Rituximab:
Rituxan®, Truxima®, Ruxience®, Riabni™
(Intravenous)

-E-

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I. Length of Authorization [1-5,23-25,44,62,80,94-98,102]

Coverage will be provided for 6 months (12 months initially for pemphigus vulgaris) and may be renewed unless otherwise specified.

- Maintenance therapy for oncology indications (excluding ALL, Hairy Cell Leukemia, and Mantle cell lymphoma) may be renewed for up to a maximum of 2 years.
  - Mantle cell lymphoma may be renewed until disease progression or intolerable toxicity
  - Acute lymphoblastic leukemia (ALL) and Hairy Cell Leukemia may not be renewed.
- Management of Immunotherapy-Related Toxicities:
  - Myalgias/Myositis/Myasthenia gravis/Encephalitis may not be renewed.
  - Bullous dermatitis may be renewed for a maximum of 18 months (4 total doses).
- Relapse therapy for pemphigus vulgaris must be at least 16 weeks past a prior infusion
- Chronic Graft-Versus-Host Disease (cGVHD) may not be renewed.

II. Dosing Limits

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

- Rituxan 100 mg/10 mL injection: 12 vials per 28 day supply
- Rituxan 500 mg/50 mL injection: 8 vials per 28 day supply
- Truxima 100 mg/10 mL injection: 12 vials per 28 day supply
- Truxima 500 mg/50 mL injection: 8 vials per 28 day supply
- Ruxience 100 mg/10 mL injection: 12 vials per 28 day supply
- Ruxience 500 mg/50 mL injection: 8 vials per 28 day supply
- Riabni 100 mg/10 mL injection: 12 vials per 28 day supply
- Riabni 500 mg/50 mL injection: 8 vials per 28 day supply

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

Oncology Indications

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Leukemia (SLL):
• Initial therapy:
  ○ Loading dose: 100 billable units x 1 dose
  ○ Subsequent doses: 130 billable units every 28 days x 5 doses per 6 months
• Renewal therapy: 100 billable units per dose every 8 weeks x 4 doses per 6 months

ALL & Hairy Cell Leukemia • 100 billable units per dose weekly x 8 doses
Immunotherapy Toxicity Treatment: • 100 billable units per dose weekly x 4 doses in a 6 month period
All other oncology indications: • Initial therapy: 100 billable units per dose weekly x 8 doses per 6 months • Renewal therapy: 100 billable units per dose every 8 weeks x 4 doses per 6 months
Non-Oncology Indications
Rheumatoid Arthritis (RA): • 100 billable units per dose every 14 days x 2 doses in a 16 week period
Pemphigus Vulgaris: • Initiation: 100 billable units every 14 days x 2 doses in a 12 month period • Maintenance: 50 billable units every 16 weeks
GPA(WG)/MPA: • Induction: 100 billable units per dose weekly x 4 doses in a 4 month period • Initial Maintenance: 50 billable units x 2 doses in a 6 month period • Subsequent Maintenance: 50 billable units every 6 months
cGVHD • 100 billable units per dose weekly x 4 doses, then 100 billable units monthly x 4 months; **OR** • 100 billable units per dose weekly x 4 - 8 doses
All other non-oncology indications: • 100 billable units per dose weekly x 4 doses in a 6 month period
Neuromyelitis Optica Spectrum Disorders (NMOSD): • 100 billable units per dose every 14 days x 2 doses in a 24 week period; **OR** • 100 billable units per dose weekly x 4 doses in a 6 month period

III. Initial Approval Criteria [1-4]

Coverage is provided in the following conditions:

Ruxience® (rituximab-pvvr) and **Truxima®** (rituximab-abbs) are the preferred rituximab products.

- Patient must have a contraindication, intolerance, or failure of Ruxience® (rituximab-pvvr) and Truxima® (rituximab-abbs) prior to the consideration of another rituximab product.

- Patient age is at least 18 years of age (unless otherwise specified); **AND**

Universal Criteria [1-4]

- Patient does not have a severe, active infection; **AND**
- Patient has been screened for the presence of hepatitis B (HBV) infection (i.e., HBsAg and anti-HBc) prior to initiating therapy and patients with evidence of current or prior HBV infection will be monitored for HBV reactivation during treatment; **AND**
- Patient has not received a live vaccine within 28 days prior to starting treatment and live vaccines will not be administered concurrently while on treatment; **AND**

Oncology Indications [1-5]

- Patient CD20 antigen expression is positive; **AND**

Acute Lymphoblastic Leukemia (ALL) ‡ [5,57-59,93]

- Induction/Consolidation Treatment
  - Patient has Philadelphia chromosome-negative (Ph-) disease; **AND**
    - Patient is at least 15 years of age and less than 60 years of age; **AND**
      - Used in combination with an anthracycline, cyclophosphamide and vincristine based regimen

Central Nervous System (CNS) Cancer ‡ [5,15,44,9e]

- Patient has primary CNS lymphoma; **AND**
  - Used as a component of induction therapy in combination with a methotrexate-containing regimen; **OR**
  - Used for relapsed or refractory disease and will receive rituximab in combination with temozolomide

Hodgkin Lymphoma ‡ [5,82,83]

- Patient has nodular lymphocyte-predominant disease

Chronic Lymphocytic Leukemia/Small lymphocytic lymphoma (CLL/SLL) † ‡ Φ [1-5,23e,24e,28e-30e,36e,38e,42e,43e,45e,61e,161e]

- Used as first-line therapy in combination with fludarabine and cyclophosphamide (FC) in patients less than 65 years of age; **OR**
- Patient has disease that is <u>without</u> del(17p)/TP53 mutation; **AND**
  - Used as first-line therapy in combination with one of the following:
    - Bendamustine (*patients ≥ 65 years, or younger patients with or without significant comorbidities; excluding use in frail patients [i.e., not able to tolerate purine analogs]*)
    - Fludarabine (*patient is without del(11q) and is <65 years without significant comorbidities*); **OR**
  - Used as subsequent therapy in combination with one of the following:
    - Bendamustine (*patients < 65 years without significant comorbidities*)
    - Idelalisib
    - Lenalidomide
    - Venetoclax; **OR**
- Patient has disease <u>with</u> del(17p)/TP53 mutation; **AND**
  - Used as subsequent therapy in combination with one of the following:
    - Idelalisib
    - Lenalidomide
    - Venetoclax; **OR**
- Used as first line therapy for histologic (Richter's) transformation to diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, and vincristine based regimens or as a component of OFAR (oxaliplatin, fludarabine, cytarabine, and rituximab)

Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma ‡ [5,67e,72e]

Non-Hodgkin's Lymphomas (NHL) † Φ [1-5,44] including, but not limited to, the following:

- AIDS-Related B-Cell Lymphoma ‡
  - Disease is related to Burkitt Lymphoma or diffuse large B-cell lymphoma *(including HHV-8 positive DLBCL, not otherwise specified, or primary effusion lymphoma)*
- Burkitt Lymphoma ‡
  - Used in combination with chemotherapy
- Castleman Disease ‡
  - Patient has multicentric disease
- Diffuse Large B-Cell Lymphoma † Φ
- Low-grade or Follicular Lymphoma † Φ
- Gastric & Non-Gastric MALT Lymphoma ‡
- High Grade B-Cell Lymphomas ‡
- Mantle Cell Lymphoma ‡
- Nodal & Splenic Marginal Zone Lymphoma ‡
- Histologic transformation of Follicular or Nodal Marginal Zone Lymphoma to Diffuse Large B-Cell Lymphoma ‡
- Post-transplant lymphoproliferative disorder (PTLD) (B-cell type) ‡
  - Patient has had solid organ transplant or allogeneic hematopoietic stem cell transplantation
- Pediatric Aggressive Mature B-Cell Lymphomas ‡
  - Patient age is 18 years and under*; **AND**
  - Used in combination with chemotherapy

**Pediatric Aggressive Mature B-Cell Lymphoma may be applicable to adolescent and young adult (AYA) patients older than 18 years of age and less than 39 years of age, who are treated in the pediatric oncology setting.*

Hairy Cell Leukemia ‡ [5]

- Used in combination with cladribine as initial therapy; **OR**
- Used for relapsed or refractory disease or in patients with a less than complete response (CR) to initial therapy

Non-Oncology Indications

- Patient is not on concurrent treatment with another TNF-inhibitor, biologic response modifier or other non-biologic agent (i.e., apremilast tofacitinib, baricitinib, upadacitinib); **AND**

Rheumatoid Arthritis (RA) † [1,2,12,13,46-49]

- Documented moderate to severe disease; **AND**
- Used in combination with methotrexate unless the patient has a contraindication or intolerance; **AND**

- Patient tried and failed at least a 3 month trial with ONE oral disease modifying anti-rheumatic drug (DMARD) (e.g., methotrexate, azathioprine, auranofin, hydroxychloroquine, penicillamine, sulfasalazine, leflunomide, etc.); **AND**
- Physician has assessed baseline disease severity utilizing an objective measure/tool; **AND**
- Patient has not had treatment with rituximab in the previous 4 months; **AND**

- Patient must try and have an inadequate response, contraindication, or intolerance to at least a three (3) month trial of Enbrel AND Humira; **OR**
- Patient is continuing treatment

Pemphigus Vulgaris † Φ [1,10,11,35,36,38,61]

- Patient has a diagnosis of pemphigus vulgaris as determined by the following:
    - One or more of the following clinical features:
        - Appearance of lesions, erosions and/or blisters
        - Nikolsky sign (induction of blistering via mechanical pressure at the edge of a blister or on normal skin)
        - Characteristic scarring and lesion distribution; **AND**
    - Histopathologic confirmation by skin/mucous membrane biopsy; **AND**
    - Presence of autoantibodies as detected by indirect immunofluorescence or enzyme-linked immunosorbent assay (ELISA); **AND**
- Patient has moderate to severe disease as assessed utilizing an objective measure/tool (i.e. PDAI, PSS, ABSIS); **AND**
- Patient is on combination glucocorticoid therapy; **AND**
- Other causes of blistering or erosive skin and mucous membrane diseases have been ruled out

Granulomatosis with Polyangiitis (GPA) (Wegener's granulomatosis) and Microscopic Polyangiitis (MPA) † Φ [1-4]

- Patient is at least 2 years of age; **AND**
- Used in combination with glucocorticoids (e.g., prednisone, methylprednisolone, etc.)

Thrombocytopenic purpura ‡ [6-9,16-18,20,21,63]

- Patient has previously failed or has a contraindication or intolerance to therapy with corticosteroids; **AND**
- Patient is at increased risk for bleeding as indicated by platelet count (within the previous 28 days) less than 30×10^9/L ($30{,}000/mm^3$); **AND**
- Patient diagnosis includes one of the following:
    - Primary thrombocytopenia
    - Idiopathic (Immune) thrombocytopenia purpura (ITP)
    - Evan's syndrome
    - Congenital and hereditary thrombocytopenic purpura

- Thrombotic thrombocytopenic purpura in patients with ADAMTS13-deficiency

Chronic Graft-Versus-Host Disease (cGVHD) ‡ [5,22-25,45]

- Patient is post-allogeneic stem cell transplant (generally 3 or more months); **AND**
- Used as additional therapy in combination with corticosteroids; **AND**
- Patient has failed one or more previous lines of systemic therapy for the treatment of cGVHD (e.g., corticosteroids or immunosuppressants such as cyclosporine); **AND**
- Patient must try and have an inadequate response, contraindication, or intolerance to at least a three (3) month trial of ibrutinib.

Autoimmune Hemolytic Anemia (AIHA) ‡ [26-32]

- Patient has warm-reactive disease refractory to or dependent on glucocorticoids; **OR**
- Patient has cold agglutinin disease with symptomatic anemia, transfusion-dependence, and/or disabling circulatory symptoms

Management of Immunotherapy-Related Toxicities ‡ [5,62]

- Patient has been receiving therapy with an immune checkpoint inhibitor (e.g., cemiplimab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, ipilimumab, etc.); **AND**
  - Patient has non-viral encephalitis related to their immunotherapy; **AND**
    - Patient is autoimmune-encephalopathy-antibody positive; **OR**
    - Patient is refractory to methylprednisolone with or without IV immunoglobulin (IVIG); **OR**
  - Patient has bullous dermatitis related to their immunotherapy; **AND**
    - Used as additional therapy for moderate (G2), severe (G3) or life-threatening (G4) disease; **OR**
  - Patient has moderate, severe, or life-threatening myalgias or myositis that are steroid-refractory; **OR**
  - Patient has severe (G3-4) myasthenia gravis related to their immunotherapy that is refractory to plasmapheresis or IV immunoglobulin (IVIG)

Neuromyelitis Optica Spectrum Disorder (NMOSD) ‡ [90-92]

- Patient has a confirmed diagnosis based on the following:
  - Patient was found to be seropositive for aquaporin-4 (AQP4) IgG antibodies; **AND**
    - Patient has at least one core clinical characteristic §; **AND**
    - Alternative diagnoses have been excluded (e.g., multiple sclerosis, sarcoidosis, cancer, chronic infection, etc.); **OR**
  - Patient was found to be seronegative for AQP-4 IgG antibodies OR has unknown AQP-4-IgG status; **AND**
    - Patient has at least two core clinical characteristics occurring as a result of one or more clinical attacks §; **AND**
    - Patient experienced ALL of the following:

- At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM*, or area postrema syndrome; **AND**
- Dissemination in space (≥2 different core clinical characteristics); **AND**
- Fulfillment of additional MRI requirements, as applicable ψ; **AND**

▪ Alternative diagnoses have been excluded (e.g., multiple sclerosis, sarcoidosis, cancer, chronic infection, etc.); **AND**

- Used as a single agent or in combination with immunosuppressive therapy (e.g., azathioprine, methotrexate, mycophenolate, etc.)

Generalized Myasthenia Gravis (gMG)

- Patient is 18 years or older; **AND**
- Documented baseline disease severity utilizing a standardized scale (e.g., Osserman score, Myasthenia Gravis Foundation of America (MGFA) clinical manifestations, etc.); **AND**
- Patient has failed treatment over at least 1 year with at least 2 immunosuppressive therapies (e.g. azathioprine, cyclosporine, mycophenolate, etc), or has failed at least 1 immunosuppressive therapy and required chronic plasmapheresis or plasma exchange (PE) or intravenous immunoglobulin (IVIG)

§ Core Clinical Characteristics of NMOSD [90]
▪ Optic neuritis ▪ Acute myelitis ▪ Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting ▪ Acute brainstem syndrome ▪ Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions ▪ Symptomatic cerebral syndrome with NMOSD-typical brain lesions
ψ Core Clinical Characteristics of NMOSD [90]
▪ Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm ▪ Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis ▪ Area postrema syndrome: requires associated dorsal medulla/area postrema lesions ▪ Acute brainstem syndrome: requires associated peri-ependymal brainstem lesions
**LETM = longitudinally extensive transverse myelitis lesions*

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-labeled indication(s); ‡ Compendia recommended indication(s); Φ Orphan Drug

IV. Renewal Criteria [1-4]

Coverage can be renewed based upon 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**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: severe infusion-related reactions, tumor lysis syndrome (TLS), severe mucocutaneous reactions, progressive multifocal leukoencephalopathy (PML), hepatitis B virus reactivation, serious bacterial, fungal, or viral infections, cardiovascular adverse reactions (e.g., ventricular fibrillation, myocardial infarction, cardiogenic shock, cardiac arrhythmias), renal toxicity, bowel obstruction or perforation, etc.; **AND**

Oncology Indications [1-5,44,50]

- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Patient has not exceeded dosing or duration limits as defined in Sections I, II, and V

Non-Oncology Indications [1-4,7-12,34,102-104]

Rheumatoid arthritis (RA)

- Disease response as indicated by improvement in signs and symptoms compared to baseline such as the number of tender and swollen joint counts, reduction of C-reactive protein, improvement of patient global assessment, and/or an improvement on a disease activity scoring tool [e.g. an improvement on a composite scoring index such as Disease Activity Score-28 (DAS28) of 1.2 points or more or a ≥20% improvement on the American College of Rheumatology-20 (ACR20) criteria]; **AND**
- Dose escalation (up to the maximum dose and frequency specified below) may occur upon clinical review on a case by case basis provided that the patient has:
  - Shown an initial response to therapy; **AND**
  - Received a minimum of one maintenance dose at the dose and interval specified below; **AND**
  - Responded to therapy with subsequent loss of response

Thrombocytopenic purpura

- Disease response as indicated by the achievement and maintenance of a platelet count of at least 50×10^9/L as necessary to reduce the risk for bleeding

Thrombotic thrombocytopenic purpura (TTP)

- Disease response as indicated by an increase in ADAMTS13 activity with a reduction in thrombotic risk

Granulomatosis with Polyangiitis (GPA) (Wegener's granulomatosis) and Microscopic polyangiitis (MPA)

- Disease response as indicated by disease control and improvement in signs and symptoms of condition compared to baseline; **AND**
- A decrease frequency in the occurrence of major relapses (defined by the reappearance of clinical and/or laboratory signs of vasculitis activity that could lead to organ failure or damage, or could be life threatening)

Pemphigus vulgaris [1,10,11,35]

- Patient is currently receiving tapering doses of corticosteroids or has discontinued use of corticosteroids; **AND**
  - Disease response as indicated by complete epithelialization of lesions and improvement in signs and symptoms of condition compared to baseline; **OR**
  - Patient has not experienced continued development of new lesions, continued extension of old lesions, or failure of established lesions to begin to heal despite therapy; **OR**
    - For Relapses ONLY: Patient has had active disease control; **AND**
    - Patient has the appearance of 3 or more new lesions a month that do not heal spontaneously within 1 week, or by the extension of established lesions

Chronic graft-versus-host disease (cGVHD)

- Coverage may not be renewed

Management of Immunotherapy-Related Toxicities

- Coverage for use in the treatment of myalgias/myositis/myasthenia gravis/encephalitis may not be renewed.
- Coverage for use in bullous dermatitis: Patient has not exceeded a maximum of 18 months of therapy (4 total doses).

Autoimmune hemolytic anemia (AIHA)

- Disease response as indicated by improvement in anemia signs and symptoms (e.g., dyspnea, fatigue, etc.) as well as: improvement in laboratory values (Hb/Hct), reduced transfusion needs, and/or reduced glucocorticoid use

NMOSD [90,91]

- Disease response as indicated by stabilization/improvement in any of the following: neurologic symptoms as evidenced by a decrease in acute relapses, stability reduced hospitalizations, reduction/discontinuation in plasma exchange treatments, and/or reduction/discontinuation of corticosteroids without relapse

Generalized Myasthenia Gravis (gMG)

- Disease response from pretreatment baseline utilizing a standardized scale

V. Dosage/Administration [1-5,9,23-26,32,34,40,42,44,50,62,80,83-89,91,94-98,102-104]

Indication		Dose
CLL/SLL	Initial Therapy	375 mg/m² intravenously (IV) weekly for 8 doses; **OR**

		375 mg/m² IV cycle 1, then 500 mg/m² every 28 days cycles 2-6 (6 total doses)
	Renewal Therapy	375 mg/m² IV once weekly for 4 doses per 6 month period; **OR** 375 mg/m² IV every 8 weeks
NHL, PTLD, Waldenström's, Castleman's, or HL	Initial Therapy	375 mg/m² IV once weekly for 4 - 8 doses in a 6 month period
	Renewal Therapy	375 mg/m² IV once weekly for 4 doses per 6 month period; **OR** 375 mg/ m² IV every 8 weeks
Pediatric Aggressive B-cell Lymphoma		**Induction*** 375 mg/m² IV once to twice during the first week of the induction cycle (typically 21-day cycle) **Consolidation*** 375 mg/m² IV once weekly on day-1 of the consolidation cycle (typically 21-day cycle) **Relapsed/Refractory** RCYVE – 375mg/m² IV on day-1 of each 21-day cycle RICE – 375 mg/m² IV on days 1 and 3 of courses 1 and 2, and on day 1 only of course 3 if needed. **Note: dosing and dosing schedules are highly variable and dependent on regimen used, please refer to NCCN for different protocols.*
CNS Lymphoma		**Intravenous administration** Initial Therapy: 375 mg/m² IV once weekly for 4 - 8 doses in a 6 month period Renewal Therapy: 375 mg/m² IV once weekly for 4 doses per 6 month period; **OR** 375 mg/ m² IV every 8 weeks **Intrathecal/Intraventricular administration** 10-40 mg weekly to every 3 weeks
ALL		375 mg/m² IV once weekly for 4 - 8 doses in a 6 month period
Hairy Cell Leukemia		375 mg/m² IV once weekly for 4 - 8 doses
RA		1,000 mg IV on days 1 and 15, repeated every 24 weeks. May repeat up to every 16 weeks in patients requiring more frequent dosing based on clinical evaluation.
Pemphigus Vulgaris		Initiation – Administer 1,000 IV mg on days 1 and 15 in combination with tapering doses of glucocorticoids Maintenance – Administer 500 mg IV at month 12 and repeat every 6 months thereafter or based on clinical evaluation. Relapse

	– Administer 1,000 IV mg upon relapse, resumption of glucocorticoids may be considered. **Subsequent infusions (maintenance and relapse) should be no sooner than 16 weeks after the previous infusion.*
Thrombocytopenia, AIHA	375 mg/m² IV weekly for 4 doses in a 6 month period
Immunotherapy Toxicity Treatment	Bullous dermatitis 1,000 mg IV every 2 weeks for 2 doses, then 500 mg IV at months 12 and 18 as needed Myalgias/Myositis 375 mg/m² IV weekly for 4 doses Myasthenia gravis 375 mg/m² IV weekly for 4 doses; **OR** 500 mg/m² IV every 2 weeks for 2 doses Encephalitis 1,000 mg IV every 2 weeks for 2 doses; **OR** 375 mg/m² IV weekly for 4 doses
GPA (WG), MPA	Induction (Pediatric and Adult) – 375 mg/m² IV weekly for 4 doses Maintenance – Pediatric: o 250 mg/m² IV on days 1 and 15, then 250 mg/m² IV every 6 months thereafter based on clinical evaluation – Adult: o 500 mg IV on days 1 and 15, then 500 mg IV every 6 months thereafter based on clinical evaluation. **Initial MAINTENANCE infusions should be no sooner than 16 weeks and no later than 24 weeks after the previous infusion if Rituxan was used for initial induction therapy.* **Initial MAINTENANCE infusions should be initiated within 4 weeks following disease control when initial induction occurred with other standard of care immunosuppressants.*
cGVHD	375 mg/m² IV weekly for 4 doses, then 375 mg/m² IV monthly for 4 months **-OR-** 375 mg/m² IV weekly for 4 doses *(Note: A second course of 4 weekly doses may be administered 8 weeks after initial therapy for patients with lack of or incomplete response.)* **-OR-** 375 mg/m² IV weekly for 4 - 8 doses
NMOSD	1,000 mg IV once on days 1 and 15, repeat every 6 months **-OR-**

	375 mg/m² once weekly for 4 weeks, repeat every 6 months
gMG	375 mg/m² weekly x 4 doses; may re-treat with an additional mg/m² monthly for up to 3 additional months

VI. Billing Code/Availability Information

HCPCS Code:

- J9312 – Injection, rituximab, 10 mg; 1 billable unit = 10 mg *(Rituxan IV only)*
- Q5115 – Injection, rituximab-abbs, biosimilar, (truxima), 10 mg; 1 billable unit = 10 mg
- Q5119 – Injection, rituximab-pvvr, biosimilar, (ruxience), 10 mg; 1 billable unit = 10 mg
- J9999 – Not otherwise classified, antineoplastic drugs *(Riabni – rituximab-arrx only)*
- C9399 – Unclassified drugs or biologicals *(Riabni – rituximab-arrx only)*

NDC:

- Rituxan 100 mg/10 mL single-use vial for injection: 50242-0051-xx
- Rituxan 500 mg/50 mL single-use vial for injection: 50242-0053-xx
- Truxima 100 mg/10 mL single-use vial for injection: 63459-0103-xx
- Truxima 500 mg/50 mL single-use vial for injection: 63459-0104-xx
- Ruxience 100 mg/10 mL single-use vial for injection: 00069-0238-xx
- Ruxience 500 mg/50 mL single-use vial for injection: 00069-0249-xx
- Riabni 100 mg/10 mL single-use vial for injection: 55513-0224-xx
- Riabni 500 mg/50 mL single-use vial for injection: 55513-0326-xx

VII. References (STANDARD)

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5. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) rituximab. 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 March 2021.
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Appendix 1 – Covered Diagnosis Codes

ICD-10	Description
C79.32	Secondary malignant neoplasm of cerebral meninges
C81.00	Nodular lymphocyte predominant Hodgkin lymphoma, unspecified site
C81.01	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.02	Nodular lymphocyte predominant Hodgkin lymphoma, intrathoracic lymph nodes
C81.03	Nodular lymphocyte predominant Hodgkin lymphoma, intra-abdominal lymph nodes
C81.04	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.05	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.06	Nodular lymphocyte predominant Hodgkin lymphoma, intrapelvic lymph nodes
C81.07	Nodular lymphocyte predominant Hodgkin lymphoma, spleen
C81.08	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of multiple sites
C81.09	Nodular lymphocyte predominant Hodgkin lymphoma, extranodal and solid organ sites
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 regional 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, unspecified site
C82.21	Follicular lymphoma grade III, unspecified, lymph nodes of head, face and neck
C82.22	Follicular lymphoma, grade III, unspecified, intrathoracic lymph nodes
C82.23	Follicular lymphoma grade III, unspecified, intra-abdominal lymph nodes
C82.24	Follicular lymphoma grade III, unspecified, lymph nodes of axilla and upper limb
C82.25	Follicular lymphoma grade III, unspecified, lymph nodes of inguinal region and lower limb
C82.26	Follicular lymphoma grade III, unspecified, intrapelvic lymph nodes
C82.27	Follicular lymphoma grade III, unspecified, spleen
C82.28	Follicular lymphoma grade III, unspecified, lymph nodes of multiple sites
C82.29	Follicular lymphoma grade III, unspecified, 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
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
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
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, 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
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
C83.50	Lymphoblastic (diffuse) lymphoma, unspecified site
C83.51	Lymphoblastic (diffuse) lymphoma, lymph nodes of head, face, and neck
C83.52	Lymphoblastic (diffuse) lymphoma, intrathoracic lymph nodes
C83.53	Lymphoblastic (diffuse) lymphoma, intra-abdominal lymph nodes
C83.54	Lymphoblastic (diffuse) lymphoma, lymph nodes of axilla and upper limb

C83.55	Lymphoblastic (diffuse) lymphoma, lymph nodes of inguinal region and lower limb
C83.56	Lymphoblastic (diffuse) lymphoma, intrapelvic lymph nodes
C83.57	Lymphoblastic (diffuse) lymphoma, spleen
C83.58	Lymphoblastic (diffuse) lymphoma, lymph nodes of multiple sites
C83.59	Lymphoblastic (diffuse) 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
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 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
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 of 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)
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
C91.40	Hairy cell leukemia not having achieved remission
C91.42	Hairy cell leukemia, in relapse
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
D47.Z2	Other neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue-Castleman
D59.10	Autoimmune hemolytic anemia, unspecified
D59.11	Warm autoimmune hemolytic anemia

D59.12	Cold autoimmune hemolytic anemia
D59.13	Mixed type autoimmune hemolytic anemia
D59.19	Other autoimmune hemolytic anemia
D69.3	Immune thrombocytopenic purpura
D69.41	Evans Syndrome
D69.42	Congenital and hereditary thrombocytopenia purpura
D69.49	Other primary thrombocytopenia
D89.811	Chronic graft-versus-host disease
D89.812	Acute on chronic graft-versus-host disease
D89.813	Graft-versus-host disease unspecified
G04.81	Other encephalitis and encephalomyelitis
G36.0	Neuromyelitis optica [Devic]
G70.00	Myasthenia gravis without (acute) exacerbation
G70.01	Myasthenia gravis with (acute) exacerbation
L10.0	Pemphigus vulgaris
L13.8	Other specified bullous disorders
L13.9	Bullous disorder, unspecified
M05.10	Rheumatoid lung disease with rheumatoid arthritis of unspecified site
M05.111	Rheumatoid lung disease with rheumatoid arthritis of right shoulder
M05.112	Rheumatoid lung disease with rheumatoid arthritis of left shoulder
M05.119	Rheumatoid lung disease with rheumatoid arthritis of unspecified shoulder
M05.121	Rheumatoid lung disease with rheumatoid arthritis of right elbow
M05.122	Rheumatoid lung disease with rheumatoid arthritis of left elbow
M05.129	Rheumatoid lung disease with rheumatoid arthritis of unspecified elbow
M05.131	Rheumatoid lung disease with rheumatoid arthritis of right wrist
M05.132	Rheumatoid lung disease with rheumatoid arthritis of left wrist
M05.139	Rheumatoid lung disease with rheumatoid arthritis of unspecified wrist
M05.141	Rheumatoid lung disease with rheumatoid arthritis of right hand
M05.142	Rheumatoid lung disease with rheumatoid arthritis of left hand
M05.149	Rheumatoid lung disease with rheumatoid arthritis of unspecified hand
M05.151	Rheumatoid lung disease with rheumatoid arthritis of right hip
M05.152	Rheumatoid lung disease with rheumatoid arthritis of left hip
M05.159	Rheumatoid lung disease with rheumatoid arthritis of unspecified hip
M05.161	Rheumatoid lung disease with rheumatoid arthritis of right knee
M05.162	Rheumatoid lung disease with rheumatoid arthritis of left knee
M05.169	Rheumatoid lung disease with rheumatoid arthritis of unspecified knee
M05.171	Rheumatoid lung disease with rheumatoid arthritis of right ankle and foot
M05.172	Rheumatoid lung disease with rheumatoid arthritis of left ankle and foot
M05.179	Rheumatoid lung disease with rheumatoid arthritis of unspecified ankle and foot

M05.19	Rheumatoid lung disease with rheumatoid arthritis of multiple sites
M05.20	Rheumatoid vasculitis with rheumatoid arthritis of unspecified site
M05.211	Rheumatoid vasculitis with rheumatoid arthritis of right shoulder
M05.212	Rheumatoid vasculitis with rheumatoid arthritis of left shoulder
M05.219	Rheumatoid vasculitis with rheumatoid arthritis of unspecified shoulder
M05.221	Rheumatoid vasculitis with rheumatoid arthritis of right elbow
M05.222	Rheumatoid vasculitis with rheumatoid arthritis of left elbow
M05.229	Rheumatoid vasculitis with rheumatoid arthritis of unspecified elbow
M05.231	Rheumatoid vasculitis with rheumatoid arthritis of right wrist
M05.232	Rheumatoid vasculitis with rheumatoid arthritis of left wrist
M05.239	Rheumatoid vasculitis with rheumatoid arthritis of unspecified wrist
M05.241	Rheumatoid vasculitis with rheumatoid arthritis of right hand
M05.242	Rheumatoid vasculitis with rheumatoid arthritis of left hand
M05.249	Rheumatoid vasculitis with rheumatoid arthritis of unspecified hand
M05.251	Rheumatoid vasculitis with rheumatoid arthritis of right hip
M05.252	Rheumatoid vasculitis with rheumatoid arthritis of left hip
M05.259	Rheumatoid vasculitis with rheumatoid arthritis of unspecified hip
M05.261	Rheumatoid vasculitis with rheumatoid arthritis of right knee
M05.262	Rheumatoid vasculitis with rheumatoid arthritis of left knee
M05.269	Rheumatoid vasculitis with rheumatoid arthritis of unspecified knee
M05.271	Rheumatoid vasculitis with rheumatoid arthritis of right ankle and foot
M05.272	Rheumatoid vasculitis with rheumatoid arthritis of left ankle and foot
M05.279	Rheumatoid vasculitis with rheumatoid arthritis of unspecified ankle and foot
M05.29	Rheumatoid vasculitis with rheumatoid arthritis of multiple sites
M05.30	Rheumatoid heart disease with rheumatoid arthritis of unspecified site
M05.311	Rheumatoid heart disease with rheumatoid arthritis of right shoulder
M05.312	Rheumatoid heart disease with rheumatoid arthritis of left shoulder
M05.319	Rheumatoid heart disease with rheumatoid arthritis of unspecified shoulder
M05.321	Rheumatoid heart disease with rheumatoid arthritis of right elbow
M05.322	Rheumatoid heart disease with rheumatoid arthritis of left elbow
M05.329	Rheumatoid heart disease with rheumatoid arthritis of unspecified elbow
M05.331	Rheumatoid heart disease with rheumatoid arthritis of right wrist
M05.332	Rheumatoid heart disease with rheumatoid arthritis of left wrist
M05.339	Rheumatoid heart disease with rheumatoid arthritis of unspecified wrist
M05.341	Rheumatoid heart disease with rheumatoid arthritis of right hand
M05.342	Rheumatoid heart disease with rheumatoid arthritis of left hand
M05.349	Rheumatoid heart disease with rheumatoid arthritis of unspecified hand
M05.351	Rheumatoid heart disease with rheumatoid arthritis of right hip
M05.352	Rheumatoid heart disease with rheumatoid arthritis of left hip

M05.359	Rheumatoid heart disease with rheumatoid arthritis of unspecified hip
M05.361	Rheumatoid heart disease with rheumatoid arthritis of right knee
M05.362	Rheumatoid heart disease with rheumatoid arthritis of left knee
M05.369	Rheumatoid heart disease with rheumatoid arthritis of unspecified knee
M05.371	Rheumatoid heart disease with rheumatoid arthritis of right ankle and foot
M05.372	Rheumatoid heart disease with rheumatoid arthritis of left ankle and foot
M05.379	Rheumatoid heart disease with rheumatoid arthritis of unspecified ankle and foot
M05.39	Rheumatoid heart disease with rheumatoid arthritis of multiple sites
M05.40	Rheumatoid myopathy with rheumatoid arthritis of unspecified site
M05.411	Rheumatoid myopathy with rheumatoid arthritis of right shoulder
M05.412	Rheumatoid myopathy with rheumatoid arthritis of left shoulder
M05.419	Rheumatoid myopathy with rheumatoid arthritis of unspecified shoulder
M05.421	Rheumatoid myopathy with rheumatoid arthritis of right elbow
M05.422	Rheumatoid myopathy with rheumatoid arthritis of left elbow
M05.429	Rheumatoid myopathy with rheumatoid arthritis of unspecified elbow
M05.431	Rheumatoid myopathy with rheumatoid arthritis of right wrist
M05.432	Rheumatoid myopathy with rheumatoid arthritis of left wrist
M05.439	Rheumatoid myopathy with rheumatoid arthritis of unspecified wrist
M05.441	Rheumatoid myopathy with rheumatoid arthritis of right hand
M05.442	Rheumatoid myopathy with rheumatoid arthritis of left hand
M05.449	Rheumatoid myopathy with rheumatoid arthritis of unspecified hand
M05.451	Rheumatoid myopathy with rheumatoid arthritis of right hip
M05.452	Rheumatoid myopathy with rheumatoid arthritis of left hip
M05.459	Rheumatoid myopathy with rheumatoid arthritis of unspecified hip
M05.461	Rheumatoid myopathy with rheumatoid arthritis of right knee
M05.462	Rheumatoid myopathy with rheumatoid arthritis of left knee
M05.469	Rheumatoid myopathy with rheumatoid arthritis of unspecified knee
M05.471	Rheumatoid myopathy with rheumatoid arthritis of right ankle and foot
M05.472	Rheumatoid myopathy with rheumatoid arthritis of left ankle and foot
M05.479	Rheumatoid myopathy with rheumatoid arthritis of unspecified ankle and foot
M05.49	Rheumatoid myopathy with rheumatoid arthritis of multiple sites
M05.50	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified site
M05.511	Rheumatoid polyneuropathy with rheumatoid arthritis of right shoulder
M05.512	Rheumatoid polyneuropathy with rheumatoid arthritis of left shoulder
M05.519	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified shoulder
M05.521	Rheumatoid polyneuropathy with rheumatoid arthritis of right elbow
M05.522	Rheumatoid polyneuropathy with rheumatoid arthritis of left elbow
M05.529	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified elbow
M05.531	Rheumatoid polyneuropathy with rheumatoid arthritis of right wrist

M05.532	Rheumatoid polyneuropathy with rheumatoid arthritis of left wrist
M05.539	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified wrist
M05.541	Rheumatoid polyneuropathy with rheumatoid arthritis of right hand
M05.542	Rheumatoid polyneuropathy with rheumatoid arthritis of left hand
M05.549	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hand
M05.551	Rheumatoid polyneuropathy with rheumatoid arthritis of right hip
M05.552	Rheumatoid polyneuropathy with rheumatoid arthritis of left hip
M05.559	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hip
M05.561	Rheumatoid polyneuropathy with rheumatoid arthritis of right knee
M05.562	Rheumatoid polyneuropathy with rheumatoid arthritis of left knee
M05.569	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified knee
M05.571	Rheumatoid polyneuropathy with rheumatoid arthritis of right ankle and foot
M05.572	Rheumatoid polyneuropathy with rheumatoid arthritis of left ankle and foot
M05.579	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified ankle and foot
M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis of multiple sites
M05.60	Rheumatoid arthritis of unspecified site with involvement of other organs and systems
M05.611	Rheumatoid arthritis of right shoulder with involvement of other organs and systems
M05.612	Rheumatoid arthritis of left shoulder with involvement of other organs and systems
M05.619	Rheumatoid arthritis of unspecified shoulder with involvement of other organs and systems
M05.621	Rheumatoid arthritis of right elbow with involvement of other organs and systems
M05.622	Rheumatoid arthritis of left elbow with involvement of other organs and systems
M05.629	Rheumatoid arthritis of unspecified elbow with involvement of other organs and systems
M05.631	Rheumatoid arthritis of right wrist with involvement of other organs and systems
M05.632	Rheumatoid arthritis of left wrist with involvement of other organs and systems
M05.639	Rheumatoid arthritis of unspecified wrist with involvement of other organs and systems
M05.641	Rheumatoid arthritis of right hand with involvement of other organs and systems
M05.642	Rheumatoid arthritis of left hand with involvement of other organs and systems
M05.649	Rheumatoid arthritis of unspecified hand with involvement of other organs and systems
M05.651	Rheumatoid arthritis of right hip with involvement of other organs and systems
M05.652	Rheumatoid arthritis of left hip with involvement of other organs and systems
M05.659	Rheumatoid arthritis of unspecified hip with involvement of other organs and systems
M05.661	Rheumatoid arthritis of right knee with involvement of other organs and systems
M05.662	Rheumatoid arthritis of left knee with involvement of other organs and systems
M05.669	Rheumatoid arthritis of unspecified knee with involvement of other organs and systems
M05.671	Rheumatoid arthritis of right ankle and foot with involvement of other organs and systems
M05.672	Rheumatoid arthritis of left ankle and foot with involvement of other organs and systems
M05.679	Rheumatoid arthritis of unspecified ankle and foot with involvement of other organs and systems
M05.69	Rheumatoid arthritis of multiple sites with involvement of other organs and systems
M05.7A	Rheumatoid arthritis with rheumatoid factor of other specified site without organ or systems

M05.711	Rheumatoid arthritis with rheumatoid factor of right shoulder without organ or systems involvement
M05.712	Rheumatoid arthritis with rheumatoid factor of left shoulder without organ or systems involvement
M05.719	Rheumatoid arthritis with rheumatoid factor of unspecified shoulder without organ or systems
M05.721	Rheumatoid arthritis with rheumatoid factor of right elbow without organ or systems involvement
M05.722	Rheumatoid arthritis with rheumatoid factor of left elbow without organ or systems involvement
M05.729	Rheumatoid arthritis with rheumatoid factor of unspecified elbow without organ or systems
M05.731	Rheumatoid arthritis with rheumatoid factor of right wrist without organ or systems involvement
M05.732	Rheumatoid arthritis with rheumatoid factor of left wrist without organ or systems involvement
M05.739	Rheumatoid arthritis with rheumatoid factor of unspecified wrist without organ or systems
M05.741	Rheumatoid arthritis with rheumatoid factor of right hand without organ or systems involvement
M05.742	Rheumatoid arthritis with rheumatoid factor of left hand without organ or systems involvement
M05.749	Rheumatoid arthritis with rheumatoid factor of unspecified hand without organ or systems
M05.751	Rheumatoid arthritis with rheumatoid factor of right hip without organ or systems involvement
M05.752	Rheumatoid arthritis with rheumatoid factor of left hip without organ or systems involvement
M05.759	Rheumatoid arthritis with rheumatoid factor of unspecified hip without organ or systems involvement
M05.761	Rheumatoid arthritis with rheumatoid factor of right knee without organ or systems involvement
M05.762	Rheumatoid arthritis with rheumatoid factor of left knee without organ or systems involvement
M05.769	Rheumatoid arthritis with rheumatoid factor of unspecified knee without organ or systems
M05.771	Rheumatoid arthritis with rheumatoid factor of right ankle and foot without organ or systems
M05.772	Rheumatoid arthritis with rheumatoid factor of left ankle and foot without organ or systems
M05.779	Rheumatoid arthritis with rheumatoid factor of unspecified ankle and foot without organ or systems
M05.79	Rheumatoid arthritis with rheumatoid factor of multiple sites without organ or systems involvement
M05.8A	Other rheumatoid arthritis with rheumatoid factor of other specified site
M05.811	Other rheumatoid arthritis with rheumatoid factor of right shoulder
M05.812	Other rheumatoid arthritis with rheumatoid factor of left shoulder
M05.819	Other rheumatoid arthritis with rheumatoid factor of unspecified shoulder
M05.821	Other rheumatoid arthritis with rheumatoid factor of right elbow
M05.822	Other rheumatoid arthritis with rheumatoid factor of left elbow
M05.829	Other rheumatoid arthritis with rheumatoid factor of unspecified elbow
M05.831	Other rheumatoid arthritis with rheumatoid factor of right wrist
M05.832	Other rheumatoid arthritis with rheumatoid factor of left wrist
M05.839	Other rheumatoid arthritis with rheumatoid factor of unspecified wrist
M05.841	Other rheumatoid arthritis with rheumatoid factor of right hand
M05.842	Other rheumatoid arthritis with rheumatoid factor of left hand
M05.849	Other rheumatoid arthritis with rheumatoid factor of unspecified hand
M05.851	Other rheumatoid arthritis with rheumatoid factor of right hip
M05.852	Other rheumatoid arthritis with rheumatoid factor of left hip
M05.859	Other rheumatoid arthritis with rheumatoid factor of unspecified hip
M05.861	Other rheumatoid arthritis with rheumatoid factor of right knee

M05.862	Other rheumatoid arthritis with rheumatoid factor of left knee
M05.869	Other rheumatoid arthritis with rheumatoid factor of unspecified knee
M05.871	Other rheumatoid arthritis with rheumatoid factor of right ankle and foot
M05.872	Other rheumatoid arthritis with rheumatoid factor of left ankle and foot
M05.879	Other rheumatoid arthritis with rheumatoid factor of unspecified ankle and foot
M05.89	Other rheumatoid arthritis with rheumatoid factor of multiple sites
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M06.0A	Rheumatoid arthritis without rheumatoid factor, other specified site
M06.011	Rheumatoid arthritis without rheumatoid factor, right shoulder
M06.012	Rheumatoid arthritis without rheumatoid factor, left shoulder
M06.019	Rheumatoid arthritis without rheumatoid factor, unspecified shoulder
M06.021	Rheumatoid arthritis without rheumatoid factor, right elbow
M06.022	Rheumatoid arthritis without rheumatoid factor, left elbow
M06.029	Rheumatoid arthritis without rheumatoid factor, unspecified elbow
M06.031	Rheumatoid arthritis without rheumatoid factor, right wrist
M06.032	Rheumatoid arthritis without rheumatoid factor, left wrist
M06.039	Rheumatoid arthritis without rheumatoid factor, unspecified wrist
M06.041	Rheumatoid arthritis without rheumatoid factor, right hand
M06.042	Rheumatoid arthritis without rheumatoid factor, left hand
M06.049	Rheumatoid arthritis without rheumatoid factor, unspecified hand
M06.051	Rheumatoid arthritis without rheumatoid factor, right hip
M06.052	Rheumatoid arthritis without rheumatoid factor, left hip
M06.059	Rheumatoid arthritis without rheumatoid factor, unspecified hip
M06.061	Rheumatoid arthritis without rheumatoid factor, right knee
M06.062	Rheumatoid arthritis without rheumatoid factor, left knee
M06.069	Rheumatoid arthritis without rheumatoid factor, unspecified knee
M06.071	Rheumatoid arthritis without rheumatoid factor, right ankle and foot
M06.072	Rheumatoid arthritis without rheumatoid factor, left ankle and foot
M06.079	Rheumatoid arthritis without rheumatoid factor, unspecified ankle and foot
M06.08	Rheumatoid arthritis without rheumatoid factor, vertebrae
M06.09	Rheumatoid arthritis without rheumatoid factor, multiple sites
M06.8A	Other specified rheumatoid arthritis, other specified site
M06.811	Other specified rheumatoid arthritis, right shoulder
M06.812	Other specified rheumatoid arthritis, left shoulder
M06.819	Other specified rheumatoid arthritis, unspecified shoulder
M06.821	Other specified rheumatoid arthritis, right elbow
M06.822	Other specified rheumatoid arthritis, left elbow
M06.829	Other specified rheumatoid arthritis, unspecified elbow
M06.831	Other specified rheumatoid arthritis, right wrist

M06.832	Other specified rheumatoid arthritis, left wrist
M06.839	Other specified rheumatoid arthritis, unspecified wrist
M06.841	Other specified rheumatoid arthritis, right hand
M06.842	Other specified rheumatoid arthritis, left hand
M06.849	Other specified rheumatoid arthritis, unspecified hand
M06.851	Other specified rheumatoid arthritis, right hip
M06.852	Other specified rheumatoid arthritis, left hip
M06.859	Other specified rheumatoid arthritis, unspecified hip
M06.861	Other specified rheumatoid arthritis, right knee
M06.862	Other specified rheumatoid arthritis, left knee
M06.869	Other specified rheumatoid arthritis, unspecified knee
M06.871	Other specified rheumatoid arthritis, right ankle and foot
M06.872	Other specified rheumatoid arthritis, left ankle and foot
M06.879	Other specified rheumatoid arthritis, unspecified ankle and foot
M06.88	Other specified rheumatoid arthritis, vertebrae
M06.89	Other specified rheumatoid arthritis, multiple sites
M06.9	Rheumatoid arthritis, unspecified
M31.1	Thrombotic microangiopathy
M31.30	Wegener's granulomatosis without renal involvement
M31.31	Wegener's granulomatosis with renal involvement
M31.7	Microscopic polyangiitis
T86.09	Other complications of bone marrow transplant

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):

Jurisdiction(s): 6, K	**NCD/LCD/LCA Document (s):** A52452
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A52452&bc=gAAAAAAAAAAAAA==	

Jurisdiction(s): 5,8	**NCD/LCD/LCA Document (s):** A55639
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A55639&bc=gAAAAAAAAAAA	

Jurisdiction(s): J,M	NCD/LCD/LCA Document (s): A56380
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A56380&bc=gAAAAAAAAAAA	

Jurisdiction(s): 15	NCD/LCD/LCA Document (s): A57160
https://www.cms.gov/medicare-coverage-database/search/document-id-search-results.aspx?DocID=A57160&bc=gAAAAAAAAAAA&	

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; CIRS = cumulative illness rating scale

Acute Lymphoblastic Leukemia (ALL)

Induction/Consolidation for Philadelphia (Ph) negative, CD20-positive disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab + GRAALL-2005 regimen	2A	No	Phase 3 (GRAALL-2005/R), randomized, multi-center	GRAALL-2005 regimen (daunorubicin, vincristine, prednisone, pegaspargase, cyclophosphamide)	EFS	Previously untreated	• Adding rituximab to the ALL chemotherapy protocol improved the outcome for younger adults with CD20-positive, Ph-negative ALL compared to standard chemotherapy.
Rituximab + modified hyper – CVAD	2A	No	Phase 2, open label, single-center	Modified Hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone)	CR	First-line	• The incorporation of rituximab into the hyper-CVAD regimen appears to improve outcome for younger patients (< 60 years old) with CD20-positive Ph-negative precursor B-lineage ALL compared to standard chemotherapy alone.

Relapsed or Refractory CD20+ disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab + MOpAD	2A	No	Phase 2, open-label	N/A	CR	Relapsed or refractory disease	• In patients with refractory ALL, clinical activity of MOpAD regimen was demonstrated including patients who received rituximab for CD20 positive disease.
Blinatumomab	1 for relapsed/ refractory Philadelphia-chromosome negative B-ALL	Yes (Not restrictive of Ph-status)	Phase 3 (TOWER), randomized	Standard of care: • FLAG ± anthracycline-based regimen • HiDAC-based regimen • High-dose methotrexate-based regimen • Clofarabine-based regimen	OS	Relapsed or refractory disease	• Treatment with blinatumomab resulted in significantly longer OS than chemotherapy
Inotuzumab ozogamicin	1 for relapsed/ refractory Philadelphia-chromosome negative B-ALL	Yes (Not restrictive of Ph-status)	Phase 3 (INO-VATE), randomized, open-label	Standard of care: • FLAG • HiDAC-based regimen	CR and OS	Relapsed or refractory CD22-positive Ph+ or Ph-negative ALL in patients due for first or second salvage treatment. Ph+ patients were required to have	• Patients receiving inotuzumab ozogamicin versus standard care achieved higher response, MRD-negativity rates, and prolonged PFS and OS

						failed treatment with at least 1 TKI and standard chemotherapy	
Tisagenlecleucel	2A for relapsed/ refractory Philadelphia-chromosome negative B-ALL in patients < 26 years and with refractory disease or ≥ 2 relapses	Yes for patients up to 25 years of age with B-cell ALL that is refractory or in second or later relapse (Not restrictive of Ph-status)	Phase 2 (ELIANA), single-cohort	N/A	ORR	Relapsed or refractory disease Excluded patients with previous anti-CD19 therapy	• Tisagenlecleucel provided durable remission with long-term persistence in pediatric and young adult patients with relapsed or refractory B-cell ALL, with transient high-grade toxic effects

CNS Cancer

Leptomeningeal metastases from lymphomas							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab + liposomal cytarabine	2A	No	Clinical series	N/A	----------	Recurrent disease	• Combination of intra-CSF rituximab and liposomal cytarabine has modest palliative activity with a median overall survival of 5 months.
Rituximab (intraventricular), alternating in	2A	No	Phase 1, multi-center	N/A	----------	Recurrent CNS NHL	• Phase I study showed that intraventricular rituximab plus methotrexate is feasible and active in the

combination with MTX every other week							treatment of refractory CNS lymphoma with a 75% rate of complete cytologic response.
Methotrexate (intrathecal)	2A	No	Randomized, prospective cooperative group study	N/A	----------	First-line	• Intrathecal methotrexate demonstrated a median survival of 15.9 weeks.
Methotrexate (intrathecal)	2A	No	Randomized controlled, multi-center, open-label	Liposomal cytarabine (intrathecal)	ORR, DOR, & time to neurological progression	No prior IT MTX	• In patients with solid tumor neoplastic meningitis, liposomal cytarabine produced a response rate comparable to that of methotrexate and significantly increased the time to neurological progression
Primary CNS lymphoma – Induction intrathecal therapy (if CSF positive or spinal MRI positive)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab	2B	No	Case report	N/A	-----	Relapsed disease	• The data suggests that intrathecal therapy with rituximab is effective in the treatment of primary CNS lymphoma with 3 out of 4 patients responding to treatment.
Methotrexate (MTX)	2A						
Cytarabine	2A						
Primary CNS lymphoma - Induction							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Rituximab + high-dose MTX	2A preferred	No	Phase 2	N/A	PFS	First-line	• Rituximab plus high-dose methotrexate demonstrated an ORR of 80%.
Rituximab + MTX + temozolomide	2A preferred	No	Phase 1/2	N/A	2-year OS rate	Induction	• Rituximab plus methotrexate and temozolomide is an effective treatment for induction therapy of primary CNS lymphoma with a 2-year OS rate of 80.5%.
Rituximab + MTX	2A preferred	No	Retrospective study	N/A	OS	First-line	• In this retrospective analysis, the addition of rituximab to high-dose methotrexate-based chemotherapy in patients with aggressive B cell CNS lymphoma was associated with improved overall survival.
Rituximab + high-dose MTX (HD-MTX/R)	2A preferred	No	Retrospective study	High-dose MTX (HD-MTX)	--------	First-line	• The addition of rituximab to HD-MTX appears to improve CR rates as well as overall and progression-free survival in patients with newly diagnosed PCNSL.
Rituximab + MBVP (MTX, carmustine, teniposide, oral prednisone)	None	No	Phase 3 (HOVON 105/ALLG NHL 24), randomized, open-label, multi-center	MBVP	EFS	First-line	• No clear benefit was observed with the addition of rituximab to methotrexate, carmustine, teniposide, and prednisone chemotherapy in primary CNS lymphoma. Therefore, the results of this study do not support the use of rituximab as a component of standard treatment in primary CNS lymphoma.
Primary CNS lymphoma – Relapsed or refractory disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
MTX rechallenge	2A	No	Retrospective, multi-center study	N/A	ORR	Relapsed disease after a complete response after treatment	• High-dose methotrexate remains effective fore relapsed CNS lymphoma in patients who initially respond to methotrexate.

						with MTX-based therapy	
Rituximab + TMZ	2A	No	Retrospective series	N/A	----------	Recurrent or refractory disease	• Combination therapy with rituximab and temozolomide demonstrated an ORR of 53%.
Rituximab + TMZ	2A	No	Phase 2, multi-center	N/A	ORR	Recurrent disease	• Rituximab plus temozolomide demonstrated modest activity with a complete response rate or 14%.
Rituximab	2A	No	Case series	N/A	----------	Recurrent or refractory disease	• Responses to IV rituximab monotherapy were observed in approximately one-third of patients.
Rituximab + lenalidomide	2A	No	Phase 1	N/A	----------	Recurrent or refractory disease	• Out of 5 patients who received rituximab plus lenalidomide, 1 patient demonstrated a partial response.
Ibrutinib	2A	No	Phase 1	N/A	ORR	Relapsed or refractory disease	• Single-agent ibrutinib showed activity in patients with recurrent or refractory primary CNS lymphoma with an ORR of 77%.
Temozolomide (TMZ)	2A	No	Retrospective study	N/A	-----	Relapsed or refractory disease	• Temozolomide resulted in a complete response (CR) in 29% of patients with relapsed or refractory primary CNS lymphoma.
Topotecan	2A	No	Phase 2, multi-center	N/A	ORR	Relapsed or refractory disease	• Topotecan as monotherapy is active in relapsed and refractory PCNSL with an ORR of 33%
Pemetrexed	2A	No	Prospective, single-center study	N/A	----------	Relapsed or refractory disease	• Pemetrexed has single-agent activity in relapsed/ refractory primary CNS lymphoma with an ORR of 55%

Pomalidomide	2A	No	Phase 1	N/A	Max tolerated dose	Relapsed or refractory disease	• Pomalidomide demonstrated clinical activity against relapsed or refractory primary CNS lymphoma with an ORR of 48%.

Hodgkin's Lymphoma

Nodular lymphocyte-predominant disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab	2A	No	Phase 2	N/A	ORR	Untreated or previously treated	• Rituximab monotherapy demonstrated an ORR of 100% however after a median follow-up of 13 months, 9 patients had relapsed and the median freedom from progression was 10.2 months.
Rituximab	2A	No	Phase 2 (GHSG)	N/A	ORR	Newly diagnosed stage IA disease	• Patients with newly diagnosed NLPHL responded to rituximab with an ORR of 100% however, relapse rate at 43 months was 25%.
Rituximab	2A	No	Phase 2 (GHSG)	N/A	ORR	Relapsed or refractory disease	• Rituximab is effective in relapsed and refractory NLPHL with an ORR of 94%.
Rituximab	2A	No	Phase 2	N/A	PFS	Untreated or previously treated	• Rituximab is an active agent against NLPHL with an ORR of 100%

Chronic lymphocytic leukemia/Small lymphocytic lymphoma (CLL/SLL)

Without del(17p) or TP53 Mutation – First line therapy – Frail patient with significant comorbidities OR patients ≥ 65 y and younger patients with significant comorbidities							
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 (Alliance 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

Chlorambucil + ofatumumab	2A	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.
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.
Obinutuzumab (6 cycles) + venetoclax (12 cycles)	2A preferred	Yes	Phase 3 (CLL 14), open-label, randomized	Obinutuzumab + chlorambucil	PFS	Previously untreated	• Among patients with untreated CLL and coexisting conditions, venetoclax-obinutuzumab was associated with longer progression-free survival than chlorambucil-obinutuzumab.
High-dose methylprednisolone + rituximab	2B	No					
Ibrutinib + obinutuzumab	2B	No					

Obinutuzumab	2B	No					
Chlorambucil	2B	No					
Rituximab	2B	No					
Without del(17p) or TP53 Mutation – First line therapy – Patients age < 65 y without significant comorbidities							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Ibrutinib	1 preferred	Yes	See ibrutinib data above.				
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	Ofatumumab	PFS	Relapsed or refractory disease	• Ibrutinib, as compared with ofatumumab, significantly improved progression-free survival, overall survival, and

			4-year follow-up study				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 (if < 65y)	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 refractory disease	• Obinutuzumab monotherapy is active in patients with heavily pretreated relapsed/ refractory CLL with an ORR of 30%.
Ofatumumab	2A	Yes	Phase 2	N/A	ORR	Fludarabine- and alemtuzumab-refractory disease OR fludarabine-refractory with bulky lymphadenopathy (>5 cm)	• Ofatumumab is an active, well-tolerated treatment with an ORR of 43-49% in fludarabine-refractory patients with very poor-prognosis 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	-----	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-	N/A	ORR	Relapsed or refractory disease	• 83% of patients with del17p relapsed or refractory CLL had a clinical response to ibrutinib.

			center, open-label, single-arm, international				
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	N/A	ORR	Fludarabine- and alemtuzumab-refractory disease OR fludarabine-refractory with bulky lymphadenopathy	• Ofatumumab is an option for patients with relapsed or refractory CLL with del17p as indicated by an ORR of 41% however, not effective for patients with bulky 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.
Histologic (Richter's) transformation to diffuse large B-cell lymphoma – First line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab + cyclophosphamide + doxorubicin + vincristine +	2A	No	Phase 2, prospective, multi-center	N/A	ORR	First- to fifth-line	• R-CHOP induces an acceptable response rate in Richter's transformation with 67%

prednisone (R-CHOP							
Rituximab + etoposide + prednisone+ vincristine cyclophosphamide + doxorubicin (R-EPOCH)	2A	No	Retrospective cohort study	N/A	-------	First-line	• R-EPOCH demonstrated to have an estimated 1-year OS of 71% in patients without a complex CLL karyotype
Rituximab + cyclophosphamide + vincristine + liposomal doxorubicin + dexamethasone alternating with methotrexate and cytarabine (modified R-hyperCVAD)	2A	No	Phase 2	N/A	CR	First- to fourth-line	• The modified R-hyperCVAD regimen demonstrated a CR of 27% and a 1-year overall survival rate of 28% in patients with Richter's transformation.
Oxaliplatin + fludarabine + cytarabine + rituximab (OFAR)	2A	No	Phase 1-2	N/A	-------	Untreated and previously treated	• The OFAR regimen is active in Richter's transformation with a 6-mon OS rate of 53% and ORR of 50%

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.

Non-Hodgkin's Lymphoma (NHL)

AIDS-related B-Cell Lymphoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab + chemotherapy	2A	No	Pooled analysis	N/A	-----	First line	• Initial therapy with rituximab resulted in higher CR rates and was associated with improved PFS and OS.
R-CHOP	2A (DLBCL)	No	Phase 3 (AMC 010), multi-center, randomized	CHOP	CR	First-line	• The addition of rituximab to CHOP in patients with HIV-NHL did not demonstrate a significant improved response compared to CHOP. Also, R-CHOP was associated with an increase

							in infectious deaths, particularly in those with a CD4+ count less than 50/mcL.
R-CHOP	2A (DLBCL)	No	Phase 2, multi-center	N/A	CR	First line	• Rituximab adjunction to CHOP produced a CR rate of 77% and a 2-year survival rate of 75% in patients with AIDS-related non-Hodgkin's lymphoma, without increasing the risk of life-threatening infections.
Cyclophosphamide + vincristine + doxorubicin + high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine + rituximab (CODOX-M/IVAC)	2A preferred (Burkitt)	No	Retrospective study	N/A	OS PFS	----------	• CODOX-M/IVAC, with or without rituximab, is a highly effective regimen for the treatment of adult BL. Rituximab decreased the recurrence rate and showed a trend in favor of improvement in PFS and OS.
Rituximab + etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin (R-EPOCH) *concurrent dosing*	2A preferred (Burkitt, DLBCL)	No	Phase 2 (AMC034), randomized	R-EPOCH sequential dosing	CR	First line	• Concurrent rituximab plus infusional EPOCH demonstrated a complete response rate of 73%.
R-EPOCH	2A preferred (Burkitt, DLBCL)		Pooled analysis of R-	N/A	EFS	First line	• The current analysis provided additional level 2 evidence supporting the use of concurrent R-EPOCH in

			CHOP or R-EPOCH				patients with HIV-associated lymphoma and a CD4 count >50/µL
Rituximab + cyclophosphamide + vincristine + doxorubicin + dexamethasone alternating with high-dose methotrexate and cytarabine (R-Hyper CVAD)	2A (Burkitt)	No	Prospective study	N/A	-------	First line	• Hyper-CVAD is an effective regimen for patients with AIDS-associated Burkitt lymphoma/leukemia with a CR of 92%.
Bendamustine + rituximab + polatuzumab vedotin-piiq	2A (after ≥ 2 prior therapies)	Yes (after ≥ 2 prior therapies)	Phase 2, randomized, multi-center, open-label	Bendamustine + rituximab	CR	Relapsed or refractory FL or DLBCL	• In a randomized setting, BR+P showed longer survival compared to BR, with median OS surpassing 12 months.
Lenalidomide + rituximab	2A	No	Phase 2	N/A	ORR	Relapsed or refractory DLBCL, FL, and transformed lymphoma (1-4 prior therapies)	• Rituximab plus lenalidomide demonstrated an ORR of 33% for patients with relapsed/refractory DLBCL and TL.
Burkitt Lymphoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab + chemotherapy	2A	No	Phase 3, randomized,	Chemotherapy	3-year EFS	First line	• Addition of rituximab to a short intensive chemotherapy improves EFS in adults with Burkitt's leukemia or lymphoma.

			controlled, open-label				
Cyclophosphamide + vincristine + doxorubicin + high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine ± rituximab (CODOX-M/IVAC)	2A	No	Single institution study	N/A	-----	----------	• CODOX-M/IVAC regimen demonstrated to be effective in patients with Burkitt lymphoma and B-cell lymphoma with a 5-year OS of 87%.
Cyclophosphamide + vincristine + doxorubicin + high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine ± rituximab (CODOX-M/IVAC)	2A	No	Retrospective study	N/A	OS PFS	Various	• CODOX-M/IVAC, with or without rituximab, is a highly effective regimen for the treatment of adult BL. Rituximab decreased the recurrence rate and showed a trend in favor of improvement in PFS and OS.
Rituximab + cyclophosphamide + vincristine + doxorubicin + dexamethasone alternating with high-dose	2A	No	Phase 2	N/A	-----	First line	• The addition of rituximab to hyper-CVAD may improve outcome in adult BL or B-ALL as indicated by a CR of 86%.

methotrexate and cytarabine (R-Hyper CVAD)							
Rituximab + chemotherapy	2A	No	Phase 4, prospective, multi-center	Chemotherapy (high-dose methotrexate, high-dose cytarabine, cyclophosphamide, etoposide, ifosfamide and corticosteroids, and a triple intrathecal therapy [MTX, AraC, Dexa])	-------	First line	• Efficacy of chemoimmunotherapy was demonstrated in this study with a CR of 91%.
Castleman's Disease - Unicentric							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab	2A	No	None				
Castleman's Disease – Multicentric disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab	2A	No	Phase 2 (ANRS 117 CastlemaB Trial),	N/A	Sustained remission	Chemotherapy-dependent	• Rituximab was effective in HIV-infected patients with chemotherapy-dependent multicentric Castleman's disease

			prospective, open-label				
Rituximab + chemotherapy	2A	No	Retrospective multi-centric analysis	Chemotherapy	-----	First to third line	• Rituximab-based regimens had significantly higher complete remission rates (91%) than those receiving chemotherapy with or without antiviral therapy (41%) and also had significantly longer overall survival.
High Grade B-Cell Lymphoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Intensive regimens (R-HyperCVAD vs. R-CODOX-M/IVAC vs. DA-EPOCH-R)	2A	Yes	Retrospective, multi-center analysis	R-CHOP	--------	Induction	• Intensive chemotherapy regimens resulted in a superior PFS compared to R-CHOP.
Intensive regimens (R-HyperCVAD vs. R-CODOX-M/IVAC vs. DA-EPOCH-R)	2A	Yes	Meta-analysis	R-CHOP	-------	Induction	• Front-line dose-escalated immunochemotherapy is associated with a PFS advantage in patients with double-hit lymphomas compared to R-CHOP.
Dose adjusted EPOCH-R	2A	Yes	Phase 2	N/A	EFS OS	First line	• DA-EPOCH-R produced durable remission in patients with MYC-rearranged aggressive B-cell lymphomas with a 48-mon OS rate of 77%.
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 + vincristine + prednisone (R-CHOP	1	Yes	Phase 3 (GELA LNH-98.5), randomized, multi-center, open-label	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 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.
Ibrutinib	2A	No	Phase 2	N/A	ORR	Relapsed or refractory DLBCL	• Ibrutinib demonstrated an ORR of 37% in patients with activated B-cell DLBCL. An ORR of 5% was seen in patients with germinal center B-cell DLBCL.
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.
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 + prednisone (R-CVP)	2A	Yes	Phase 3 (FOLL05), randomized, open-label, multi-center	R-CHOP vs. rituximab + fludarabine + mitoxantrone (R-FM)	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.

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
Lenalidomide + rituximab	2A preferred	Yes	Phase 3 (RELEVANCE), multi-center, randomized, open-label	Chemotherapy + rituximab (RCHOP, RCVP, BR)	CR PFS	First line	• Among patients with previously untreated follicular lymphoma, efficacy results were similar with rituximab plus lenalidomide and rituximab plus chemotherapy (with both regimens followed by rituximab maintenance therapy).
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
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.
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.
Obinutuzumab + CHOP or FC (fludarabine +	2A	Yes	Phase 1b (GAUDI),	N/A	Safety	Relapsed or refractory FL	Obinutuzumab plus chemotherapy resulted in 93% to 96% response rates

cyclophosphamide)			randomized, open-label				
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	2A preferred (in patients	Yes	Phase 3 (GADOLIN), randomized, controlled,	Bendamustine (B)	PFS	Refractory to rituximab (no response to or progressed	• Obinutuzumab plus bendamustine followed by obinutuzumab maintenance has improved efficacy (PFS and OS) over bendamustine

obinutuzumab in non-progressing patients	refractory to rituximab)		open-label, multi-center Updated analysis			within 6 months of therapy with a rituximab-containing regimen)	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 for anti-H. pylori therapy	• This study demonstrated the clinical activity of rituximab in gastric MALT NHL patients resistant/refractory to antibiotics treatment or not presenting 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.

Hairy Cell Leukemia – Relapsed or Refractory Disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Cladribine followed by rituximab	2A	No	Phase 2	N/A	-----	Untreated and relapsed HCL	• Cladribine followed by rituximab is highly effective even in patients with relapsed HCL with a CR rate of 100%.
Rituximab + pentostatin or cladribine	2A	No	Retrospective study	N/A	-----	Relapsed HCL	• The combination of a purine analog with rituximab was effective for patients with recurrent HCL with a CR rate of 89%.
Rituximab	2A (if unable to receive purine analogs)	No	Phase 2	N/A	-----	Refractory disease after prior cladribine	• Rituximab has only modest single-agent activity in cladribine-failed HCL with an ORR of 25% and CR of 13%.
Rituximab	2A (if unable to receive purine analogs)	No	Phase 2	N/A	-----	Refractory disease after prior cladribine	• Rituximab demonstrated clinical activity in refractory HCL with an ORR of 80% and CR of 32%.
Cladribine re-treatment	2A	Yes	Extended follow-up	N/A	-----	Relapsed disease	• Retreatment with cladribine is an effective treatment for relapsed HCL with a CR rate of 75% after first relapse and 60% after subsequent relapse.
Ibrutinib	2A	No	Phase 2	N/A	-----	Treatment naïve and relapsed disease	• Ibrutinib can induce remission in HCL including heavily pre-treated patients with an ORR of 46%.
Vemurafenib	2A	No	Phase 2	N/A	ORR	Relapsed or refractory	• High response rates with vemurafenib monotherapy in patients with relapsed

						disease after purine analogs	or refractory HCL was confirmed with an ORR of 86% at a median 24-month follow up.
Vemurafenib + rituximab	2A (after therapy for relapsed or refractory disease)	No	Phase 2	N/A	-----	Relapsed or refractory HCL	• Vemurafenib plus rituximab represents a regimen that produces deep and durable responses in heavily pre-treated relapsed/refractory HCL patients with a CR rate and 14-mon PFS rate of 100%.
Moxetumomab pasudotox	2A	Yes (after at least 2 prior therapies, including a purine analog)	Phase 3, multi-center, single-arm, open-label	N/A	CR	Relapsed or refractory HCL after at least 2 prior therapies	• Moxetumomab pasudotox treatment achieved a high response rate of 75% and MRD eradication in heavily pretreated patients with HCL.
Mantle Cell Lymphoma – Induction Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab + dexamethasone + cytarabine (RDHA) + platinum (carboplatin, cisplatin, or oxaliplatin), followed by maintenance rituximab	2A preferred	No	Phase 3, randomized	RDHA + platinum, followed by observation	EFS	Induction	• Induction therapy with RDHA plus platinum resulted in an ORR of 89%.
Alternating RCHOP and RDHAP	2A preferred	No	Phase 3	RCHOP	TTF	Induction	• Induction therapy with alternating RCHOP/RDHAP is associated with a higher time to treatment failure and

							complete response rates compared to RCHOP alone.
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 treated disease	• In patients with indolent or mantle cell lymphoma, R-chemo is superior to chemotherapy alone with respect to overall survival
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-	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.

			center, randomized				
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**
Acalabrutinib	2A preferred (short response duration to prior treatment)	Yes (after at least one prior therapy)	Phase 2, open-label	N/A	ORR	Relapsed or refractory MCL	• Acalabrutinib treatment provided a high rate of durable responses and a favorable safety profile in patients with relapsed or refractory mantle cell lymphoma.
Ibrutinib	2A preferred (short response duration to prior treatment)	Yes (after at least one prior therapy)	Phase 3 (RAY), randomized, open-label	Temsirolimus	PFS	Relapsed or refractory MCL	• Ibrutinib demonstrated significant improvement in ORR and PFS over temsirolimus in patients with relapsed or refractory MCL.
Ibrutinib + rituximab	2A preferred (short response duration to prior tre**at**ment)	Yes (after at least one prior therapy)	Phase 2, single-center, single-arm, open-label	N/A	ORR	Relapsed or refractory MCL	• Ibrutinib combined with rituximab demonstrated an ORR of 88%.

Lenalidomide	2A preferred (short response duration to prior treatment)	Yes (after two prior therapies, one of which included bortezomib)	Phase 2 (EMERGE), multi-center	N/A	ORR	Relapsed or refractory MCL after prior bortezomib	• The EMERGE study demonstrate durable efficacy of lenalidomide (ORR 28%; DOR 17mon) in heavily pretreated patients with MCL who had all relapsed or progressed after or were refractory to bortezomib
Lenalidomide + rituximab	2A preferred (short response duration to prior treatment)	Yes (after two prior therapies, one of which included bortezomib)	Phase 1/2	N/A	ORR	Relapsed or refractory MCL	• Lenalidomide plus rituximab is effective for patients with relapsed or refractory MCL with an ORR of 57%.
Venetoclax	2A preferred (short response duration to prior treatment)	No	Phase 1	N/A	-----	Relapsed or refractory NHL	• Venetoclax resulted in responses across all NHL subtypes with higher ORR and median PFS in patients with MCL than other NHL subtypes.
Bendamustine + rituximab	2A preferred (extended response duration to prior treatment)	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 (extended response	Yes	Phase 2 (PINNACLE)	N/A	-----	Relapsed or refractory MCL	• Single agent bortezomib induced an ORR of 33% in patients with relapsed or refractory MCL.

	duration to prior treatment)					after at least one prior therapy	
Bortezomib + rituximab	2A preferred (extended response duration to prior treatment)	Yes	Phase 2	N/A	-----	Relapsed or refractory MCL	• R-bortezomib had significant activity in patients with relapsed or refractory MCL with an ORR of 29%.
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%.
Post-transplant lymphoproliferative disorder (PTLD)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab	2A	No	Phase 2, prospective, multi-center	N/A	ORR	PTLD after solid organ transplant	• Rituximab is an effective treatment in PTLD with an ORR of 44% and 1-year OS rate of 67%.
Rituximab	2A	No	Retrospective analysis, multi-center	N/A	-----	PTLD after solid organ transplant and initial reduced immunosuppression	• This retrospective analysis suggests significantly improved PFS and OS associated with early rituximab-based treatment in PTLD.

Rituximab, followed by cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP	2A	No	Phase 2, prospective, multi-center	N/A	ORR	Failure to initial reduced immunosuppression	• Use of sequential immunochemotherapy with rituximab and CHOP demonstrated an ORR of 90%.
Pediatric Aggressive Mature B-Cell Lymphoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab + LMB chemotherapy regimen	2A	No	Phase 3, randomized	LMB chemotherapy regimen	EFS	----------	• Rituximab in addition to standard LMB therapy improves EFS of children/adolescents with high risk B-cell non-Hodgkin lymphoma and mature acute leukemia.
Primary Cutaneous B-Cell Lymphomas (PCBCL)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab IV	2A	No	Retrospective analysis	N/A	-----	----------	• Rituximab demonstrated to be effective for indolent PCBCL with an ORR of 87%.
Rituximab intralesional	2A	No	Observational multi-center study	N/A	-----	----------	• Intralesional rituximab is an effective treatment for PCBCL with a CR rate of 71% and PR rate of 23%.

Management of Immunotherapy-Related Toxicities

Non-viral encephalitis							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Rituximab	2A	No	Retrospective case study	N/A	N/A	--------	• Treatment with rituximab resulted in improved neurologic symptoms in patients autoimmune encephalitis in patients receiving immune checkpoint blockade therapy