CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Rituximab (Rituxan®) and Biosimilars:

Rituximab-abbs (Truxima®)

Rituximab-arrx (Riabni®)

Rituximab-pvvr (Ruxience®)

Version: 1.0

EFFECTIVE DATE: 9/30/2025

NantHealth® | Eviti®

Please note the following:

For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Rituximab (Rituxan®), Rituximab-abbs (Truxima®), Rituximab-arrx (Riabni®), Rituximab-pvvr (Ruxience®)

Discussion

Rituximab is a type of biological drug called a monoclonal antibody, which targets the CD20 protein antigen displayed on the surface of B-cells, also called B-lymphocytes, and a type of white blood cell. They are part of the body's humoral immune response, which is mediated by antibodies (also known as immunoglobulins). When a B-cell encounters a foreign invader, a process is initiated that leads to the production of antibodies that circulate, target, and destroy the invader. CD20 is an antigen displayed on specific B-cells, providing a target to which rituximab can attach.[1]

Rituximab biosimilars are a biologic product that is very similar to a licensed biologic ("originator") such that there are no clinically meaningful differences in safety, purity, or potency between the biosimilar and the originator, rituximab.[2]

Common adverse reactions include infusion-related reactions, fever, lymphopenia, chills, infections, asthenia, febrile neutropenia, stomatitis, enteritis, sepsis, alanine aminotransferase increased, hypokalemia, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema, and depression. Clinically significant adverse reactions include infusion-related reactions, severe mucocutaneous reactions, hepatitis B reactivation with fulminant hepatitis, progressive multifocal leukoencephalopathy, tumor lysis syndrome, infections, cardiovascular adverse reactions, renal toxicity, and bowel obstruction and perforation.

Rituximab and its biosimilars are approved by the Food and Drug Administration (FDA) for chronic lymphocytic leukemia and certain non-Hodgkin's Lymphoma (NHL) types.[3,4,5,6]

The National Comprehensive Cancer Network (NCCN) endorses rituximab for the following cancer types: acute lymphoblastic leukemia, B-cell lymphomas, Castleman disease, central nervous system cancers, chronic lymphocytic leukemia/small lymphocytic lymphoma, hairy cell leukemia, hematopoietic cell transplantation, histiocytic neoplasms, Kaposi sarcoma, management of immunotherapy-related toxicities, pediatric aggressive mature B-cell lymphoma, pediatric Hodgkin lymphoma, primary cutaneous lymphomas, and Waldenström's macroglobulinemia.[7,8,910,11,12,13,14,15,16,17,18,19,20]

Definitions

- **AYA (Adolescents and Young Adults)** - Individuals within the range of 15 to 39 years of age.[21]
- **Biosimilar Drug** - An FDA-approved biological drug that is like another biological drug (called the reference drug), which is made from living organisms, but may be made in a different way from the reference drug and of slightly different substances. A biosimilar drug must be shown to be as safe, same dose, work as well, works in the same way, and for the same condition as the reference drug.[22]
- **Del(17p)/TP53 Mutation** - The loss of all or part of the short arm (also called the p arm) of chromosome 17. The deletion 17p leads to the loss of the tumor suppressor gene TP53.[23]

TP53 gene makes a protein that is found inside the nucleus of cells and plays a key role in controlling cell division and cell death. Mutations (changes) in the TP53 gene may cause cancer cells to grow and spread in the body.[24]

- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.[25]
- **Indolent Lymphoma** - A type of lymphoma that tends to grow and spread slowly and has few symptoms. It is also called low-grade lymphoma.[26]
- **International Prognostic Index (IPI)** - Used to define risk groups for specific lymphomas using a 0-8 score range, based on age, stage, number of extranodal sites of involvement, patient's performance status, and pretreatment LDH level.[27]
- **MYC and BCL2 and/or BCL6** - Translocation of these oncogenes are associated with an aggressive clinical course and are considered as double-hit or triple-hit high-grade B-cell lymphoma where the vast majority are germinal center B-cell–like lymphomas.[28]
- **National Comprehensive Cancer Network (NCCN)** - An alliance of more than 30 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.[29]
- **Tyrosine Kinase Inhibitor (TKI)** - A substance that disrupts the signal transduction pathways of protein kinases by several modes of inhibition.[30]

Policy

Coverage will be considered for FDA approved indications and for NCCN category 1, 2A, or 2B recommendations when the following criteria are met:

Acute Lymphoblastic Leukemia (ALL)

1. At least 18 years of age or 15 years of age and older for adolescents and young adults (AYA); AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Therapy as a component of MOpAD: methotrexate, vincristine, pegaspargase, and dexamethasone for CD20-positive Philadelphia chromosome-positive B-ALL that is relapsed or refractory as a consideration if refractory to TKI's; OR
4. Frontline therapy for CD20-positive Philadelphia chromosome-negative B-All in AYA without substantial comorbidities and adults as a component for one of the following:
   a) ECOG1910: induction (cyclophosphamide, cytarabine, daunorubicin, dexamethasone, mercaptopurine, pegaspargase if aged <55 years, vincristine)

b) ECOG1910: consolidation (cyclophosphamide, cytarabine, daunorubicin, dexamethasone, etoposide, mercaptopurine, high-dose methotrexate, leucovorin, pegaspargase, vincristine alternating with blinatumomab); OR

5. Frontline therapy for CD20-positive Philadelphia chromosome-negative B-All (AYA and adults aged <65 years) without substantial comorbidities as a component for one of the following:
   a) HyperCVAD: induction/consolidation (hyperfractionated cyclophosphamide, mesna, vincristine, doxorubicin, dexamethasone, IT methotrexate, IT cytarabine alternating with high-dose methotrexate, leucovorin, dose-adjusted cytarabine, IT methotrexate, IT cytarabine; with sequential blinatumomab as part of consolidation
   b) POMP: maintenance (mercaptopurine, vincristine, methotrexate, prednisone alternating with blinatumomab) if induced with HyperCVAD + blinatumomab; OR
6. Frontline therapy for CD20-positive Philadelphia chromosome-negative B-All adults aged ≥65 years or adults with substantial comorbidities as a component for one of the following:
   a) Mini-hyperCVD induction/consolidation: hyperfractionated cyclophosphamide, mesna, vincristine, dexamethasone, alternating with cytarabine, methotrexate
   b) GMALL (useful in certain circumstances): induction (cyclophosphamide, cytarabine, dexamethasone, idarubicin, vincristine)
   c) GMALL (useful in certain circumstances): consolidation (cytarabine, methotrexate)
   d) ALL-INITIAL-1: consolidation (cyclophosphamide, cytarabine, dexamethasone, idarubicin, high-dose methotrexate, leucovorin pegaspargase, vincristine; OR
7. Relapsed or refractory disease and CD20-positive Philadelphia chromosome-negative B-All as a component for MOpAD: methotrexate, vincristine, pegaspargase, dexamethasone

Note: Blinatumomab (preferred) is incorporated with multiagent consolidation therapy.[7]

B-Cell Lymphomas

Burkitt Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Induction therapy for low-risk disease in patients <60 years of age as a component of one of the following:
   a) CODOX-M (cyclophosphamide, doxorubicin, and vincristine, with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) (original or modified)
   b) Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) (day 1 and 5)
   c) HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine regimen (regimen includes intrathecal therapy)

Note: Subsequent dose of rituximab, length of therapy, and addition of CNS prophylaxis is based on PET scan results after 2 cycles of therapy; OR

4. Induction therapy for high-risk disease in patients <60 years of age as a component of one of the following:
   a) CODOX-M (cyclophosphamide, doxorubicin, and vincristine, with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) regimen (original or modified) alternating with IVAC (ifosfamide, cytarabine, etoposide, and intrathecal methotrexate)
   b) HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine (regimen includes intrathecal therapy)

   Note: Initiate treatment with the portion of the systemic therapy that contains central nervous system (CNS) penetrating drugs for patients presenting with symptomatic CNS disease.

   c) Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) and intrathecal methotrexate (for high-risk patients with baseline central nervous system disease who are not able to tolerate aggressive treatments)

   Note: In patients presenting with symptomatic central nervous system (CNS) disease, the management of the CNS disease should be addressed with the initial regimen; OR

5. Induction therapy in patients ≥60 years of age for one of the following:
   a) Low risk disease as a component of dose-adjusted EPOCH-RR (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab (day 1 and 5)
   b) High-risk disease as a component of dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab and intrathecal methotrexate

   Note:
   1. Subsequent dose of rituximab, length of therapy, and addition of CNS prophylaxis is based on PET scan results after 2 cycles of therapy
   2. In high-risk patients present with symptomatic central nervous system (CNS) disease, the management of the CNS disease should be addressed with the initial regimen; OR

6. Second-line therapy for disease relapse >6-18 months after appropriate first-line therapy OR for partial response to second-line therapy as additional therapy (if not previously given) for relapsed or refractory disease as a component of one of the following:
   a) Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) and intrathecal methotrexate
   b) RICE (rituximab, ifosfamide, carboplatin, and etoposide) with intrathecal methotrexate
   c) R-IVAC (rituximab, ifosfamide, cytarabine, and etoposide) with intrathecal methotrexate
   d) RGDP (rituximab, gemcitabine, dexamethasone, and cisplatin)

e) High dose cytarabine; OR

Classic Follicular Lymphoma

For **FDA** required criteria coverage:

7. Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent; OR
8. Previously untreated follicular, CD20-positive, B-cell NHL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single agent maintenance therapy; OR
9. Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy;[3,4,5,6] OR

For **NCCN** required criteria coverage:

10. First-line therapy for stage I, contiguous stage II, non-contiguous stage II disease, or for patients with stage III or IV disease with one of the following:
    a) Single agent (in those that were initially observed and have progressed with a low tumor burden)
    b) R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
    c) RCVP (rituximab, cyclophosphamide, vincristine, and prednisone)
    d) In combination with bendamustine or lenalidomide; OR
11. Single agent or in combination with cyclophosphamide in the elderly or infirmed when tolerability of combination chemotherapy is a concern as one of the following:
    a) First-line therapy for stage I, contiguous stage II, non-contiguous stage II disease, or for treatment with stage III or IV disease
    b) Second line and subsequent therapy (if not previously given) for no response, relapsed, or progressive disease; OR
12. First-line therapy for stage I, contiguous stage II, non-contiguous stage II disease, or for patients with indications for treatment with stage III or IV disease in combination with chlorambucil in older or infirm patients; OR
13. First-line therapy for stage I, II pediatric-type follicular lymphoma in adults with extensive local disease who are not candidates for excision or involved site radiation therapy as a component of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone); OR
14. Second-line and subsequent therapy (if not previously given) for no response, relapsed, or progressive disease as a single agent or in combination with one of the following:
    a) Bendamustine (not recommended if previously treated with bendamustine)
    b) R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
    c) RCVP (rituximab, cyclophosphamide, vincristine, and prednisone)
    d) Lenalidomide
    e) Tafasitamab-cxix and lenalidomide (≥ 1 prior systemic therapy including an anti-CD20 monoclonal antibody); OR

15. Third line and subsequent therapy in combination with loncastuzimab tesirine-lpyl for partial response, no response, relapsed, or progressive disease; OR
16. Maintenance therapy as first-line extended therapy in patients with indications for treatment if initially treated with single-agent rituximab; OR
17. Maintenance therapy for one of the following:
    a) First-line extended therapy for patients initially presenting with high tumor burden (stage III, IV) who achieve a complete or partial response following treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, and prednisone) or RCVP (rituximab, cyclophosphamide, vincristine, and prednisone)
    b) Second-line extended therapy; OR

Diffuse Large B-Cell Lymphoma

For **FDA** required criteria coverage:

18. Previously untreated, diffuse large B-cell, CD20-positive NHL, in combination with (cyclophosphamide, doxorubicin, vincristine, and prednisone) (CHOP) or other anthracycline-based chemotherapy regimens; OR

For **NCCN** required criteria coverage:

19. First-line therapy for one of the following:
    a) Stage I-II (excluding stage II with extensive mesenteric disease) as a component of one of the following:
        i. RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
        ii. Pola-R-CHP (polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, and prednisone) regimen for stage modified International Prognostic Index (smIPI) >1
    b) Stage II with extensive mesenteric disease or stage III-IV disease as a component of one of the following:
        i. RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen
        ii. Pola-R-CHP (polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, and prednisone) for IPI ≥2
        iii. Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin); OR
    c) Stage I-IV disease in patients with poor left ventricular function as a component of one of the following:
        i. RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, and procarbazine)
        ii. RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone)
        iii. Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)
        iv. RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, and prednisone)
        v. RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisone); OR

d) Stage I-IV disease in very frail patients and patients >80 years of age with comorbidities as a component of one of the following:
   i. RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, and procarbazine)
   ii. RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone)
   iii. R-mini-CHOP (rituximab with reduced dose cyclophosphamide, doxorubicin, vincristine, and prednisone)
   iv. RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisone); OR

20. First-line therapy for primary mediastinal large B-cell lymphoma as a component of one of the following:
    a) RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
    b) Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab; OR
21. Consolidation therapy for primary mediastinal large B-cell lymphoma as a component of ICE (ifosfamide, carboplatin, and etoposide) with rituximab regimen following 4 cycles of RCHOP-14 (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone); OR
22. First-line therapy for mediastinal gray zone lymphoma and extracutaneous primary cutaneous diffuse large B-cell lymphoma, leg type, for one of the following:
    a) As a component of one of the following:
       i. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
       ii. Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) with rituximab
       iii. Pola-R-CHP (polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, and prednisone) regimen for IPI ≥2 (extracutaneous primary)
    b) As a component of one of the following for patients with poor left ventricular function:
       i. RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, and procarbazine)
       ii. RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone)
       iii. Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) with rituximab
       iv. RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, and prednisone)
       v. RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisone); OR
    c) For very frail patients or >80 years of age with comorbidities as a component of one of the following:
       i. RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, and procarbazine)
       ii. RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone)
       iii. R-mini-CHOP (rituximab with reduced dose cyclophosphamide, doxorubicin, vincristine, and prednisone)
       iv. RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisone); OR

23. Used for primary cutaneous, leg type, as first-line with involved site radiation therapy or as second-line therapy (if not previously received) for solitary regional, T1-2 disease, or as first-line therapy for generalized (skin only), T3 disease for one of the following:
    a) R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
    b) For patients with poor left ventricular function as a component of the following regimens:
        i. RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, and procarbazine)
        ii. RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone)
        iii. Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)
        iv. RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, and prednisone)
        v. RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, or prednisone); OR
    c) For very frail patients and those >80 years of age with comorbidities as a component of one of the following:
        i. RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, and procarbazine)
        ii. RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone)
        iii. R-mini-CHOP (rituximab with reduced dose cyclophosphamide, doxorubicin, vincristine, and prednisone)
        iv. RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, or prednisone); OR
24. Second-line and subsequent therapy for one of the following:
    a) Relapsed disease <12 months after completion of first-line therapy or primary refractory disease in non-candidates for CAR T-Cell therapy (includes patients that do not have access to CAR T-cell therapy) as a component of one of the following:
        i. Polatuzumab vedotin-piiq with or without bendamustine
        ii. CEOP (cyclophosphamide, etoposide, vincristine, and prednisone)
        iii. DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
        iv. ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin)
        v. GDP (gemcitabine, dexamethasone, and cisplatin)
        vi. Gemcitabine, dexamethasone, and carboplatin
        vii. GemOx (gemcitabine and oxaliplatin) (if unable to receive glofitamab-gxbm)
        viii. ICE (ifosfamide, carboplatin, and etoposide)
        ix. MINE (mitoxantrone, ifosfamide, mesna and etoposide)
        x. Lenalidomide and rituximab (useful in certain circumstances for non-germinal center diffuse large B-cell lymphoma); OR
    b) Relapsed disease >12 months after completion of first-line therapy if intention to proceed to transplant for one of the following:
        i. DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
        ii. GDP (gemcitabine, dexamethasone, and cisplatin)
        iii. Gemcitabine, dexamethasone, and carboplatin
        iv. ICE (ifosfamide, carboplatin, and etoposide)

v. ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin)
vi. GemOx (gemcitabine and oxaliplatin)
vii. MINE (mitoxantrone, ifosfamide, mesna and etoposide); OR

c) Relapsed disease >12 months after completion of first-line therapy if no intention to proceed to transplant for one of the following:
i. Single agent
ii. Polatuzumab vedotin-piiq with or without bendamustine
iii. Lenalidomide (non-germinal center diffuse large B-cell lymphoma)
iv. DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
v. CEOP (cyclophosphamide, etoposide, vincristine, and prednisone)
vi. GDP (gemcitabine, dexamethasone, and cisplatin)
vii. Gemcitabine, dexamethasone, and carboplatin
viii. GemOx (gemcitabine and oxaliplatin) (if unable to receive glofitamab-gxbm)

Note: Rituximab should be included in second-line therapy if there is relapse after a reasonable remission (>6 month); however, rituximab can be omitted in patients with primary refractory disease; OR

25. Third-line and subsequent therapy in combination with brentuximab vedotin and lenalidomide for partial response, relapsed, progressive or refractory disease

Note: Responses with brentuximab vedotin (BV) have been seen in patients with a low level of CD30 positivity—any level is acceptable for the use of BV-based regimens; OR

Extranodal Marginal Zone Lymphoma of Nongastric Sites (Noncutaneous)

For **NCCN** required criteria coverage:

26. Initial therapy as a single agent for stage IE or contiguous stage IIE disease; OR
27. First-line therapy for stage IV disease or recurrent stage IE or contiguous stage IIE disease as one of the following:
    a) In combination with bendamustine
    b) As a component of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with rituximab OR CVP (cyclophosphamide, vincristine, and prednisone) with rituximab; OR
28. First-line therapy as a single agent for multifocal disease or in combination with lenalidomide for stage IV disease or recurrent stage IE or contiguous stage IIE disease; OR
29. Single-agent OR in combination with chlorambucil or cyclophosphamide for stage IV or recurrent stage IE or contiguous stage IIE in elderly or infirmed patients when tolerability of combination chemoimmunotherapy is a concern as first line or second line and subsequent therapy for relapsed, refractory, or progressive disease; OR
30. Maintenance as optional first-line extended therapy; OR
31. Second-line and subsequent therapy for relapsed, refractory, or progressive disease for one of the following:
    a) Single agent (if longer duration of remission)

b) With bendamustine (not recommended if previously treated with bendamustine)
c) With lenalidomide including for the elderly or infirm when tolerability of combination chemoimmunotherapy is a concern
d) Component of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with rituximab or CVP (cyclophosphamide, vincristine, and prednisone) with rituximab; OR

Extranodal Marginal Zone Lymphoma of the Stomach

For **NCCN** required criteria coverage:

32. Initial therapy (if involved site radiation therapy is contraindicated) as a single agent for stage I_1, or I_2, or stage II_1 disease in patients who are H. pylori-positive and t(11;18) positive or who are H. pylori-negative; OR
33. Given as a component of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with rituximab, CVP (cyclophosphamide, vincristine, and prednisone) with rituximab, OR in combination with bendamustine for one of the following indications:
    a) First-line therapy for stage II_2, or II_E, or stage IV disease (distant nodal, advanced stage)
    b) Additional therapy for stage I_1, or I_2, or stage II_1 H. pylori positive disease if repeat endoscopy shows no response or recurrence after antibiotic therapy and involved site radiation therapy (ISRT)
    c) Additional therapy after ISRT or rituximab alone for stage I_1, or I_2, or stage II_1 disease that is lymphoma positive after restaging with endoscopy
    d) For recurrence if lymphoma positive after previous antibiotic therapy and locoregional ISRT; OR
34. Single agent for multifocal disease for one of the following:
    a) First-line therapy for stage II_2, or II_E, or stage IV disease (distant nodal, advanced stage)
    b) Second-line and subsequent therapy for relapsed, refractory, or progressive disease
    c) Stage I_1, or I_2, or stage II_1 H. pylori positive disease if repeat endoscopy shows no response or recurrence after antibiotic therapy and ISRT
    d) After ISRT alone for stage I_1, or I_2, or stage II_1 disease that is lymphoma positive after restaging with endoscopy
    e) Recurrence if lymphoma positive after previous antibiotic therapy and locoregional ISRT
    f) Second-line and subsequent therapy for stage I_1, or I_2, or stage II_1 relapsed, refractory, or progressive disease (if longer duration of remission); OR
35. As a single agent OR in combination with chlorambucil or cyclophosphamide in the elderly or infirm when tolerability of combination chemoimmunotherapy is a concern for one of the following:
    a) First-line therapy for stage II_2, or II_E, or stage IV disease (distant nodal, advanced stage)
    b) For stage I_1, or I_2, or stage II_1 H. pylori positive and if repeat endoscopy shows no response or recurrence after antibiotic therapy and ISRT

c) After ISRT or rituximab alone for stage I_1, or I_2, or stage II_1 disease that is lymphoma positive after restaging with endoscopy
d) Additional therapy for recurrence if lymphoma positive after previous antibiotic therapy and locoregional ISRT
e) Second line and subsequent therapy for relapsed, refractory, or progressive disease; OR

36. First-line therapy for stage I_1, I_2, or stage II_1 in combination with lenalidomide for one of the following:
    a) If H. pylori positive and repeat endoscopy shows no response or recurrence after antibiotic therapy and involved site radiation therapy (ISRT)
    b) After ISRT or rituximab alone if lymphoma positive after restaging with endoscopy; OR
37. First-line therapy for stage II_2, or II_E, or stage IV disease (distant nodal, advanced stage) in combination with lenalidomide; OR
38. Maintenance as optional first-line extended therapy; OR
39. Second-line and subsequent therapy for relapsed, refractory, or progressive disease with one of the following:
    a) Single agent (if longer duration of remission)
    b) Bendamustine (not recommended if previously treated with bendamustine)
    c) Lenalidomide (including for the elderly or infirm when tolerability of combination chemoimmunotherapy is a concern)
    d) CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with rituximab
    e) CVP (cyclophosphamide, vincristine, and prednisone) with rituximab; OR

High-Grade B-Cell Lymphomas

For **NCCN** required criteria coverage:

40. Induction therapy in patients with MYC and BCL2 with or without BCL6 rearrangements as a component of one of the following:
    a) R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
    b) Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) with rituximab
    c) Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine
    d) R-CODOX-M (rituximab, cyclophosphamide, vincristine, and doxorubicin with methotrexate) alternating with R-IVAC (rituximab, ifosfamide, etoposide, and cytarabine)
    e) Consider for induction therapy in frail or elderly patients as a component of R-mini-CHOP

    Note: RCHOP may be associated with a sub-optimal outcome in high-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6 (double-hit/triple-hit lymphomas)—consider for low-risk IPI patients; OR

41. Induction therapy as a component of Pola-R-CHP (polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, and prednisone); OR

42. Third-line and subsequent therapy in combination with brentuximab vedotin and lenalidomide for partial response, relapsed, progressive or refractory disease

    Note: Responses with brentuximab vedotin (BV) have been seen in patients with a low level of CD30 positivity—any level is acceptable for the use of BV-based regimens; OR

Histologic Transformation of Indolent Lymphomas to Diffuse Large B-Cell Lymphoma

For **NCCN** required criteria coverage:

43. Diffuse large B-cell or high-grade B-cell lymphoma with translocations of MYC and BCL6 and without BCL2 rearrangements after minimal or no prior chemotherapy as a component of one of the following:
    a) R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
    b) Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) with rituximab
    c) Pola-R-CHP (polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, and prednisone) regimen for IPI ≥2
    d) If poor left ventricular function as a component of one of the following:
        i. RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, and procarbazine)
        ii. RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone)
        iii. Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) with rituximab
        iv. RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, and prednisone)
        v. RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisone)
    e) If very frail and/or >80 years of age with comorbidities as a component of one of the following:
        i. RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, and procarbazine)
        ii. RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone)
        iii. R-mini-CHOP (rituximab with reduced dose cyclophosphamide, doxorubicin, vincristine, and prednisone)
        iv. RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisone)

    Note: Anthracycline-based regimens are preferred unless contraindicated; OR

44. Additional therapy for partial response, no response, progressive or relapsed disease following chemoimmunotherapy after minimal or no prior therapy or after multiple lines of prior therapies including ≥2 chemoimmunotherapy for indolent or transformed disease as one of the following:
    a) Without regard to transplant if not previously given as a component of RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)

b) If the intention is to proceed to transplant and if previously treated with an anthracycline-based regimen as a component of one of the following:
   i. RDHA (rituximab, dexamethasone, and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
   ii. GDP (gemcitabine, dexamethasone, and cisplatin) with rituximab
   iii. Gemcitabine, dexamethasone, and carboplatin with rituximab
   iv. ICE (ifosfamide, carboplatin, and etoposide) with rituximab
c) If no intention to proceed to transplant and as a component of one of the following:
   i. Polatuzumab vedotin-piiq with or without bendamustine and with rituximab, if previously treated with an anthracycline-based regimen
   ii. CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) with rituximab
   iii. GDP (gemcitabine, dexamethasone, and cisplatin) with rituximab
   iv. Gemcitabine, dexamethasone, and carboplatin with rituximab
   v. GemOx (gemcitabine and oxaliplatin) with rituximab; OR

HIV-Related B-Cell Lymphomas

For **NCCN** required criteria coverage:

45. First-line therapy for HIV-related Burkitt lymphoma as a component of one of the following:
    a) Dose adjusted EPOCH-R (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)
    b) Modified CODOX-M (cyclophosphamide, doxorubicin, and vincristine, with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) alternating with IVAC (ifosfamide, cytarabine, etoposide, and intrathecal methotrexate)
    c) R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine); OR
46. First-line therapy for CD20+ HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and HHV8-positive diffuse large B-cell lymphoma, not otherwise specified as a component of one of the following:
    a) R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)
    b) R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone); OR
47. Second-line therapy for relapse of HIV-related Burkitt lymphoma >6-18 months as a component of one of the following:
    a) Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) (if not previously given) with rituximab
    b) RICE (rituximab, ifosfamide, carboplatin, and etoposide) (in combination with intrathecal methotrexate if not previously given)
    c) RIVAC (rituximab, ifosfamide, cytarabine, etoposide) (in combination with intrathecal methotrexate if not previously given)
    d) RGDP (rituximab, gemcitabine, dexamethasone, cisplatin)
    e) High-dose cytarabine + rituximab; OR

48. Relapsed HIV-related diffuse large B-cell lymphoma, HHV8-positive diffuse large B-cell lymphoma, not otherwise specified (NOS), and primary effusion lymphoma as a component of bortezomib-ICE (ifosfamide, carboplatin, and etoposide) with or without rituximab; OR
49. Second line and subsequent therapy for HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and HHV8-positive diffuse large B-cell lymphoma, not otherwise specified, or for HIV-related plasmablastic lymphoma for:
    a) Relapsed or refractory disease as a bridging option in candidates for CAR T-cell therapy as a component of one of the following:
        i. DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
        ii. Polatuzumab vedotin-piiq with or without bendamustine with rituximab
        iii. GDP (gemcitabine, dexamethasone, and cisplatin)
        iv. Gemcitabine, dexamethasone, and carboplatin
        v. GemOx (gemcitabine and oxaliplatin)
        vi. ICE (ifosfamide, carboplatin, and etoposide); OR
    b) Relapsed disease <12 months after completion of first-line therapy or primary refractory disease and a non-candidate for CAR T-Cell therapy as a component of one of the following:
        i. Polatuzumab vedotin-piiq with or without bendamustine
        ii. CEOP (cyclophosphamide, etoposide, vincristine, and prednisone)
        iii. DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
        iv. ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin)
        v. GDP (gemcitabine, dexamethasone, and cisplatin)
        vi. Gemcitabine, dexamethasone, and carboplatin
        vii. GemOx (gemcitabine and oxaliplatin) regimen (if unable to receive epcoritamab-bysp or glofitamab-gxbm)
        viii. ICE (ifosfamide, carboplatin, and etoposide)
        ix. MINE (mitoxantrone, ifosfamide, mesna and etoposide)
        x. lenalidomide and rituximab for non-germinal center diffuse large B-cell lymphoma; OR
    c) Relapsed disease >12 months after completion of first-line therapy if intention is to proceed to a transplant as a component of one of the following:
        i. DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
        ii. GDP (gemcitabine, dexamethasone, and cisplatin)
        iii. Gemcitabine, dexamethasone, and carboplatin
        iv. ICE (ifosfamide, carboplatin, and etoposide)
        v. ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin)
        vi. GemOx (gemcitabine and oxaliplatin)
        vii. MINE (mitoxantrone, ifosfamide, mesna, and etoposide); OR
    d) Relapsed disease >12 months after completion of first-line therapy if no intention to proceed to transplant as a component of one of the following:
        i. Polatuzumab vedotin-piiq with or without bendamustine

ii. GemOx (gemcitabine and oxaliplatin) (if unable to receive epcoritamab-bysp or glofitamab-gxbm)
iii. Lenalidomide (non-germinal center diffuse large B-cell lymphoma)
iv. CEOP (cyclophosphamide, etoposide, vincristine, and prednisone)
v. GDP (gemcitabine, dexamethasone, and cisplatin)
vi. Gemcitabine, dexamethasone, and carboplatin
vii. Single agent

Note: Rituximab should be included in second-line therapy if there is relapse after a reasonable remission (>6 mo.); however, rituximab can be omitted in patients with primary refractory disease; OR

e) Third-line and subsequent therapy in combination with brentuximab vedotin and lenalidomide for partial response, relapsed, progressive, or refractory disease

Note: Responses with brentuximab vedotin (BV) have been seen in patients with a low level of CD30 positivity—any level is acceptable for the use of BV-based regimens; OR

Mantle Cell Lymphoma

For **NCCN** required criteria coverage:

50. Aggressive induction therapy for one of the following:
    a) Additional therapy for stage I-II disease following partial response, progression, or relapse after initial treatment with involved site radiation therapy alone
    b) Re-induction therapy for stage I-II disease, in selected cases, for relapse after initial treatment with chemoimmunotherapy
    c) Classical or indolent TP53 wildtype stage II bulky noncontiguous, III, or IV disease
    d) Rituximab can be used as a component of the following regimens for the above indications:
        i. LyMA regimen: RDHA (rituximab, dexamethasone, and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) conditionally followed by R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for non-PET complete response
        ii. NORDIC regimen (dose-intensified induction immunochemotherapy with rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone [maxi-CHOP] alternating with rituximab and high-dose cytarabine)
        iii. Bendamustine with rituximab followed by rituximab in combination with high dose cytarabine
        iv. TRIANGLE regimen: alternating R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) + Bruton tyrosine kinase inhibitor (BTKi) (acalabrutinib, ibrutinib, or zanubrutinib)/RDHAP (rituximab, dexamethasone, and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
        v. HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine)

vi. RBAC500 (rituximab, bendamustine, and cytarabine)

Note:

1. Rituximab + cBTKi (acalabrutinib, ibrutinib, or zanubrutinib) can be used as a pre-treatment to limit the number of cycles of R HyperCVAD/rituximab maintenance
2. Alternate covalent BTKi (acalabrutinib and zanubrutinib) were not evaluated in the TRIANGLE study; OR

51. Less aggressive induction therapy for one of the following:
    a) Initial therapy for stage I-II disease
    b) Additional therapy for stage I-II disease and partial response, progression, or relapse after initial treatment with involved site radiation therapy alone
    c) Re-induction therapy for stage I-II disease, in selected cases, for relapses after initial treatment with chemoimmunotherapy if not suitable for aggressive therapy
    d) Classical or indolent TP53 wildtype stage II bulky or noncontiguous, III, or IV disease if not suitable for aggressive therapy
    e) Rituximab can be used as a component of or in combination with one of the following regimens for the above indications:
        i. Bendamustine
        ii. Acalabrutinib and bendamustine
        iii. VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone)
        iv. Lenalidomide
        v. RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone); OR
52. Induction therapy for classical or indolent TP53 mutated stage II bulky or noncontiguous, III, or IV disease for one of the following:
    a) If not suitable for aggressive therapy, use as a component of or in combination with one of the following:
        i. Bendamustine
        ii. Lenalidomide
        iii. Acalabrutinib and bendamustine
        iv. VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone)
        v. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
    b) If suitable for aggressive therapy, used as a component of TRIANGLE regimen: Alternating R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) + Bruton tyrosine kinase inhibitor (BTKi) (acalabrutinib, ibrutinib, or zanubrutinib)/RDHAP (rituximab, dexamethasone, and cytarabine) + platinum (carboplatin, cisplatin or oxaliplatin)

Notes:

1. TP53 mutation has been associated with poor prognosis in patients treated with conventional therapy, including transplant—clinical trial is strongly recommended.
2. Alternate covalent BTKi (acalabrutinib and zanubrutinib) were not evaluated in the TRIANGLE study; OR

53. Second-line and subsequent therapy in combination with lenalidomide or ibrutinib for the following indications:
    a) Stage I-II disease with partial response, relapse, or progression after prior treatment with chemoimmunotherapy
    b) Classical or indolent TP53 wildtype stage II bulky or noncontiguous, III, or IV disease in patients who have no response or progressive disease or partial response with substantial disease after induction therapy
    c) Relapsed or refractory disease (if not previously given); OR
54. Second-line and subsequent therapy in combination with one of the following:
    a) Bendamustine (if not previously treated with bendamustine)
    b) RBAC500 (rituximab, bendamustine and cytarabine) regimen (if not previously treated with bendamustine)
    c) Bortezomib
    d) DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) + rituximab (if not previously given)
    e) GemOx (gemcitabine, oxaliplatin) with rituximab
    f) Venetoclax; OR
55. In combination with covalent Bruton tyrosine kinase inhibitor (acalabrutinib, ibrutinib, or zanubrutinib) as maintenance therapy for one of the following:
    a) complete response following aggressive induction therapy or following high dose therapy/autologous stem cell rescue

    Note: The benefit of 2 years of ibrutinib maintenance after alternating RCHOP + ibrutinib/RDHAP was shown in the TRIANGLE study. The value of ibrutinib maintenance after other aggressive induction therapy regimens has not been established; alternate covalent Bruton tyrosine kinase inhibitors (acalabrutinib and zanubrutinib) were not evaluated in the TRIANGLE study; OR

56. Single agent maintenance therapy for classical or indolent TP53 wildtype following complete response or very good partial response to less aggressive induction therapy with BR (bendamustine and rituximab) or RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)

    Note: Maintenance therapy following VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone) or RBAC500 (rituximab, bendamustine and cytarabine) therapy has not been evaluated; OR

Nodal Marginal Zone Lymphoma

For **NCCN** required criteria coverage:

57. First-line therapy for stage I, contiguous stage II, non-contiguous stage II, or stage III, IV disease as a component of, or in combination with one of the following:
    a) Single agent
    b) Chlorambucil or cyclophosphamide for the elderly or infirm when tolerability of combination chemoimmunotherapy is a concern

c) Bendamustine
d) Lenalidomide
e) CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with rituximab
f) CVP (cyclophosphamide, vincristine, and prednisone) with rituximab; OR

58. Maintenance as optional first-line extended therapy; OR
59. Second line and subsequent therapy for stage I, contiguous stage II, non-contiguous stage II, or stage III, IV, relapsed, refractory, or progressive disease in older or infirm patients when tolerability of combination chemoimmunotherapy is a concern as one of the following:
    a) Single agent (if longer duration of remission)
    b) In combination with chlorambucil or cyclophosphamide; OR
60. Second-line and subsequent therapy for relapsed, refractory, or progressive disease in combination with one of the following:
    a) Bendamustine (not recommended if previously treated with bendamustine)
    b) Lenalidomide including for the older or infirm patients when tolerability of combination chemoimmunotherapy is a concern
    c) CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with rituximab
    d) CVP (cyclophosphamide, vincristine, and prednisone) with rituximab; OR

Post-Transplant Lymphoproliferative Disorders (PTLD)

For **NCCN** required criteria coverage:

61. Single-agent therapy for one of the following:
    a) First-line therapy for monomorphic (B-cell type) or polymorphic (B-cell type) PTLD
    b) Second-line therapy for partial response, persistent or progressive non-destructive lesions or for partial response, persistent or progressive monomorphic (B-cell type) PTLD if immunosuppressive was reduced in first-line therapy or consider for patients with partial response to initial treatment with rituximab monotherapy and IPI 0-2
    c) Maintenance therapy for polymorphic (B-cell type) PTLD achieving complete response on first-line therapy; OR
62. Concurrent chemoimmunotherapy for one of the following:
    a) First-line therapy for monomorphic (B-cell type) or systemic polymorphic (B-cell type) PTLD
    b) Second-line therapy for partial response, persistent or progressive monomorphic (B-cell type) or polymorphic (B-cell type) PTLD
    c) As a component of one of the following regimens for the above indications:
        i. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with rituximab
        ii. Pola-R-CHP (polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, and prednisone) with rituximab regimen for IPI ≥2
    d) For frail patients who cannot tolerate anthracyclines, as a component of one of the following:
        i. CVP (cyclophosphamide, vincristine, and prednisone)
        ii. CEPP (cyclophosphamide, etoposide, prednisone, and procarbazine)
        iii. CEOP (cyclophosphamide, etoposide, vincristine, and prednisone); OR

63. Sequential chemoimmunotherapy as a single agent followed by CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) as a component of one of the following:
    a) First-line therapy for monomorphic (B-cell type) or systemic polymorphic (B-cell type) PTLD
    b) Second-line therapy for partial response, persistent or progressive monomorphic (B-cell type) or polymorphic (B-cell type) PTLD; OR
64. In combination with high-dose methotrexate for primary CNS PTLD (B-cell type); OR
65. Second line and subsequent therapy in patients with monomorphic PTLD (B-cell type) for one of the following indications:
    a) Relapsed disease >12 months after completion of first-line therapy with chemoimmunotherapy if intention to proceed to transplant as a component of one of the following:
        i. DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
        ii. ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin)
        iii. GDP (gemcitabine, dexamethasone, and cisplatin)
        iv. Gemcitabine, dexamethasone, and carboplatin
        v. GemOx (gemcitabine and oxaliplatin)
        vi. ICE (ifosfamide, carboplatin, and etoposide)
        vii. MINE (mesna, ifosfamide, mitoxantrone, and etoposide)
    b) Relapsed disease >12 months after completion of first-line therapy with chemoimmunotherapy if no intention to proceed to transplant as a component of one of the following:
        i. Polatuzumab vedotin-piiq with or without bendamustine
        ii. CEOP (cyclophosphamide, etoposide, vincristine, prednisone)
        iii. GDP (gemcitabine, dexamethasone, and cisplatin)
        iv. Gemcitabine, dexamethasone, and carboplatin
        v. GemOx (gemcitabine and oxaliplatin) (if unable to receive glofitamab-gxbm)
        vi. As a single agent
        vii. Lenalidomide for non-germinal center diffuse large B-cell lymphoma

    Note: Rituximab should be included in second-line therapy if there is relapse after a reasonable remission (>6 mo.); however, rituximab can be omitted in patients with primary refractory disease; OR

    c) Relapsed disease <12 months after completion of first-line therapy with chemoimmunotherapy or primary refractory disease if used in non-candidates for CAR T-cell therapy as a component of one of the following:
        i. Polatuzumab vedotin-piiq with or without bendamustine
        ii. CEOP (cyclophosphamide, etoposide, vincristine, and prednisone)
        iii. DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
        iv. ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin)
        v. GDP (gemcitabine, dexamethasone, and cisplatin)
        vi. Gemcitabine, dexamethasone, and carboplatin

vii. GemOx (gemcitabine and oxaliplatin) (if unable to receive glofitamab-gxbm)
viii. ICE (ifosfamide, carboplatin, and etoposide)
ix. MINE (mitoxantrone, ifosfamide, mesna and etoposide)
x. Lenalidomide and rituximab for non-germinal center diffuse large B-cell lymphoma; OR

d) As a bridging option for relapsed or refractory disease in candidates for CAR T-cell therapy until CAR T-cell product is available as a component of:
i. DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
ii. Polatuzumab vedotin-piiq with or without bendamustine (consider/add bendamustine only after leukapheresis)
iii. GDP (gemcitabine, dexamethasone, and cisplatin)
iv. Gemcitabine, dexamethasone, and carboplatin
v. GemOx (gemcitabine and oxaliplatin)
vi. ICE (ifosfamide, carboplatin, and etoposide)

Note: Rituximab should be included in second-line therapy if there is relapse after a reasonable remission (>6 mo.); however, rituximab can be omitted in patients with primary refractory disease; OR

66. Third line and subsequent therapy in combination with brentuximab vedotin and lenalidomide for partial response, relapsed, progressive or refractory disease

Note: Responses with brentuximab vedotin (BV) have been seen in patients with a low level of CD30 positivity—any level is acceptable for the use of BV-based regimens; OR

Splenic Marginal Zone Lymphoma

For **NCCN** required criteria coverage:

67. First-line therapy for disease recurrence following initial management of splenomegaly in treatment naive patients as a single agent, in combination with bendamustine or as a component of one of the following:
a) CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with rituximab
b) CVP (cyclophosphamide, vincristine, and prednisone) with rituximab; OR
68. First-line therapy in combination with lenalidomide for disease recurrence following initial management of splenomegaly in treatment naïve patients; OR
69. Single agent or in combination with chlorambucil or cyclophosphamide for disease recurrence following initial management of splenomegaly in elderly or infirm patients when tolerability of combination chemoimmunotherapy is a concern as one of the following:
a) First-line therapy (if treatment naïve)
b) Second-line and subsequent therapy; OR
70. Therapy as a single agent for symptomatic patients with splenomegaly who are one of the

following:
a) Hepatitis C negative
b) Hepatitis C positive with contraindications for hepatitis treatment
c) Hepatitis C positive with no response to appropriate hepatitis treatment; OR

71. Maintenance as optional first-line extended therapy; OR
72. Second-line (if previously treated with rituximab) and subsequent therapy for disease recurrence in combination with one of the following:
    a) Single agent (with longer duration of remission)
    b) Bendamustine (not recommended if previously treated with bendamustine)
    c) CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with rituximab
    d) CVP (cyclophosphamide, vincristine, and prednisone) with rituximab
    e) Lenalidomide (including the elderly or infirm when tolerability of combination chemoimmunotherapy is a concern).[8]

Castleman Disease

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Surgically unresectable unicentric disease with or without prednisone and/or cyclophosphamide for one of the following:
    a) First-line therapy
    b) Second-line and subsequent therapy for relapsed/ refractory disease or progressive disease; OR
4. Active idiopathic multicentric disease (nonsevere) with no organ failure with or without prednisone for disease that is human immunodeficiency virus 1-negative and human herpesvirus-8-negative for one of the following:
    a) First-line therapy
    b) Alternate treatment for relapsed disease
    c) No response to alternate first-line therapy; OR
5. Therapy for active idiopathic multicentric disease (nonsevere) with no organ failure as a component of R-CVP (cyclophosphamide, vincristine and prednisone) with rituximab for disease that is human immunodeficiency virus 1-negative and human herpesvirus 8-negative for one of the following:
    a) First-line therapy
    b) Alternate treatment for relapsed disease
    c) If no response to alternate first-line therapy; OR
6. Active multicentric disease with no organ failure with or without liposomal doxorubicin and/or prednisone for disease that is human herpesvirus 8-positive for one of the following:
    a) First-line therapy
    b) Alternate treatment for relapsed disease
    c) No response to alternate first-line therapy; OR

7. With or without prednisone for active multicentric disease with no organ failure for progression ≥6 months following completion of rituximab; OR
8. First-line therapy with or without rituximab for multicentric CD (fulminant/severe) that is human herpesvirus 8-negative with or without organ failure for one of the following:
   a) In combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)
   b) In combination with CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone)
   c) In combination with CVP (cyclophosphamide, vincristine, and prednisone)
   d) Single agent (if patient is not a candidate for combination therapy); OR
9. First-line therapy for multicentric CD (fulminant/severe) for disease that is human herpesvirus 8-positive with or without organ failure for one of the following:
   a) In combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)
   b) In combination with CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone)
   c) In combination with CVP (cyclophosphamide, vincristine, and prednisone)
   d) In combination with liposomal doxorubicin with or without prednisone
   e) Single agent (if patient is not a candidate for combination therapy); OR
10. Second-line and subsequent therapy (if not previously given) for relapsed/refractory or progressive multicentric disease (for fulminant/severe disease with organ failure) in combination with one of the following:
    a) CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)
    b) CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone)
    c) CVP (cyclophosphamide, vincristine, and prednisone)
    d) Liposomal doxorubicin; OR
11. Subsequent therapy for multicentric disease that has progressed following treatment of relapsed/refractory or progressive disease in combination with the following:
    a) Bortezomib
    b) Lenalidomide
    c) Thalidomide.[9]

Central Nervous System Cancers

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Primary CNS Lymphomas

For **NCCN** required criteria coverage:

3. Induction therapy for primary CNS lymphoma (PCNSL) or primary vitreoretinal lymphoma/PCNSL ocular variant (without other CNS involvement) in combination with one of the following:
   a) High-dose methotrexate
   b) High-dose methotrexate and temozolomide
   c) R-MPV (rituximab, methotrexate, procarbazine, and vincristine)
   d) High-dose methotrexate, cytarabine, and thiotepa

e) Single agent, or in combination with temozolomide or lenalidomide if the patient is unsuitable for or intolerant to high-dose methotrexate; OR

4. Intra-cerebrospinal fluid (CSF) therapy if CSF positive or spinal MRI positive as part of induction therapy if not a candidate for systemic therapy or primary vitreoretinal lymphoma/PCNSL ocular variant (without other CNS involvement) or as treatment alone or in combination with systemic therapy for relapsed or refractory disease in patients with prior whole brain radiation therapy; OR
5. Consolidation (monthly maintenance) therapy as a continuation of induction regimen in those with a complete response or complete response unconfirmed (CRu) to induction therapy as single agent or in combination with high-dose methotrexate; OR
6. Treatment as a single agent, or in combination with temozolomide or lenalidomide, or as a component of rituximab, methotrexate, carmustine, etoposide, and prednisone (R-MBVP) regimen for relapsed or refractory disease for one of the following:
   a) Prior whole brain radiation therapy
   b) Prior high-dose methotrexate-based regimen without prior radiation therapy (RT)
   c) In combination with whole brain RT or involved field RT in patients who received a prior high-dose methotrexate-based regimen without prior RT after no response or short response duration (<12 months) to the prior regimen
   d) Prior high-dose systemic therapy with stem cell rescue; OR
7. Treatment in combination with high-dose methotrexate with or without ibrutinib for relapsed or refractory disease for patients who previously received one of the following therapies:
   a) Whole brain radiation therapy
   b) High-dose methotrexate-based regimen without prior radiation therapy (RT) and a previous long response duration (≥12 months) to prior regimen
   c) High-dose methotrexate-based regimen without prior RT and a previous short response duration (<12 months) to prior regimen if clinically indicated; OR
8. High dose cytarabine + rituximab + thiotepa followed by thiotepa + rituximab + carmustine for treatment with autologous stem cell reinfusion (if the recurrent disease goes into complete remission with reinduction systemic therapy) for relapsed or refractory disease in eligible patients who received one of the following:
   a) Prior whole brain radiation therapy
   b) Prior high-dose methotrexate-based regimen without prior radiation therapy; OR

Leptomeningeal Metastases

For **NCCN** required criteria coverage:

9. Intra-cerebrospinal fluid (CSF) treatment for disease metastases from lymphomas as one of the following:
   a) Primary treatment in patients with good risk status (KPS ≥60, no major neurologic deficits, minimal systemic disease, and reasonable systemic treatment options if needed)
   b) Maintenance treatment in patients with negative CSF cytology or clinically stable patients with persistently positive CSF cytology.[10]

Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Previously untreated and treated CD20-positive CLL in combination with fludarabine and cyclophosphamide;[3,4,5,6] OR

For **NCCN** required criteria coverage:

4. First-line therapy without del(17p)/TP53 mutation for one of the following:
   a) In combination with ibrutinib
   b) IGHV-mutated CLL in patients <65 years of age without significant comorbidities as a component of FCR (fludarabine, cyclophosphamide, and rituximab); OR
5. First-line therapy without del(17p)/TP53 mutation in patients who have indications for treatment (consider when covalent Bruton Tyrosine Kinase inhibitor and venetoclax are not available or contraindicated or rapid disease de-bulking is needed) in combination with one of the following:
   a) Bendamustine (not recommended for frail patients)
   b) High-dose methylprednisolone (HDMP); OR
6. First-line therapy in combination with high-dose methylprednisolone with del(17p)/TP53 mutation in patients who have indications for treatment (consider when covalent Bruton Tyrosine Kinase inhibitor and B-cell lymphoma 2 inhibitor are not available or contraindicated or rapid disease de-bulking is needed); OR
7. Initial therapy for treatment of histologic (Richter's) transformation to diffuse large B-cell lymphoma (clonally related or unknown clonal status) as a component of one of the following:
   a) RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
   b) Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) with rituximab
   c) HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) with rituximab
   d) OFAR (oxaliplatin, fludarabine, cytarabine, and rituximab)
   e) Venetoclax + RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone); OR
8. Second-line or subsequent therapy in combination with venetoclax without del(17p)/TP53 mutation in patients with one of the following indications:
   a) Intolerance to first-line therapy with a covalent Bruton Tyrosine Kinase inhibitor (cBTKi)
   b) Intolerance to first-line therapy with a cBTKi and following second-line therapy with an alternative cBTKi-based regimen
   c) Disease progression while on first-line therapy with a cBTKi-based regimen
   d) Disease relapse after first-line therapy with BCL2i containing regimens chemoimmunotherapy or immunotherapy

e) Third-line therapy for disease relapse following treatment with BCL2i-containing regimens if fixed-duration treatment with chemoimmunotherapy or immunotherapy was given as first-line therapy; OR
f) Disease progression or intolerance while on first-line therapy with chemoimmunotherapy or immunotherapy and following second-line therapy with a cBTKi; OR
g) Venetoclax with or without anti-CD20 monoclonal antibody is a treatment option for relapse after a period of remission; OR

9. Subsequent therapy for relapsed or refractory disease without del(17p)/TP53 mutation after prior therapy with Bruton Tyrosine Kinase inhibitor based and B-cell lymphoma 2 inhibitor-containing regimens in combination with one of the following:
   a) Idelalisib
   b) FCR (fludarabine, cyclophosphamide, and rituximab)
   c) Lenalidomide
   d) Bendamustine (not recommended for frail patients)
   e) High-dose methylprednisolone (HDMP)

   Note: Recommended only in patients <65 years of age without significant comorbidities; OR

10. Relapsed or refractory disease with del(17p)/TP53 after prior therapy with Bruton Tyrosine Kinase inhibitor-based regimens or B-cell lymphoma 2 inhibitor-containing regimens in patients who have indications for treatment in combination with one of the following:
    a) Alemtuzumab
    b) High-dose methylprednisolone
    c) Idelalisib
    d) Lenalidomide

    Note: While alemtuzumab is no longer commercially available, it may be obtained for clinical use in patients with CLL.[11]

Hairy Cell Leukemia

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Therapy in combination with one of the following:
   a) Cladribine as initial therapy
   b) Vemurafenib for incomplete hematologic recovery after initial therapy or relapse within 2 years of full hematologic recovery consistent with complete response following initial therapy (if not previously given)
   c) Cladribine or pentostatin for relapse ≥2 years following initial therapy
   d) Cladribine for relapse ≥2 years following initial treatment with pentostatin
   e) Pentostatin for relapse ≥2 year following initial treatment with cladribine
   f) Vemurafenib for progression after therapy for relapsed/refractory disease

g) Cladribine for incomplete hematologic recovery after initial therapy or relapse within 2 years of full hematologic recovery consistent with complete response following initial therapy with pentostatin
h) Pentostatin for incomplete hematologic recovery after initial therapy or relapse within 2 years of full hematologic recovery consistent with complete response following initial therapy with cladribine
i) Venetoclax for progression after therapy for relapsed/refractory disease, for patients with disease resistant to BRAF inhibitor therapy; OR

4. Initial therapy or for relapse ≥2 years after initial therapy in combination with vemurafenib in patients with indications for treatment who are not candidates for purine analogs including patients who are frail and those with active infection; OR
5. Single agent in patients with indications for treatment who are unable to receive purine analogs in one of the following conditions after initial therapy:
   a) Incomplete hematologic recovery
   b) Relapse within 2 years of full hematologic recovery consistent with complete response
   c) Relapse ≥2 years.[12]

Hematopoietic Cell Transplantation

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. For chronic graft-versus-host disease (GVHD) as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options; OR
4. Conditioning for allogeneic transplant as part of a non-myeloablative regimen in combination with cyclophosphamide and fludarabine.[13]

Histiocytic Neoplasms - Rosai-Dorfman Disease

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent for first-line or subsequent therapy, irrespective of mutation, for IgG4-related, nodal, and immune-cytopenia diseases, for one of the following indications:
   a) Symptomatic unresectable (bulky/site of disease) unifocal disease
   b) Symptomatic multifocal disease
   c) Relapsed/refractory disease.[14]

Hodgkin Lymphoma - Nodular Lymphocyte-Predominant Hodgkin Lymphoma (Age ≥18 years)

1. At least 18 years of age; AND

2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Primary treatment as a component of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) + rituximab, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab, or CVbP (cyclophosphamide, vinblastine, prednisolone) + rituximab for one of the following:
   a) ISRT for stage IA (bulky) or IIA disease (bulky or non-contiguous)
   b) ISRT for stage IB or IIB disease
   c) with or without ISRT for stage III-IV disease; OR
4. Primary treatment as a single agent may be used for palliation for one of the following:
   a) Stage IIA disease (non-contiguous)
   b) Stage III-IV disease (based on clinical judgement); OR
5. Second-line or subsequent systemic therapy (if not previously used) for lack of response, progressive, relapsed, or refractory disease as a single agent; OR
6. Second-line (for symptomatic or bulky disease) or subsequent systemic therapy (if not previously used) for lack of response, progressive, relapsed, or refractory disease in combination with one of the following:
   a) DHAP (dexamethasone, cisplatin, high-dose cytarabine)
   b) ICE (ifosfamide, carboplatin, etoposide)
   c) IGEV (ifosfamide, gemcitabine, vinorelbine)
   d) Bendamustine
   e) ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) + rituximab
   f) CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
   g) CVbP (cyclophosphamide, vinblastine, prednisolone) + rituximab; OR
7. Maintenance therapy for patients treated with second-line systemic therapy with rituximab alone for asymptomatic and non-bulky, or lack of response, progressive, relapsed, or refractory disease.[15]

Management of Immunotherapy-Related Toxicities - Immune Checkpoint Inhibitor-Related Toxicities

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Management of the following immunotherapy-related toxicities for one of the following:
   a) Additional therapy for moderate (G2), if diagnosis of bullous pemphigoid is confirmed by biopsy or serology, severe (G3) or life-threatening (G4) bullous dermatitis
   b) For G3 hemolytic anemia with hemolysis if no response to corticosteroids after 5-7 days and G4 hemolytic anemia with hemolysis if no response to corticosteroids after 3-5 days
   c) For G3 or G4 thrombocytopenia if no response to corticosteroids after 1-2 weeks
   d) Moderate, severe, or life-threatening corticosteroid-refractory myositis (proximal muscle weakness, neck flexor weakness, with or without myalgias) for significant dysphagia, life-threatening situations, or cases refractory to corticosteroids

e) Additional therapy for severe (G3-4) myasthenia gravis in patients refractory to plasmapheresis or intravenous immune globulin (IVIG)
f) Encephalitis in patients positive for autoimmune encephalopathy antibody, or who have had limited or no improvement after 7-14 days on high-dose corticosteroids with or without IVIG
g) Stage 3 acute kidney injury/elevated serum creatinine if toxicity remains >stage 2 after 4-6 weeks of corticosteroids or if creatinine increases during corticosteroid taper (or once off corticosteroids).[16]

Pediatric Aggressive Mature B-Cell Lymphomas

Pediatric Mature B-cell Non-Hodgkin Lymphoma and Mature B-Cell Acute Leukemia

1. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

2. Pediatric patients aged 6 months and older; AND
3. Previously untreated, advanced stage, CD20-positive, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL) or mature B-cell acute leukemia (B-AL) in combination with chemotherapy

   Note: The above excludes the biosimilar drugs: rituximab-abbs, rituximab-arrx and rituximab-pvvr; OR[3]

For **NCCN** required criteria coverage:

4. Under 18 years of age; AND

Burkitt Lymphoma and Diffuse Large B-cell Lymphoma

For **NCCN** required criteria coverage:

5. Induction therapy for patients with ≥20% reduction after COP (cyclophosphamide, vincristine, prednisone) reduction phase as a component of COG ANHL1131 regimen B/induction 1 and 2 with COPADM (cyclophosphamide, vincristine, prednisone, doxorubicin, methotrexate, and intrathecal therapy with methotrexate and hydrocortisone) with rituximab for one of the following:
   a) Group B patients with low-risk disease [unresected stage I or non-abdominal stage II patients or any stage III patient with LDH ≤2 times the upper limit of normal (ULN)]
   b) Group B patients with high-risk disease (any stage III patient with LDH >2 times ULN, and all non-CNS stage IV patients with <25% bone marrow involvement); OR
6. Induction therapy as a component of COG ANHL1131 regimen C1/induction 1 and 2 with R-COPADM (cyclophosphamide, vincristine, prednisone, doxorubicin, methotrexate, and intrathecal therapy with methotrexate, cytarabine, and hydrocortisone) with rituximab for one of the following:
   a) Group B patients with <20% size reduction after COP reduction phase

b) Group C patients with CNS negative disease after initial treatment with COP reduction phase
c) Group C patients with CNS positive and CSF negative or positive disease after initial treatment with COP reduction phase; OR

7. Alternative induction therapy as a component of COG ANHL1131 regimen C3/induction 1 and 2 with R-COPADM (cyclophosphamide, vincristine, prednisone, doxorubicin, methotrexate, and intrathecal therapy with methotrexate, cytarabine, and hydrocortisone) with rituximab for one of the following:
   a) Group C patients with CNS and CSF positive disease
   b) Group C patients on regimen C1 therapy with <20% size reduction after COP reduction phase

   Note: COG protocol ANHL1131 is distinguished between lymphomatous central nervous system or para meningeal disease (CNS positive) and lymphoma cells in the cerebrospinal fluid (CSF positive) disease. CSF positive patients were treated on arm C3. The relative efficacy of arm C1 and arm C3 regimens has not been evaluated. Therefore, either regimen is an acceptable choice for the treatment of CSF positive patients; OR

8. Consolidation therapy 1 for patients with ≥20% reduction after COP (cyclophosphamide, vincristine, prednisone) reduction phase as a component of COG ANHL1131 regimen B with CYM (cytarabine, methotrexate, and intrathecal therapy with methotrexate, cytarabine, and hydrocortisone) with rituximab for one of the following:
   a) Group B patients with low-risk disease [unresected stage I or non-abdominal stage II patients or any stage III patient with LDH ≤2 times the upper limit of normal (ULN)]
   b) Group B patients with high-risk disease (any stage III patient with LDH >2 times ULN, and all non-CNS stage IV patients with <25% bone marrow involvement); OR
9. Consolidation therapy 1 and 2 as a component of COG ANHL1131 regimen C1 with R-CYVE (cytarabine, etoposide and intrathecal therapy with methotrexate and hydrocortisone) with rituximab for one of the following:
   a) Group B patients with less than complete response after first cycle of consolidation with CYM (cytarabine, methotrexate, and intrathecal therapy with methotrexate, cytarabine, and hydrocortisone)
   b) Group C patients with CNS negative disease
   c) Group C patients with CNS positive disease, plus high-dose methotrexate, and additional intrathecal therapy with methotrexate, cytarabine, and hydrocortisone after R-CYVE 1 only; OR
10. Consolidation therapy 1 and 2 as a component of COG ANHL1131 regimen C3 with R-CYVE (cytarabine, etoposide and intrathecal therapy with methotrexate and hydrocortisone) with rituximab for group C patients with CNS and CSF positive disease, plus high-dose methotrexate, and additional intrathecal therapy with methotrexate, cytarabine, and hydrocortisone after R-CYVE 1 only; OR
11. For relapsed or refractory disease as a component with one of the following:
    a) R-CYVE (rituximab, cytarabine, etoposide, and intrathecal therapy with methotrexate and hydrocortisone) (if not previously received as a part of initial therapy)
    b) R-ICE (rituximab, ifosfamide, carboplatin, and etoposide); OR

Pediatric Post-Transplant Lymphoproliferative Disorders

For **NCCN** required criteria coverage:

12. First-line therapy with or without reduction of immunosuppression (RIS) for polymorphic PTLD (P-PTLD) as a single agent with or without surgery; OR
13. First-line therapy with, if possible, reduction of immunosuppression (RIS) for monomorphic PTLD (M-PTLD) (B-cell type, non-Burkitt lymphoma-type) as a single agent; OR
14. First-line therapy for primary central nervous system (CNS) PTLD (B-cell type) in combination with high-dose methotrexate; OR
15. Second-line therapy for partial response or disease that is persistent or progressive for monomorphic PTLD (M-PTLD) (B-cell type, non-Burkitt lymphoma-type) as a single agent if reduction of immunosuppression (RIS) was initial therapy; OR
16. Second-line therapy for partial response or disease that is persistent or progressive for hyperplastic non-destructive PTLD (ND-PTLD) as a single agent; OR
17. In combination with low-dose R-CP (cyclophosphamide, prednisone), R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), R-CEPP (cyclophosphamide, etoposide, prednisone, procarbazine), R-CEOP (cyclophosphamide, etoposide, vincristine, prednisone), or R-CVP (cyclophosphamide, vincristine, prednisone) as chemoimmunotherapy for one of the following indications:
    a) First-line therapy with or without reduction of immunosuppression (RIS) for polymorphic PTLD (P-PTLD)
    b) First-line therapy with, if possible, reduction of immunosuppression (RIS) for monomorphic PTLD (M-PTLD) (B-cell type, non-Burkitt lymphoma-type)
    c) First-line therapy for primary central nervous system (CNS) PTLD (B-cell type) including intrathecal methotrexate
    d) Second-line therapy for partial response or disease that is persistent or progressive for hyperplastic non-destructive PTLD (ND-PTLD)
    e) Second-line therapy for partial response or disease that is persistent or progressive for polymorphic PTLD (P-PTLD), if not previously used as first line therapy
    f) Second-line therapy for partial response or disease that is persistent or progressive for monomorphic PTLD (M-PTLD) (B-cell type, non-Burkitt lymphoma-type), if not previously used as first-line therapy; OR

Primary Mediastinal Large B-Cell Lymphoma

For **NCCN** required criteria coverage:

18. Induction therapy/initial treatment as a component of one of the following:
    a) DA-EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin) with rituximab
    b) R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with rituximab
    c) Lymphome Malin de Burkitt (LMB) modified B/C chemotherapy with rituximab for R-COPADM (cyclophosphamide, vincristine, prednisone, doxorubicin, methotrexate, and intrathecal therapy with methotrexate and hydrocortisone); OR
19. For relapsed or refractory disease as a component of one of the following:

a) DHAP (dexamethasone, cytarabine, and cisplatin or carboplatin) with rituximab
b) R-ICE (ifosfamide, carboplatin, and etoposide) with rituximab; OR

20. Consolidation therapy as a component of LMB-modified B/C chemotherapy with rituximab for R-CYVE (cytarabine and etoposide) with rituximab regimen.[17]

Pediatric Hodgkin Lymphoma - Nodular Lymphocyte-Predominant Hodgkin Lymphoma

1. Under 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Primary treatment for Stage IA or IIA (incomplete resection and non-bulky disease) as a component of CVbP (cyclophosphamide, vinblastine, prednisolone) with rituximab.[18]

Primary Cutaneous B-Cell Lymphomas

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Primary cutaneous marginal zone or follicle center lymphoma with one of the following:
   a) Solitary/regional, T1-2 disease that is refractory to initial therapy
   b) Generalized disease (skin only), T3 disease.[19]

Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. As a component of CaRD (carfilzomib, rituximab, and dexamethasone) or in combination with bortezomib, dexamethasone and cyclophosphamide for one of the following:
   a) Primary therapy
   b) Relapse if previously used as primary therapy that was well tolerated and elicited a prolonged response; OR
4. Rituximab may be used for the following indications:
   a) Primary therapy
   b) Relapse if previously used as primary therapy that was well tolerated and elicited a prolonged response
   c) Alternative therapy for previously treated disease with persistent symptoms following primary therapy or that does not respond to primary therapy
   d) Progressive or relapsed disease
   e) As a single agent or in combination with one of the following regimens for the above indications:
      i. Bendamustine

ii. Bortezomib and dexamethasone
iii. Ibrutinib
iv. Ixazomib and dexamethasone
v. Cyclophosphamide and dexamethasone
vi. Cyclophosphamide and prednisone; OR

5. Alternative therapy for previously treated disease with persistent symptoms following primary therapy or that does not respond to primary therapy or for progressive or relapsed disease in combination with or as a component of one of the following:
   a) RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
   b) Cladribine or fludarabine in patients who are not potential autologous stem cell transplant candidates
   c) FCR (fludarabine, cyclophosphamide, and rituximab) in patients who are not potential autologous stem cell transplant candidates; OR
6. Management of symptomatic Bing-Neel syndrome if systemic control is needed in combination with one of the following:
   a) Ibrutinib
   b) Zanubrutinib
   c) Bendamustine
   d) Cytarabine
   e) Fludarabine
   f) Methotrexate; OR
7. Maintenance therapy after chemo-immunotherapy regimens.[20]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Coding (CPT®, ICD 10 and HCPCS)

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

Code	Description
C72.9	Malignant neoplasm of central nervous system, unspecified
C81.00	Nodular lymphocyte predominant Hodgkin lymphoma
C82	Follicular lymphoma

C82.60	Cutaneous follicle center lymphoma, unspecified site
C83	Non-follicular lymphoma
C83.10	Mantle cell lymphoma, unspecified site
C83.3	Diffuse large b-cell lymphoma
C83.7	Burkitt lymphoma
C83.80	Other non-follicular lymphoma, unspecified site
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]
C91.0	Acute lymphocytic leukemia
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.40	Hairy cell leukemia not having achieved remission
D47.Z1	Post-transplant lymphoproliferative disorders
D47.Z2	Castleman disease
D76.3	Other histiocytosis syndromes
J9312	Injection, rituximab
Q5115	Rituximab-abbs (truxima)

Q5119	Rituximab-pvvr (ruxience)
Q5123	Rituximab-arrx (riabni)

Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	9/30/2025
2	Policy Annual Review Dates:	
3	Department Owner:	Medical Affairs
4	NH Advisory Committee Approval Dates:	9/30/2025
5	Revision Changes:	

References

[1] How does the drug Rituxan work? Drugs.com. https://www.drugs.com/medical-answers/drug-rituxan-work-3539794/. Accessed September 23, 2025.

[2] Greenwald M, Tesser J, Sewell KL. Biosimilars Have Arrived: Rituximab. *Arthritis*. 2018;2018:3762864. Published 2018 Mar 22. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5885398/. Accessed September 23, 2025.

[3] Rituxan (Rituximab) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103705s5467lbl.pdf. Accessed September 23, 2025.

[4] Truxima (Rituximab-abbs) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761088s018lbl.pdf. Accessed September 23, 2025.

[5] Riabni (Rituximab-arrx) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761140s001lbl.pdf. Accessed September 23, 2025.

[6] Ruxience (Rituximab-pvvr) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761103s005lbl.pdf. Accessed September 23, 2025.

[7] National Comprehensive Cancer Network. NCCN Guidelines: Acute Lymphoblastic Leukemia. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed September 24, 2025.

[8] National Comprehensive Cancer Network. NCCN Guidelines: B-Cell Lymphomas. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed September 24, 2025.

[9] National Comprehensive Cancer Network. NCCN Guidelines: Castleman Disease. https://www.nccn.org/professionals/physician_gls/pdf/castleman.pdf. Accessed September 23, 2025.

[10] National Comprehensive Cancer Network. NCCN Guidelines: Central Nervous System Cancers. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed September 23, 2025.

[11] National Comprehensive Cancer Network. NCCN Guidelines: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed September 24, 2025.

[12] National Comprehensive Cancer Network. NCCN Guidelines: Hairy Cell Leukemia. https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf. Accessed September 24, 2025.

[13] National Comprehensive Cancer Network. NCCN Guidelines: Hematopoietic Cell Transplantation (HCT). https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf. Accessed September 23, 2025.

[14] National Comprehensive Cancer Network. NCCN Guidelines: Histiocytic Neoplasms. https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf. Accessed September 24, 2025.

[15] National Comprehensive Cancer Network. NCCN Guidelines: Hodgkin Lymphoma. https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf. Accessed September 24, 2025.

[16] National Comprehensive Cancer Network. NCCN Guidelines: Management of Immunotherapy-Related Toxicities. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed September 24, 2025.

[17] National Comprehensive Cancer Network. NCCN Guidelines: Pediatric Aggressive Mature B-Cell Lymphomas. https://www.nccn.org/professionals/physician_gls/pdf/ped_b-cell.pdf. Accessed September 24, 2025.

[18] National Comprehensive Cancer Network. NCCN Guidelines: Pediatric Hodgkin Lymphoma. https://www.nccn.org/professionals/physician_gls/pdf/ped_hodgkin.pdf. Accessed September 23, 2025.

[19] National Comprehensive Cancer Network. NCCN Guidelines: Primary Cutaneous Lymphomas. https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf. Accessed September 24, 2025.

[20] National Comprehensive Cancer Network. NCCN Guidelines: Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma. https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf. Accessed September 24, 2025.

[21] Adolescents and young adults with cancer. National Cancer Institute. https://www.cancer.gov/types/aya. Accessed September 17, 2025.

[22] Biosimilar drug. National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/biosimilar-drug. Accessed September 17, 2025.

[23] Deletion 17p. National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/deletion-17p. Accessed September 17, 2025.

[24] TP53 gene. National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/tp53-gene. Accessed September 17, 2025.

[25] U.S. Food & Drug Administration. https://www.fda.gov/about-fda/what-we-do. Accessed September 17, 2025.

[26] Indolent lymphoma. National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/indolent-lymphoma. Accessed September 17, 2025.

[27] EOD data. National Cancer Institute. https://staging.seer.cancer.gov/naaccr/item/eod_public/2.1/3896/?version=/tnm/home/1.4/#:~:text=The%20NCCN%20International%20Prognostic%20Index,status%20and%20pretreatment%20LDH%20level. Accessed September 24, 2025.

[28] Zeng Y, Wei R, Bao L, et al. Characteristics and Clinical Value of MYC , BCL2, and BCL6 Rearrangement Detected by Next-generation Sequencing in DLBCL. Am J Surg Pathol. 2024;48(8):919-929. https://pmc.ncbi.nlm.nih.gov/articles/PMC11251499/. Accessed September 17, 2025.

[29] National Comprehensive National Cancer Network. https://www.nccn.org/home. Accessed September 17, 2025.

[30] Thomson RJ, Moshirfar M, Ronquillo Y. Tyrosine Kinase Inhibitors. In: StatPearls. Treasure Island (FL): StatPearls Publishing; July 18, 2023. https://pubmed.ncbi.nlm.nih.gov/33090752/. Accessed September 17, 2025.