	-----	H. pylori refractory or extragastric MALT lymphoma	• Ofatumumab is clinically active with an ORR of 81% for the treatment of MALT lymphoma
Nodal Marginal Zone Lymphoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine + rituximab (BR)	2A	No	See clinical trials above for Gastric MALT lymphomas				
Ibrutinib	2A	Yes	Phase 2, single-arm, open-label	N/A	ORR	Relapsed after ≥ 1 prior therapy with CD20 monoclonal antibody regimen	• Single-agent ibrutinib induced durable responses with an ORR of 48% and median PFS of 14 months.

Lenalidomide + rituximab	2A	No	Phase 3 (AUGMENT), multi-center, randomized	Rituximab + placebo	PFS	Relapsed or refractory disease	• Lenalidomide plus rituximab more than doubled the media PFS however, a subgroup analysis did not reveal a PFS benefit for patients with marginal zone lymphoma.
Bendamustine + obinutuzumab	2A	No	See Follicular Lymphoma above				
Splenic Marginal Zone Lymphoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab	2A preferred	No	Retrospective study	N/A	CR	Treatment naïve and previously treated disease	• Rituximab was found to have major activity in patients with splenic MZL with an ORR of 88% and CR of 42%.
Rituximab ± chemotherapy	2A	No	Retrospective study	Chemotherapy	-----	Treatment naïve and previously treated disease	• The CR and DFS rates after rituximab, given alone or with chemotherapy, were significantly better than after chemotherapy without rituximab.
Diffuse Large B-Cell Lymphoma (DLBCL) – First line							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab + cyclophosphamide + doxorubicin +	1	Yes	Phase 3 (GELA LNH-98.5),	CHOP	EFS	First line	• Rituximab plus CHOP improved overall survival by 15.5% compared to CHOP alone at a 10-year median follow-up and

vincristine + prednisone (R-CHOP			randomized, multi-center, open-label				confirm the benefit of adding rituximab to CHOP for the treatment of patients with DLBCL.
Rituximab + chemotherapy	1	Yes	Phase 3 (MInT), randomized, open-label	Chemotherapy (CHOP, CHOP + etoposide, MACOP-B, PMitCEBO)	EFS	First line	• Rituximab added to six cycles of CHOP-like chemotherapy improved long-term outcomes for young patients with good-prognosis diffuse large-B-cell lymphoma.
Diffuse Large B-Cell Lymphoma (DLBCL) – Relapsed or Refractory Disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab + ifosfamide + etoposide + carboplatin (R-ICE), followed by ASCT	2A	No	Phase 3 (CORAL), randomized	Rituximab + dexamethasone, high-dose cytarabine + cisplatin (R-DHAP), followed by ASCT	EFS	Relapsed or refractory after 1 prior line of therapy	• No difference was observed between treatment with R-ICE and R-DHAP in patients with relapsed or refractory DLBCL.
Bendamustine + rituximab (BR)	2A (non-candidates for transplant)	No	Phase 2, multi-center	N/A	ORR	Relapsed or refractory DLBCL	• Bendamustine plus rituximab demonstrating an ORR of 63% and CR of 37% in patients with relapsed or refractory DLBCL, including in patients previously treated with rituximab-containing chemotherapy.
Brentuximab vedotin	2A (CD30+ disease; non-candidates for transplant)	No	Phase 2, open-label	N/A	ORR	Relapsed or refractory DLBCL	• Activity with brentuximab vedotin was observed in relapsed/refractory DLBCL (ORR 44%), and responses occurred across a range of CD30 expression.

Ofatumumab + cisplatin + cytarabine + dexamethasone (O-DHAP)	2A (as a substitute for rituximab or obinutuzumab)	No	Phase 3 (ORCHARRD)	Rituximab + cisplatin + cytarabine + dexamethasone (R-DHAP)	PFS	Relapsed or refractory DLBCL	• No difference in efficacy was found between O-DHAP and R-DHAP as salvage treatment of relapsed or refractory DLBCL.
Mantle Cell Lymphoma – Induction Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab + fractionated cyclophosphamide + vincristine + doxorubicin + dexamethasone (R-hyper-CVAD), alternating with rituximab + methotrexate + cytarabine	2A preferred	No	Phase 2	N/A	FFS	First line	Rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine is effective in untreated aggressive MCL with a 3-year FFS rate of 64%. Longer FFS was observed in patients 65 years or younger.
Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP)	2A preferred	No	Phase 3	Cyclophosphamide + doxorubicin + vincristine + prednisone (CHOP)	ORR CR	First line	• The addition of rituximab to CHOP chemotherapy was associated with high response rates but did not translate to prolonged PFS or OS.
Rituximab + chemotherapy	2A preferred	No	Meta-analysis	N/A	-----	Untreated and previously	• In patients with indolent or mantle cell lymphoma, R-chemo is superior to chemotherapy alone with respect to overall survival

						treated disease	
Bendamustine ± ofatumumab	2A	No	Phase 2	N/A	ORR	First line	• Ofatumumab-bendamustine is effective as first line treatment for older pts with MCL as demonstrated by an ORR of 92%.
Bendamustine + rituximab (BR)	2A preferred (less aggressive therapy)	No	Phase 3 (StiL), open-label, multi-center, randomized	R-CHOP	PFS	First line	• The primary endpoint of PFS was significantly longer with BR compared with R-CHOP however OS outcomes were not significantly different between treatment arms.
Bortezomib + rituximab _ cyclophosphamide + doxorubicin + prednisone (VR-CAP)	2A preferred (less aggressive therapy)	Yes	Phase 3, randomized	R-CHOP	PFS	First line (not candidates for HDT/ASCR)	• VR-CAP significantly prolonged PFS and consistently improved secondary efficacy endpoints vs R-CHOP in newly diagnosed, BMT-ineligible MCL pts, with additional but manageable toxicity.
Mantle Cell Lymphoma – Second-line Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bendamustine + rituximab	2A preferred	No	Phase 3, randomized, multi-center, open-label, non-inferiority	Fludarabine + rituximab	PFS	Relapsed or refractory disease	• In combination with rituximab, bendamustine was more effective than fludarabine with higher response rate and superior PFS.
Bortezomib	2A preferred	Yes	Phase 2 (PINNACLE)	N/A	-----	Relapsed or refractory MCL after at least one prior therapy	• Single agent bortezomib induced an ORR of 33% in patients with relapsed or refractory MCL.

Ofatumumab	2A (as a substitute for rituximab or obinutuzumab)	No	Phase 2	N/A	-----	Relapsed or refractory disease	• In relapsed or refractory MCL patients, ofatumumab demonstrated a low ORR of 8.3%.

Waldenström's macroglobulinemia/Lymphoplasmacytic Lymphoma (WM/LPL)

Primary Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab + bendamustine	2A preferred	No	Phase 3 (StiL), randomized, multi-center	R-CHOP	PFS	First-line	• Bendamustine plus rituximab demonstrated a significantly longer PFS than R-CHOP and may be a preferable option to R-CHOP as primary therapy.
Bortezomib (IV) + dexamethasone + rituximab (BDR)	2A preferred	No	Phase 2	N/A	-----	First line	• BDR induced durable responses in previously untreated WM with an ORR of 85% and 3-year OS rate of 81%.
Rituximab + cyclophosphamide + dexamethasone (R-CD)	2A preferred	No	Phase 2	N/A	-----	First line	• R-DC demonstrated an ORR of 83% and 2-year PFS of 67%.
Previously Treated							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Bendamustine ± ofatumumab or rituximab	2A preferred for BR 2A for BO (for rituximab-intolerant individuals) 2A for bendamustine	No	Prospective study	N/A	-----	Relapsed or refractory WM	• Bendamustine based therapy including regimens with ofatumumab demonstrated clinical activity with an overall ORR of 83.3%
Ofatumumab	2A (for rituximab-intolerant individuals)	No	Phase 2	N/A	ORR	Untreated and previously treated	• Ofatumumab shows clinical activity with an ORR of 43% in patients with WM, including those who relapse after rituximab therapy.
Bendamustine + rituximab	2A preferred	No	Phase 2	Rituximab + cyclophosphamide + dexamethasone (R-CD)	-----	Untreated and previously treated	• A trend for longer PFS was observed with BR compared to DRC.
Bortezomib	2A		Multi-center trial	N/A	-----	Untreated and previously treated	• Bortezomib is an active agent in relapsed or refractory WM with an ORR of 85%.
Everolimus	2A		Phase 2 (RAD001)	N/A	-----	Relapsed or refractory WM	• Everolimus demonstrated high single-agent activity with an ORR of 73% however grade 3 or higher toxicities were observed in 67% of patients.