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

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
  - 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]:

Document Number: OHSU HEALTH SERVICES-0477
## 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
- 100 billable units per dose twice weekly x 18 doses

### 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 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

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.

Universal Criteria

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

- Patient CD20 antigen expression is positive; AND

Acute Lymphoblastic Leukemia (ALL) ‡

- 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; OR
      - Used in combination with Linker 4-drug regimen (daunorubicin, vincristine, pegasparagase, and prednisone)

Central Nervous System (CNS) Cancer ‡

- 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 ‡

- Patient has nodular lymphocyte-predominant disease

Chronic Lymphocytic Leukemia/Small lymphocytic lymphoma (CLL/SLL) ‡

- 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 without 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 with 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**

**Non-Hodgkin’s Lymphomas (NHL)**

- 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
- Low-grade or Follicular Lymphoma
- 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) ¶
  o Patient has had solid organ transplant or allogeneic hematopoietic stem cell transplantation
• Pediatric Aggressive Mature B-Cell Lymphomas ¶
  o Patient age is 18 years and under*; AND
  o 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 ¶
• 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 1,10,11,35,36,61,80
• Patient has a diagnosis of pemphigus vulgaris as determined by the following:
  o 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
  o 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/mm³); **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, dostarlimab, etc.); AND
  o 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
  o Patient has bullous dermatitis related to their immunotherapy; AND
    ▪ Used as additional therapy for moderate (G2), severe (G3) or life-threatening (G4) disease; OR
  o Patient has moderate, severe, or life-threatening myalgias or myositis that are steroid-refractory; OR
  o 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:
  o 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
  o 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

- 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

- 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

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: 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**

**Oncoogy 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** 1-5,7-12,34,102-104

**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 x 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**
  o Disease response as indicated by complete epithelialization of lesions and improvement in signs and symptoms of condition compared to baseline; **OR**
  o 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 previously 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)** 23-26

• 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** 1-5,9,23-26,32,34,40,42,44,50,62,80,83-89,91,94-98,102-111
<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLL/SLL</strong></td>
<td><strong>Initial Therapy</strong> 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)</td>
</tr>
<tr>
<td></td>
<td><strong>Renewal Therapy</strong> 375 mg/m² IV once weekly for 4 doses per 6 month period; OR 375 mg/m² IV every 8 weeks</td>
</tr>
<tr>
<td><strong>NHL, PTLD, Waldenström’s, Castleman’s, or HL</strong></td>
<td><strong>Initial Therapy</strong> 375 mg/m² IV once weekly for 4 - 8 doses in a 6 month period</td>
</tr>
<tr>
<td></td>
<td><strong>Renewal Therapy</strong> 375 mg/m² IV once weekly for 4 doses per 6 month period; OR 375 mg/m² IV every 8 weeks</td>
</tr>
<tr>
<td><strong>Pediatric Aggressive B-cell Lymphoma</strong></td>
<td><strong>Induction</strong> 375 mg/m² IV once to twice during the first week of the induction cycle (typically 21-day cycle)</td>
</tr>
<tr>
<td></td>
<td><strong>Consolidation</strong> 375 mg/m² IV once weekly on day-1 of the consolidation cycle (typically 21-day cycle)</td>
</tr>
<tr>
<td></td>
<td><strong>Relapsed/Refractory</strong> RCYVE – 375mg/m² IV on day-1 of each 21-day cycle</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>*Note: dosing and dosing schedules are highly variable and dependent on regimen used, please refer to NCCN for different protocols.</td>
</tr>
<tr>
<td><strong>CNS Lymphoma</strong></td>
<td><strong>Intravenous administration</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Initial Therapy</strong> 375 mg/m² IV once weekly for 4 - 8 doses in a 6 month period</td>
</tr>
<tr>
<td></td>
<td><strong>Renewal Therapy</strong> 375 mg/m² IV once weekly for 4 doses per 6 month period; OR 375 mg/ m² IV every 8 weeks</td>
</tr>
<tr>
<td></td>
<td><strong>Intrathecal/Intraventricular administration</strong> 10-40 mg weekly to every 3 weeks</td>
</tr>
<tr>
<td><strong>ALL</strong></td>
<td>375 mg/m² IV up to twice weekly for a total of 16 to 18 infusions (e.g., induction [days 1 and 7], salvage reinduction when necessary [days 1 and 7], consolidation [4 infusions: blocks 1, 3, 4, and 6], late intensification [days 1 and 7], late consolidation [2 infusions: blocks 7 and 9], and maintenance [6 infusions])</td>
</tr>
<tr>
<td><strong>Hairy Cell Leukemia</strong></td>
<td>375 mg/m² IV once weekly for 4 - 8 doses</td>
</tr>
<tr>
<td><strong>RA</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>
### 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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>375 mg/m²</td>
<td>IV weekly for 4 doses in a 6 month period</td>
</tr>
</tbody>
</table>

### 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:
  - 250 mg/m² IV on days 1 and 15, then 250 mg/m² IV every 6 months thereafter based on clinical evaluation
- Adult:
  - 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.*
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-arrrx only)*
- C9399 – Unclassified drugs or biologicals *(Riabni – rituximab-arrrx only)*
- Q5123 – Injection, rituximab-arrrx, biosimilar, (Riabnil), 10 mg; 1 billable unit = 10 mg

**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)


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 June 2021.


101. Burmester, G., Drescher, E., Hrycaj, P. et al. Efficacy and safety results from a randomized double-blind study comparing proposed biosimilar ABP 798 with rituximab reference product in


VIII. References (ENHANCED)


159e. Sehn LH, Herrera AF, Matasar MJ, et al. Polatuzumab Vedotin (Pola) Plus Bendamustine (B) with Rituximab (R) or Obinutuzumab (G) in Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): Updated Results of a Phase (Ph) Ib/II Study. Blood 2018;132:Abstract 1683.


### Appendix 1 – Covered Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C79.32</td>
<td>Secondary malignant neoplasm of cerebral meninges</td>
</tr>
<tr>
<td>C81.00</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, unspecified site</td>
</tr>
<tr>
<td>C81.01</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of head, face, and neck</td>
</tr>
<tr>
<td>C81.02</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, intrathoracic lymph nodes</td>
</tr>
<tr>
<td>C81.03</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, intra-abdominal lymph nodes</td>
</tr>
<tr>
<td>C81.04</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of axilla and upper limb</td>
</tr>
<tr>
<td>C81.05</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of inguinal region and lower limb</td>
</tr>
<tr>
<td>C81.06</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, intrapelvic lymph nodes</td>
</tr>
<tr>
<td>C81.07</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, spleen</td>
</tr>
<tr>
<td>C81.08</td>
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<td>Mediastinal (thymic) large B-cell lymphoma, spleen</td>
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<td>C85.28</td>
<td>Mediastinal (thymic) large B-cell lymphoma, lymph nodes of multiple sites</td>
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<td>Mediastinal (thymic) large B-cell lymphoma, extranodal and solid organ sites</td>
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<td>M05.719</td>
<td>Rheumatoid arthritis with rheumatoid factor of unspecified shoulder without organ or systems involvement</td>
</tr>
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<td>M05.721</td>
<td>Rheumatoid arthritis with rheumatoid factor of right elbow without organ or systems involvement</td>
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<td>M05.722</td>
<td>Rheumatoid arthritis with rheumatoid factor of left elbow without organ or systems involvement</td>
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<td>M05.729</td>
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<td>M05.742</td>
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<tr>
<td>M05.761</td>
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<td>M05.762</td>
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<td>M05.769</td>
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<td>M05.772</td>
<td>Rheumatoid arthritis with rheumatoid factor of left ankle and foot without organ or systems involvement</td>
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<td>M05.779</td>
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<td>M05.8A</td>
<td>Other rheumatoid arthritis with rheumatoid factor of other specified site</td>
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<td>M05.811</td>
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<td>M05.812</td>
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<td>M06.862</td>
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<tr>
<td>M06.869</td>
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</table>
## Chapter 1 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](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):

<table>
<thead>
<tr>
<th>Jurisdiction(s)</th>
<th>NCD/LCD/LCA Document(s)</th>
<th>Jurisdiction(s)</th>
<th>NCD/LCD/LCA Document(s)</th>
<th>Jurisdiction(s)</th>
<th>NCD/LCD/LCA Document(s)</th>
</tr>
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<tr>
<td>6, K</td>
<td>A52452</td>
<td>5, 8</td>
<td>A55639</td>
<td>J, M</td>
<td>A56380</td>
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</table>
Jurisdiction(s): 15
NCD/LCD/LCA Document(s): A57160


### Medicare Part B Administrative Contractor (MAC) Jurisdictions

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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NCCN Category</th>
<th>FDA Approved</th>
<th>Trial Design</th>
<th>Comparator</th>
<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab + GRAALL-2005 regimen</td>
<td>2A</td>
<td>No</td>
<td>Phase 3 (GRAALL-2005/R), randomized, multi-center</td>
<td>GRAALL-2005 regimen (daunorubicin, vincristine, prednisone, pegaspargase, cyclophosphamide)</td>
<td>EFS</td>
<td>Previously untreated</td>
<td>• Adding rituximab to the ALL chemotherapy protocol improved the outcome for younger adults with CD20-positive, Ph-negative ALL compared to standard chemotherapy.</td>
</tr>
<tr>
<td>Rituximab + modified hyper – CVAD</td>
<td>2A</td>
<td>No</td>
<td>Phase 2, open label, single-center</td>
<td>Modified Hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone)</td>
<td>CR</td>
<td>First-line</td>
<td>• The incorporation of rituximab into the hyper-CVAD regimen appears to improve outcome for younger patients (&lt; 60 years old) with CD20-positive Ph-negative precursor B-lineage ALL compared to standard chemotherapy alone.</td>
</tr>
<tr>
<td>Daunorubicin + vincristine + pegaspargase + prednisone + rituximab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>3-year EFS</td>
<td>Newly diagnosed</td>
<td>• The Linker 4-drug regimen demonstrated a 3 year event free survival of 50%. Patients with CD20 positive B-ALL received rituximab.</td>
</tr>
<tr>
<td>Regimen</td>
<td>NCCN Category</td>
<td>FDA Approved</td>
<td>Trial Design</td>
<td>Comparator</td>
<td>Primary End-Point</td>
<td>Line of Therapy</td>
<td>Conclusion</td>
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<tr>
<td>-------------------------------</td>
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<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Rituximab + MOpAD</td>
<td>2A</td>
<td>No</td>
<td>Phase 2, open-label</td>
<td>N/A</td>
<td>CR</td>
<td>Relapsed or refractory disease</td>
<td>• In patients with refractory ALL, clinical activity of MOpAD regimen was demonstrated including patients who received rituximab for CD20 positive disease.</td>
</tr>
</tbody>
</table>
| Blinatumomab                  | 1             | 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             | 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 failed treatment with at least 1 TKI and standard chemotherapy | • Patients receiving inotuzumab ozogamicin versus standard care achieved higher response, MRD-negativity rates, and prolonged PFS and OS |
### Tisagenlecleucel

| Regimen | 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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NCCN Category</th>
<th>FDA Approved</th>
<th>Trial Design</th>
<th>Comparator</th>
<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab + liposomal cytarabine</td>
<td>2A</td>
<td>No</td>
<td>Clinical series</td>
<td>N/A</td>
<td>----------</td>
<td>Recurrent disease</td>
<td>• Combination of intra-CSF rituximab and liposomal cytarabine has modest palliative activity with a median overall survival of 5 months.</td>
</tr>
<tr>
<td>Rituximab (intraventricular), alternating in combination with MTX every other week</td>
<td>2A</td>
<td>No</td>
<td>Phase 1, multi-center</td>
<td>N/A</td>
<td>----------</td>
<td>Recurrent CNS NHL</td>
<td>• Phase I study showed that intraventricular rituximab plus methotrexate is feasible and active in the treatment of refractory CNS lymphoma with a 75% rate of complete cytologic response.</td>
</tr>
<tr>
<td>Methotrexate (intrathecal)</td>
<td>2A</td>
<td>No</td>
<td>Randomized, prospective cooperative group study</td>
<td>N/A</td>
<td>----------</td>
<td>First-line</td>
<td>• Intrathecal methotrexate demonstrated a median survival of 15.9 weeks.</td>
</tr>
</tbody>
</table>
**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)**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NCCN Category</th>
<th>FDA Approved</th>
<th>Trial Design</th>
<th>Comparator</th>
<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>2B</td>
<td>No</td>
<td>Case report</td>
<td>N/A</td>
<td>-----</td>
<td>Relapsed disease</td>
<td>• 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.</td>
</tr>
<tr>
<td>Methotrexate (MTX)</td>
<td>2A</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cytarabine</td>
<td>2A</td>
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**Primary CNS lymphoma - Induction**

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<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab + high-dose MTX</td>
<td>2A preferred</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>PFS</td>
<td>First-line</td>
<td>• Rituximab plus high-dose methotrexate demonstrated an ORR of 80%.</td>
</tr>
<tr>
<td>Rituximab + MTX + temozolomide</td>
<td>2A preferred</td>
<td>No</td>
<td>Phase 1/2</td>
<td>N/A</td>
<td>2-year OS rate</td>
<td>Induction</td>
<td>• 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%.</td>
</tr>
<tr>
<td>Rituximab + MTX</td>
<td>2A preferred</td>
<td>No</td>
<td>Retrospective study</td>
<td>N/A</td>
<td>OS</td>
<td>First-line</td>
<td>• 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.</td>
</tr>
<tr>
<td>Rituximab + high-dose MTX (HD-MTX/R)</td>
<td>2A preferred</td>
<td>No</td>
<td>Retrospective study</td>
<td>High-dose MTX (HD-MTX)</td>
<td>-----</td>
<td>First-line</td>
<td>• 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.</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NCCN Category</th>
<th>FDA Approved</th>
<th>Trial Design</th>
<th>Comparator</th>
<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX rechallenge</td>
<td>2A</td>
<td>No</td>
<td>Retrospective, multi-center study</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed disease</td>
<td>• High-dose methotrexate remains effective for relapsed CNS lymphoma in patients who initially respond to methotrexate.</td>
</tr>
<tr>
<td>Rituximab + TMZ</td>
<td>2A</td>
<td>No</td>
<td>Retrospective series</td>
<td>N/A</td>
<td>----------</td>
<td>Recurrent or refractory disease</td>
<td>• Combination therapy with rituximab and temozolomide demonstrated an ORR of 53%.</td>
</tr>
<tr>
<td>Rituximab + TMZ</td>
<td>2A</td>
<td>No</td>
<td>Phase 2, multi-center</td>
<td>N/A</td>
<td>ORR</td>
<td>Recurrent disease</td>
<td>• Rituximab plus temozolomide demonstrated modest activity with a complete response rate of 14%.</td>
</tr>
<tr>
<td>Rituximab</td>
<td>2A</td>
<td>No</td>
<td>Case series</td>
<td>N/A</td>
<td>----------</td>
<td>Recurrent or refractory disease</td>
<td>• Responses to IV rituximab monotherapy were observed in approximately one-third of patients.</td>
</tr>
<tr>
<td>Rituximab + lenalidomide</td>
<td>2A</td>
<td>No</td>
<td>Phase 1</td>
<td>N/A</td>
<td>----------</td>
<td>Recurrent or refractory disease</td>
<td>• Out of 5 patients who received rituximab plus lenalidomide, 1 patient demonstrated a partial response.</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>2A</td>
<td>No</td>
<td>Phase 1</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory disease</td>
<td>• Single-agent ibrutinib showed activity in patients with recurrent or refractory primary CNS lymphoma with an ORR of 77%.</td>
</tr>
</tbody>
</table>
### Temozolomide (TMZ)
- **Regimen**: Temozolomide
- **NCCN Category**: 2A
- **FDA Approved**: No
- **Trial Design**: Retrospective study
- **Comparator**: N/A
- **Primary End-Point**: ----- 
- **Line of Therapy**: Relapsed or refractory disease
- **Conclusion**: Temozolomide resulted in a complete response (CR) in 29% of patients with relapsed or refractory primary CNS lymphoma.

### Topotecan
- **Regimen**: Topotecan
- **NCCN Category**: 2A
- **FDA Approved**: No
- **Trial Design**: Phase 2, multi-center
- **Comparator**: N/A
- **Primary End-Point**: ORR 
- **Line of Therapy**: Relapsed or refractory disease
- **Conclusion**: Topotecan as monotherapy is active in relapsed and refractory PCNSL with an ORR of 33%

### Pemetrexed
- **Regimen**: Pemetrexed
- **NCCN Category**: 2A
- **FDA Approved**: No
- **Trial Design**: Prospective, single-center study
- **Comparator**: N/A
- **Primary End-Point**: ------
- **Line of Therapy**: Relapsed or refractory disease
- **Conclusion**: Pemetrexed has single-agent activity in relapsed/refractory primary CNS lymphoma with an ORR of 55%

### Pomalidomide
- **Regimen**: Pomalidomide
- **NCCN Category**: 2A
- **FDA Approved**: No
- **Trial Design**: Phase 1
- **Comparator**: N/A
- **Primary End-Point**: Max tolerated dose
- **Line of Therapy**: Relapsed or refractory disease
- **Conclusion**: Pomalidomide demonstrated clinical activity against relapsed or refractory primary CNS lymphoma with an ORR of 48%.

### Hodgkin’s Lymphoma

#### Nodular lymphocyte-predominant disease

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NCCN Category</th>
<th>FDA Approved</th>
<th>Trial Design</th>
<th>Comparator</th>
<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>ORR</td>
<td>Untreated or previously treated</td>
<td>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.</td>
</tr>
<tr>
<td>Rituximab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2 (GHSG)</td>
<td>N/A</td>
<td>ORR</td>
<td>Newly diagnosed stage IA disease</td>
<td>Patients with newly diagnosed NLPHL responded to rituximab with an ORR of 100% however, relapse rate at 43 months was 25%.</td>
</tr>
<tr>
<td>Rituximab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2 (GHSG)</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory disease</td>
<td>Rituximab is effective in relapsed and refractory NLPHL with an ORR of 94%.</td>
</tr>
</tbody>
</table>
### 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**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NCCN Category</th>
<th>FDA Approved</th>
<th>Trial Design</th>
<th>Comparator</th>
<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>1 preferred</td>
<td>Yes</td>
<td>Phase 3 (RESONATE-2), randomized, open-label</td>
<td>Chlorambucil</td>
<td>PFS</td>
<td>First line</td>
<td>• 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.</td>
</tr>
<tr>
<td>Ibrutinib + rituximab (BR)</td>
<td>2A</td>
<td>No</td>
<td>Phase 2 (CLL2M), multi-center</td>
<td>Chlorambucil + rituximab vs. Bendamustine + rituximab (BR)</td>
<td>PFS</td>
<td>First line</td>
<td>• 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.</td>
</tr>
<tr>
<td>Bendamustine + rituximab (BR)</td>
<td>2A</td>
<td>No</td>
<td>Phase 3 (MABLE), randomized</td>
<td>Chlorambucil + rituximab</td>
<td>CR</td>
<td>First line</td>
<td>• Chemoimmunotherapy with BR is effective (ORR 88%) and safe in patients with previously untreated CLL</td>
</tr>
<tr>
<td>Bendamustine + rituximab (BR)</td>
<td>2A</td>
<td>No</td>
<td>Phase 3 (MABLE), randomized</td>
<td>Chlorambucil + rituximab</td>
<td>CR</td>
<td>First line</td>
<td>• Bendamustine plus rituximab demonstrated a complete response rate of 24% and was superior to</td>
</tr>
<tr>
<td>Chlorambucil + ofatumumab</td>
<td>2A</td>
<td>Yes (for whom fludarabine based therapy is considered inappropriate)</td>
<td>Phase 3 (COMPLEMENT 1), randomized, multi-center, open-label</td>
<td>Chlorambucil</td>
<td>PFS</td>
<td>First line</td>
<td>• 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.</td>
</tr>
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<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Chlorambucil + obinutuzumab</td>
<td>2A</td>
<td>Yes</td>
<td>Phase 3 (CLL11), randomized, open-label</td>
<td>Chlorambucil + rituximab vs. Chlorambucil</td>
<td>PFS</td>
<td>First line</td>
<td>• 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.</td>
</tr>
<tr>
<td>Chlorambucil + obinutuzumab</td>
<td>2A</td>
<td>Yes</td>
<td>Phase 3 (CLL11), randomized, open-label</td>
<td>Chlorambucil + rituximab vs. Chlorambucil</td>
<td>PFS</td>
<td>First line</td>
<td>• 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.</td>
</tr>
<tr>
<td>Obinutuzumab (6 cycles) + venetoclax (12 cycles)</td>
<td>2A preferred</td>
<td>Yes</td>
<td>Phase 3 (CLL 14), open-label, randomized</td>
<td>Obinutuzumab + chlorambucil</td>
<td>PFS</td>
<td>Previously untreated</td>
<td>• Among patients with untreated CLL and coexisting conditions, venetoclax-obinutuzumab was associated with longer progression-free survival than chlorambucil-obinutuzumab.</td>
</tr>
<tr>
<td>High-dose methylprednisolone + rituximab</td>
<td>2B</td>
<td>No</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ibrutinib + obinutuzumab</td>
<td>2B</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>2B</td>
<td>No</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
### Regimen

<table>
<thead>
<tr>
<th>Chlorambucil</th>
<th>2B</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>2B</td>
<td>No</td>
</tr>
</tbody>
</table>

**Without del(17p) or TP53 Mutation – First line therapy – Patients age < 65 y without significant comorbidities**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NCCN Category</th>
<th>FDA Approved</th>
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<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>1 preferred</td>
<td>Yes</td>
<td>See ibrutinib data above.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibrutinib + rituximab</td>
<td>2B</td>
<td>No</td>
<td>Phase 3 (ECOG-ACRIN E1912), randomized</td>
<td>Fludarabine + cyclophosphamide + rituximab (FCR)</td>
<td>PFS</td>
<td>First-line</td>
<td>● The combination of ibrutinib and rituximab provides superior PFS and OS relative to FCR for patients with previously untreated CLL age &lt;70.</td>
</tr>
<tr>
<td>Fludarabine + cyclophosphamide + rituximab (FCR)</td>
<td>2A</td>
<td>Yes</td>
<td>Phase 3 (CLL8), randomized</td>
<td>Fludarabine + cyclophosphamide (FC)</td>
<td>PFS</td>
<td>First line</td>
<td>● 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.</td>
</tr>
<tr>
<td>Fludarabine + cyclophosphamide + rituximab (FCR)</td>
<td>2A</td>
<td>Yes</td>
<td>Phase 3 (CLL10), randomized, open-label, international</td>
<td>Bendamustine + rituximab (BR)</td>
<td>PFS</td>
<td>First line</td>
<td>● 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.</td>
</tr>
<tr>
<td>Fludarabine + rituximab (FR) concurrently</td>
<td>2A [not recommended for CLL with del(11q)]</td>
<td>No</td>
<td>Phase 2 (CALGB 9712), randomized</td>
<td>Fludarabine + rituximab (FR) sequentially</td>
<td>PFS</td>
<td>First line</td>
<td>• Long-term follow-up of CALGB 9712 demonstrates extended OS (85 months) and PFS (42 months) with fludarabine plus rituximab.</td>
</tr>
<tr>
<td>Bendamustine + rituximab (BR)</td>
<td>2A</td>
<td>No</td>
<td>Phase 2 (CLL2M), multi-center</td>
<td>N/A</td>
<td>ORR</td>
<td>First line</td>
<td>• Chemoimmunotherapy with BR is effective (ORR 88%) and safe in</td>
</tr>
</tbody>
</table>
patients with previously untreated CLL

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NCCN Category</th>
<th>FDA Approved</th>
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<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine + ofatumumab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2, open-label, single-arm, multi-center</td>
<td>N/A</td>
<td>ORR</td>
<td>First line and relapsed disease</td>
<td>• 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</td>
</tr>
<tr>
<td>Bendamustine + obinutuzumab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2, multi-center</td>
<td>N/A</td>
<td>CR</td>
<td>First line</td>
<td>• 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.</td>
</tr>
</tbody>
</table>

With del(17p) or TP53 Mutation – First-line therapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NCCN Category</th>
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<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>1 preferred</td>
<td>Yes</td>
<td>Phase 2</td>
<td>N/A</td>
<td>ORR</td>
<td>First line</td>
<td>• Long-term administration of ibrutinib was associated with an ORR of 97% and 5-year OS of 85%.</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>2A</td>
<td>No</td>
<td>Phase 3 (CAM307), randomized</td>
<td>Chlorambucil</td>
<td>PFS</td>
<td>First line</td>
<td>• As first-line treatment for patients with CLL, alemtuzumab demonstrated significantly improved PFS, ORR, and CR compared with chlorambucil.</td>
</tr>
<tr>
<td>HDMP + rituximab</td>
<td>2A</td>
<td>No</td>
<td>Single institution study</td>
<td>N/A</td>
<td>ORR</td>
<td>First line</td>
<td>• 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.</td>
</tr>
<tr>
<td>Regimen</td>
<td>NCCN Category</td>
<td>FDA Approved</td>
<td>Trial Design</td>
<td>Comparator</td>
<td>Primary End-Point</td>
<td>Line of Therapy</td>
<td>Conclusion</td>
</tr>
<tr>
<td>---------------------------------</td>
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<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Venetoclax + rituximab (VenR)</td>
<td>1 preferred</td>
<td>Yes (after at least one prior therapy)</td>
<td><strong>Phase 3</strong> <em>(MURANO)</em>, randomized</td>
<td>Bendamustine + rituximab (BR)</td>
<td>PFS</td>
<td>Relapsed or refractory disease</td>
<td>• 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.</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>1 preferred</td>
<td>Yes</td>
<td><strong>Phase 3</strong> <em>(RESONATE)</em>, randomized, open-label</td>
<td>Ofatumumab</td>
<td>PFS</td>
<td>Relapsed or refractory disease</td>
<td>• Ibrutinib, as compared with ofatumumab, significantly improved progression-free survival, overall survival, and response rate among patients with previously treated CLL or SLL.</td>
</tr>
<tr>
<td>Idelalisib + rituximab</td>
<td>2A preferred</td>
<td>Yes</td>
<td><strong>Phase 3</strong>, randomized, multi-center, double-blind, placebo-controlled</td>
<td>Placebo + rituximab</td>
<td>PFS</td>
<td>Relapsed disease</td>
<td>• 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.</td>
</tr>
</tbody>
</table>

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).
<table>
<thead>
<tr>
<th>Treatment</th>
<th>2A</th>
<th>Yes or No</th>
<th>Study Phase</th>
<th>ORR/Remission/Study Type</th>
<th>PFS/Study Endpoint</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duvelisib</td>
<td>2A</td>
<td>Yes</td>
<td>Phase 3 (DUO), randomized</td>
<td>Ofatumumab</td>
<td>PFS</td>
<td>• 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.</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>2A</td>
<td>Yes (for B-CLL)</td>
<td>Phase 2</td>
<td>N/A</td>
<td>ORR</td>
<td>• Alemtuzumab induced an ORR of 33% in patients with relapsed or refractory CLL after fludarabine therapy.</td>
</tr>
<tr>
<td>Alemtuzumab + rituximab</td>
<td>2A</td>
<td>No</td>
<td>Exploration study</td>
<td>N/A</td>
<td>ORR</td>
<td>• The combination of alemtuzumab plus rituximab has an ORR of 53% in patients with relapsed or refractory CLL.</td>
</tr>
<tr>
<td>Fludarabine + cyclophosphamide + rituximab (FCR)</td>
<td>2A</td>
<td>No (first-line only)</td>
<td>Phase 3 (REACH), randomized</td>
<td>Fludarabine + cyclophosphamide (FC)</td>
<td>PFS</td>
<td>• FCR significantly improved PFS in patients with previously treated CLL however, the difference is OS was not significantly different.</td>
</tr>
<tr>
<td>Fludarabine + cyclophosphamide + ofatumumab</td>
<td>2A (if &lt; 65y)</td>
<td>Yes</td>
<td>Phase 3 (COMPLEMENT 2), multi-center, open-label, randomized</td>
<td>Fludarabine + cyclophosphamide (FC)</td>
<td>PFS</td>
<td>• Ofatumumab plus fludarabine and cyclophosphamide improved PFS with manageable safety for patients with relapsed CLL compared with FC alone.</td>
</tr>
<tr>
<td>High-dose methylprednisolone (HDMP) + rituximab</td>
<td>2A</td>
<td>No</td>
<td>Small study</td>
<td>N/A</td>
<td>ORR</td>
<td>• HDMP combined with rituximab was effective in patients with heavily pretreated CLL (ORR 93%).</td>
</tr>
<tr>
<td>Lenalidomide + rituximab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>ORR</td>
<td>• 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.</td>
</tr>
<tr>
<td>Drug</td>
<td>Phase</td>
<td>Randomized</td>
<td>Trial Details</td>
<td>Adverse events ORR (secondary endpoint)</td>
<td>Disease Type</td>
<td>Comments</td>
</tr>
<tr>
<td>-----------------------</td>
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<td>-------------------------------------------------------------------------------</td>
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<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>2A</td>
<td>No</td>
<td>Phase 2 (CLL-009 trial), randomized, multi-center</td>
<td>Adverse events</td>
<td>Relapsed or refractory disease</td>
<td>Lenalidomide monotherapy is active in patients with relapsed or refractory CLL with an ORR of 40%.</td>
</tr>
<tr>
<td>Acalabrutinib</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>Safety ORR</td>
<td>Relapsed or refractory to at least 1 prior treatment</td>
<td>Treatment with acalabrutinib was associated with high response rates (ORR 85%) and durable remissions in patients with relapsed or refractory CLL.</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>ORR</td>
<td>Idealalisib monotherapy demonstrated clinical activity in patients with relapsed or refractory SLL with an ORR of 61%.</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>2A</td>
<td>No</td>
<td>Phase 1/2 (GAUGUIN)</td>
<td>N/A</td>
<td>ORR</td>
<td>Obinutuzumab monotherapy is active in patients with heavily pretreated relapsed/ refractory CLL with an ORR of 30%.</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>2A</td>
<td>Yes</td>
<td>Phase 2</td>
<td>N/A</td>
<td>ORR</td>
<td>Ofatumumab is an active, well-tolerated treatment with an ORR of 43-49% in fludarabine-refractory patients with very poor-prognosis CLL.</td>
</tr>
<tr>
<td>Pentostatin + cyclophosphamide +</td>
<td>2A</td>
<td>No</td>
<td>Small series</td>
<td>N/A</td>
<td>ORR</td>
<td>The PCR regimen is safe and effective in patients with previously treated CLL (ORR 75%).</td>
</tr>
<tr>
<td>Treatment</td>
<td>Phase</td>
<td>Randomized</td>
<td>Study Design</td>
<td>End Point</td>
<td>Evidence</td>
<td>Notes</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
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<td>-----------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>rituximab (PCR) – reduced dose</strong></td>
<td></td>
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</tr>
<tr>
<td>Venetoclax</td>
<td>2A</td>
<td>No</td>
<td>Phase 2, multi-center, open-label, non-randomized</td>
<td>N/A</td>
<td>ORR</td>
<td>Ibrutinib-refractory or relapsed disease</td>
</tr>
<tr>
<td>Venetoclax demonstrated an ORR of 65% in patients with relapsed or refractory CLL whose disease progressed during or after discontinuation of ibrutinib therapy.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bendamustine + rituximab (BR)</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>-----</td>
<td>Relapsed or refractory disease</td>
</tr>
<tr>
<td>Chemoimmunotherapy with BR is effective and safe in patients with relapsed CLL and has notable activity in fludarabine-refractory disease.</td>
<td></td>
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</tr>
<tr>
<td>Bendamustine + rituximab + idelalisib</td>
<td>2B/3</td>
<td>No</td>
<td>Phase 3, randomized</td>
<td>Bendamustine + rituximab + placebo</td>
<td>PFS</td>
<td>Relapsed or refractory disease</td>
</tr>
<tr>
<td>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.</td>
<td></td>
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</tr>
<tr>
<td>Bendamustine + rituximab + ibrutinib</td>
<td>2B/3</td>
<td>No</td>
<td>Phase 3 (HELIOS), randomized, double-blind</td>
<td>Bendamustine + rituximab + placebo</td>
<td>PFS</td>
<td>Relapsed or refractory disease following 1 or more lines of therapy</td>
</tr>
<tr>
<td>The addition of ibrutinib to bendamustine and rituximab results in significant improvements in PFS.</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Chlorambucil + rituximab</td>
<td>2A</td>
<td>No</td>
<td></td>
<td>No evidence in relapsed or refractory disease.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**With del(17p) or TP53 Mutation – Relapsed/Refractory therapy**
<table>
<thead>
<tr>
<th>Regimen</th>
<th>NCCN Category</th>
<th>FDA Approved</th>
<th>Trial Design</th>
<th>Comparator</th>
<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>1 preferred</td>
<td>Yes</td>
<td>Phase 2 (RESONATE-17), multi-center, open-label, single-arm, international</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory disease</td>
<td>• 83% of patients with del17p relapsed or refractory CLL had a clinical response to ibrutinib.</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>1 preferred</td>
<td>Yes</td>
<td>Phase 3 (RESONATE) subgroup analysis</td>
<td>Ofatumumab</td>
<td>PFS</td>
<td>Relapsed or refractory disease</td>
<td>• 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.</td>
</tr>
<tr>
<td>Venetoclax + rituximab</td>
<td>1 preferred</td>
<td>Yes (after at least one prior therapy)</td>
<td>Phase 3 (MURANO), randomized</td>
<td>Bendamustine + rituximab (BR)</td>
<td>PFS</td>
<td>Relapsed or refractory disease</td>
<td>• 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.</td>
</tr>
<tr>
<td>Idelalisib + rituximab</td>
<td>2A preferred</td>
<td>Yes</td>
<td>Phase 3 second interim analysis</td>
<td>Placebo + rituximab</td>
<td>PFS</td>
<td>Relapsed disease</td>
<td>• 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.</td>
</tr>
<tr>
<td>Treatment</td>
<td>Status</td>
<td>Preferred</td>
<td>Clinical Trial</td>
<td>comparator</td>
<td>Endpoints</td>
<td>Disease Status</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------</td>
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<td>-------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Duvelisib</td>
<td>2A</td>
<td>Yes</td>
<td>Phase 3 (DUO), randomized</td>
<td>Ofatumumab</td>
<td>PFS</td>
<td>Relapsed or refractory disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>▪ 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.</td>
<td></td>
</tr>
<tr>
<td>Venetoclax</td>
<td>2A</td>
<td>Yes</td>
<td>Phase 2</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ Venetoclax monotherapy is active in patients with relapsed or refractory del(17p) CLL with an ORR of 79.4%.</td>
<td></td>
</tr>
<tr>
<td>Alemtuzumab + rituximab</td>
<td>2A</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td>No clinical evidence to support use of alemtuzumab in combination with rituximab for relapsed or refractory CLL&gt;</td>
<td></td>
</tr>
<tr>
<td>Alemtuzumab subcutaneous</td>
<td>2A</td>
<td>No</td>
<td>Phase 2 (CLL2H)</td>
<td>N/A</td>
<td>ORR</td>
<td>Fludarabine-refractory</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ 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.</td>
<td></td>
</tr>
<tr>
<td>HDMP + rituximab</td>
<td>2A</td>
<td>No</td>
<td>Exploration study</td>
<td>N/A</td>
<td>----</td>
<td>Relapsed disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ HDMP-rituximab is an active regimen in patients with relapsed and cytogenetically high-risk CLL with a 3-year survival rate of 41%.</td>
<td></td>
</tr>
<tr>
<td>Lenalidomide + rituximab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ The combination of lenalidomide and rituximab is active in patients with recurrent del17p CLL with an ORR of 53%.</td>
<td></td>
</tr>
<tr>
<td>Idelalisib</td>
<td>2A</td>
<td>No</td>
<td>Phase 1</td>
<td>N/A</td>
<td>----</td>
<td>Relapsed or refractory disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ Idelalisib demonstrated an ORR of 54% in patients with del17p and/or...</td>
<td></td>
</tr>
</tbody>
</table>
### TP53 mutated relapsed or refractory CLL.

<table>
<thead>
<tr>
<th>Ofatumumab</th>
<th>2A</th>
<th>Yes</th>
<th>Phase 2</th>
<th>N/A</th>
<th>ORR</th>
<th>Fludarabine- and alemtuzumab-refractory disease OR fludarabine-refractory with bulky lymphadenopathy</th>
</tr>
</thead>
</table>

- 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.

<table>
<thead>
<tr>
<th>Ofatumumab</th>
<th>2B (Post second-line maintenance therapy following complete or partial response to treatment for relapsed or refractory disease)</th>
<th>Yes</th>
<th>Phase 3 (PROLONG), randomized, open-label, multi-center</th>
<th>Observation</th>
<th>PFS</th>
<th>Maintenance for relapsed CLL in complete or partial remission after second-or third-line treatment</th>
</tr>
</thead>
</table>

- 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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NCCN Category</th>
<th>FDA Approved</th>
<th>Trial Design</th>
<th>Comparator</th>
<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP)</td>
<td>2A</td>
<td>No</td>
<td>Phase 2, prospective, multi-center</td>
<td>N/A</td>
<td>ORR</td>
<td>First- to fifth-line</td>
<td>R-CHOP induces an acceptable response rate in Richter’s transformation with 67%</td>
</tr>
</tbody>
</table>

| Rituximab + etoposide + prednisone+ | 2A | No | Retrospective cohort study | N/A | ------ | First-line | R-EPOCH demonstrated to have an estimated 1-year OS of 71% in |
**Waldenström’s macroglobulinemia/Lymphoplasmacytic Lymphoma (WM/LPL)**

<table>
<thead>
<tr>
<th>Primary Therapy</th>
<th>NCCN Category</th>
<th>FDA Approved</th>
<th>Trial Design</th>
<th>Comparator</th>
<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab + bendamustine</td>
<td>2A preferred</td>
<td>No</td>
<td>Phase 3 (StiL), randomized, multi-center</td>
<td>R-CHOP</td>
<td>PFS</td>
<td>First-line</td>
<td>• Bendamustine plus rituximab demonstrated a significantly longer PFS than R-CHOP and may be a preferable option to R-CHOP as primary therapy.</td>
</tr>
</tbody>
</table>

<p>| vincristine cyclophosphamide + doxorubicin (R-EPOCH) | 2A | No | Phase 2 | N/A | CR | First- to fourth-line | 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% |</p>
<table>
<thead>
<tr>
<th>Regimen</th>
<th>NCCN Category</th>
<th>FDA Approved</th>
<th>Trial Design</th>
<th>Comparator</th>
<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib (IV) + dexamethasone + rituximab (BDR)</td>
<td>2A preferred</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>-----</td>
<td>First line</td>
<td>• BDR induced durable responses in previously untreated WM with an ORR of 85% and 3-year OS rate of 81%.</td>
</tr>
<tr>
<td>Rituximab + cyclophosphamide + dexamethasone (R-CD)</td>
<td>2A preferred</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>-----</td>
<td>First line</td>
<td>• R-DC demonstrated an ORR of 83% and 2-year PFS of 67%.</td>
</tr>
</tbody>
</table>

### Previously Treated

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

### Non-Hodgkin’s Lymphoma (NHL)

#### AIDS-related B-Cell Lymphoma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NCCN Category</th>
<th>FDA Approved</th>
<th>Trial Design</th>
<th>Comparator</th>
<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab + chemotherapy</td>
<td>2A</td>
<td>No</td>
<td>Pooled analysis</td>
<td>N/A</td>
<td>-----</td>
<td>First line</td>
<td>• Initial therapy with rituximab resulted in higher CR rates and was associated with improved PFS and OS.</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>2A (DLBCL)</td>
<td>No</td>
<td>Phase 3 (AMC 010), multi-center, randomized</td>
<td>CHOP</td>
<td>CR</td>
<td>First-line</td>
<td>• 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.</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>2A (DLBCL)</td>
<td>No</td>
<td>Phase 2, multi-center</td>
<td>N/A</td>
<td>CR</td>
<td>First line</td>
<td>• 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.</td>
</tr>
<tr>
<td>Cyclophosphamide + vincristine + doxorubicin + high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine +</td>
<td>2A preferred (Burkitt)</td>
<td>No</td>
<td>Retrospective study</td>
<td>N/A</td>
<td>OS</td>
<td>PFS</td>
<td>• 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.</td>
</tr>
<tr>
<td>Regimen</td>
<td>Phase</td>
<td>Randomized</td>
<td>Dosing</td>
<td>CR</td>
<td>First line</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>---------</td>
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<td></td>
</tr>
<tr>
<td>Rituximab + etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin (R-EPOCH) concurrent dosing</td>
<td>2A preferred (Burkitt, DLBCL)</td>
<td>No</td>
<td>Phase 2 (AMC034), randomized</td>
<td>R-EPOCH sequential dosing</td>
<td>CR</td>
<td>First line</td>
<td></td>
</tr>
<tr>
<td>R-EPOCH</td>
<td>2A preferred (Burkitt, DLBCL)</td>
<td>No</td>
<td>Pooled analysis of R-CHOP or R-EPOCH</td>
<td>N/A</td>
<td>EFS</td>
<td>First line</td>
<td></td>
</tr>
<tr>
<td>Rituximab + cyclophosphamide + vincristine + doxorubicin + dexamethasone alternating with high-dose methotrexate and cytarabine (R-Hyper CVAD)</td>
<td>2A (Burkitt)</td>
<td>No</td>
<td>Prospective study</td>
<td>N/A</td>
<td>-------</td>
<td>First line</td>
<td></td>
</tr>
<tr>
<td>Bendamustine + rituximab + polatuzumab vedotin-piqt</td>
<td>2A (after ≥ 2 prior therapies)</td>
<td>Yes (after ≥ 2 prior therapies)</td>
<td>Phase 2, randomized, multi-center, open-label</td>
<td>Bendamustine + rituximab</td>
<td>CR</td>
<td>Relapsed or refractory FL or DLBCL</td>
<td></td>
</tr>
<tr>
<td>Lenalidomide + rituximab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory DLBCL, FL, and transformed</td>
<td></td>
</tr>
</tbody>
</table>

- Concurrent rituximab plus infusional EPOCH demonstrated a complete response rate of 73%.
- The current analysis provided additional level 2 evidence supporting the use of concurrent R-EPOCH in patients with HIV-associated lymphoma and a CD4 count >50/μL.
- Hyper-CVAD is an effective regimen for patients with AIDS-associated Burkitt lymphoma/leukemia with a CR of 92%.
- In a randomized setting, BR+P showed longer survival compared to BR, with median OS surpassing 12 months.
- Rituximab plus lenalidomide demonstrated an ORR of 33% for patients with relapsed/refractory DLBCL and TL.
<table>
<thead>
<tr>
<th>Burkitt Lymphoma</th>
<th>Regimen</th>
<th>NCCN Category</th>
<th>FDA Approved</th>
<th>Trial Design</th>
<th>Comparator</th>
<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab + chemotherapy</td>
<td>2A</td>
<td>No</td>
<td>Phase 3, randomized, controlled, open-label</td>
<td>Chemotherapy</td>
<td>3-year EFS</td>
<td>First line</td>
<td>• Addition of rituximab to a short intensive chemotherapy improves EFS in adults with Burkitt’s leukemia or lymphoma.</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide + vincristine + doxorubicin + high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine ± rituximab (CODOX-M/IVAC)</td>
<td>2A</td>
<td>No</td>
<td>Single institution study</td>
<td>N/A</td>
<td>-----</td>
<td>--------------</td>
<td>• CODOX-M/IVAC regimen demonstrated to be effective in patients with Burkitt lymphoma and B-cell lymphoma with a 5-year OS of 87%.</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide + vincristine + doxorubicin + high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine ± rituximab (CODOX-M/IVAC)</td>
<td>2A</td>
<td>No</td>
<td>Retrospective study</td>
<td>N/A</td>
<td>OS PFS</td>
<td>Various</td>
<td>• 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.</td>
<td></td>
</tr>
<tr>
<td>Rituximab + cyclophosphamide + vincristine + doxorubicin +</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>-----</td>
<td>First line</td>
<td>• The addition of rituximab to hyper-CVAD may improve outcome in adult BL or B-ALL as indicated by a CR of 86%.</td>
<td></td>
</tr>
<tr>
<td>Regimen</td>
<td>NCCN Category</td>
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<td>Line of Therapy</td>
<td>Conclusion</td>
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</tr>
<tr>
<td>Rituximab</td>
<td>2A</td>
<td>No</td>
<td>None</td>
<td>none</td>
<td>N/A</td>
<td>None</td>
<td>• Efficacy of chemomunotherapy was demonstrated in this study with a CR of 91%.</td>
<td></td>
</tr>
<tr>
<td>Castleman’s Disease – Unicentric</td>
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<tr>
<td>Rituximab</td>
<td>2A</td>
<td>No</td>
<td>None</td>
<td>none</td>
<td>N/A</td>
<td>None</td>
<td></td>
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</tr>
<tr>
<td>Castleman’s Disease – Multicentric disease</td>
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<tr>
<td>Rituximab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2 (ANRS 117 CastlemB Trial), prospective, open-label</td>
<td>N/A</td>
<td>Sustained remission</td>
<td>Chemotherapy-dependent</td>
<td>• Rituximab was effective in HIV-infected patients with chemotherapy-dependent multicentric Castleman’s disease</td>
<td></td>
</tr>
</tbody>
</table>
Rituximab + chemotherapy

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Intensive regimens (R-HyperCVAD vs. R-CODOX-M/IVAC vs. DA-EPOCH-R)</td>
<td>2A</td>
<td>Yes</td>
<td>Retrospective, multi-centric analysis</td>
<td>R-CHOP</td>
<td>------</td>
<td>Induction</td>
<td>• Intensive chemotherapy regimens resulted in a superior PFS compared to R-CHOP.</td>
</tr>
<tr>
<td>Intensive regimens (R-HyperCVAD vs. R-CODOX-M/IVAC vs. DA-EPOCH-R)</td>
<td>2A</td>
<td>Yes</td>
<td>Meta-analysis</td>
<td>R-CHOP</td>
<td>------</td>
<td>Induction</td>
<td>• Front-line dose-escalated immunochemotherapy is associated with a PFS advantage in patients with double-hit lymphomas compared to R-CHOP.</td>
</tr>
<tr>
<td>Dose adjusted EPOCH-R</td>
<td>2A</td>
<td>Yes</td>
<td>Phase 2</td>
<td>N/A</td>
<td>EFS</td>
<td>First line</td>
<td>• DA-EPOCH-R produced durable remission in patients with MYC-rearranged aggressive B-cell lymphomas with a 48-mon OS rate of 77%.</td>
</tr>
</tbody>
</table>

Diffuse Large B-Cell Lymphoma (DLBCL) – First line

<table>
<thead>
<tr>
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<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP)</td>
<td>1</td>
<td>Yes</td>
<td>Phase 3 (GELA LNH-98.5), randomized, multi-center, open-label</td>
<td>CHOP</td>
<td>EFS</td>
<td>First line</td>
<td>• 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.</td>
</tr>
</tbody>
</table>
## Diffuse Large B-Cell Lymphoma (DLBCL) – Relapsed or Refractory Disease

<table>
<thead>
<tr>
<th>Regimen</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Rituximab + ifosfamide + etoposide + carboplatin (R-ICE), followed by ASCT</td>
<td>2A</td>
<td>No</td>
<td>Phase 3 (CORAL), randomized</td>
<td>Rituximab + dexamethasone, high-dose cytarabine + cisplatin (R-DHAP), followed by ASCT</td>
<td>EFS</td>
<td>Relapsed or refractory after 1 prior line of therapy</td>
<td>• No difference was observed between treatment with R-ICE and R-DHAP in patients with relapsed or refractory DLBCL.</td>
</tr>
<tr>
<td>Bendamustine + rituximab (BR)</td>
<td>2A (non-candidates for transplant)</td>
<td>No</td>
<td>Phase 2, multi-center</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory DLBCL</td>
<td>• 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.</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>2A (CD30+ disease; non-candidates for transplant)</td>
<td>No</td>
<td>Phase 2, open-label</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory DLBCL</td>
<td>• Activity with brentuximab vedotin was observed in relapsed/refractory DLBCL (ORR 44%), and responses occurred across a range of CD30 expression.</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory DLBCL</td>
<td>• 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.</td>
</tr>
<tr>
<td>Ofatumumab + cisplatin + cytarabine +</td>
<td>2A (as a substitute for</td>
<td>No</td>
<td>Phase 3 (ORCHARRD)</td>
<td>Rituximab + cisplatin + cytarabine +</td>
<td>PFS</td>
<td>Relapsed or refractory DLBCL</td>
<td>• No difference in efficacy was found between O-DHAP and R-DHAP as salvage</td>
</tr>
<tr>
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</tr>
<tr>
<td>dexamethasone (O-DHAP)</td>
<td></td>
<td></td>
<td></td>
<td>dexamethasone (R-DHAP)</td>
<td></td>
<td></td>
<td>treatment of relapsed or refractory DLBCL.</td>
</tr>
<tr>
<td>Low-grade or Follicular Lymphoma – First line</td>
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</tr>
<tr>
<td>Rituximab + cyclophosphamide + vincristine + prednisone (R-CVP)</td>
<td>2A</td>
<td>Yes</td>
<td>Phase 3 (MARCUS), multi-center, open-label</td>
<td>Cyclophosphamide + vincristine + prednisone (CVP)</td>
<td>TTF</td>
<td>First line</td>
<td>• 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</td>
</tr>
<tr>
<td>Rituximab + cyclophosphamide + vincristine + prednisone (R-CVP)</td>
<td>2A</td>
<td>Yes</td>
<td>Phase 3 (FOLL05), randomized, open-label, multi-center</td>
<td>R-CHOP vs. rituximab + fludarabine + mitoxantrone (R-FM)</td>
<td>TTF</td>
<td>First line</td>
<td>• 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.</td>
</tr>
<tr>
<td>Bendamustine + rituximab (BR)</td>
<td>2A preferred</td>
<td>No</td>
<td>Phase 3 (StiL), open-label, multi-center</td>
<td>R-CHOP</td>
<td>PFS</td>
<td>First line</td>
<td>• The primary endpoint of PFS was significantly longer with BR compared with R-CHOP.</td>
</tr>
<tr>
<td>Obinutuzumab + bendamustine, CHOP, or CVP, followed by obinutuzumab maintenance</td>
<td>2A preferred</td>
<td>Yes</td>
<td>Phase 3 (GALLIUM), randomized, open-label, multi-center</td>
<td>Rituximab + bendamustine, CHOP, or CVP, followed by rituximab</td>
<td>PFS</td>
<td>First line</td>
<td>• 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.</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>2A (as a substitute for rituximab or obinutuzumab)</td>
<td>No</td>
<td>Phase 2 (CALGB 50901)</td>
<td>N/A</td>
<td>ORR</td>
<td>First line</td>
<td>• Ofatumumab monotherapy demonstrated clinical activity in patients with untreated low or intermediate risk follicular lymphoma with an ORR of 84%.</td>
</tr>
<tr>
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</tr>
<tr>
<td>Rituximab + chemotherapy</td>
<td>2A</td>
<td>Yes</td>
<td><strong>Meta-analysis</strong></td>
<td>N/A</td>
<td>OS</td>
<td>Untreated and previously treated</td>
<td>• In patients with indolent or mantle cell lymphoma, R-chemo is superior to chemotherapy alone with respect to overall survival</td>
</tr>
<tr>
<td>Lenalidomide + rituximab</td>
<td>2A preferred</td>
<td>Yes</td>
<td><strong>Phase 3 (RELEVANCE)</strong>, multi-center, randomized, open-label</td>
<td>Chemotherapy + rituximab (RCHOP, RCVP, BR)</td>
<td>CR PFS</td>
<td>First line</td>
<td>• 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).</td>
</tr>
</tbody>
</table>

### Low-grade or Follicular Lymphoma – Second line or subsequent therapy

<table>
<thead>
<tr>
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<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab (weekly x4)</td>
<td>2A</td>
<td>Yes</td>
<td><strong>Single-arm</strong>, multi-center</td>
<td>N/A</td>
<td>-----</td>
<td>Relapsed disease</td>
<td>• The response rate of 48% with rituximab is comparable to results with single-agent cytotoxic chemotherapy. Toxicity was mild.</td>
</tr>
<tr>
<td>Bendamustine + obinutuzumab (BO), followed by maintenance obinutuzumab in non-progressing patients</td>
<td>2A preferred (in patients refractory to rituximab)</td>
<td>Yes</td>
<td><strong>Phase 3 (GADOLIN)</strong>, randomized, controlled, open-label, multi-center</td>
<td>Bendamustine (B)</td>
<td>PFS</td>
<td>Refractory to rituximab</td>
<td>• 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</td>
</tr>
<tr>
<td>Bendamustine + rituximab</td>
<td>2A preferred</td>
<td>No</td>
<td><strong>Phase 3</strong>, randomized, multi-center, open-label, non-inferiority</td>
<td>Fludarabine + rituximab</td>
<td>PFS</td>
<td>Relapsed or refractory disease</td>
<td>• In combination with rituximab, bendamustine was more effective than fludarabine with higher response rate and superior PFS.</td>
</tr>
<tr>
<td>Copanlisib</td>
<td>2A</td>
<td>Yes</td>
<td><strong>Phase 2 (CHRONOS-1)</strong></td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory</td>
<td>• Copanlisib demonstrated significant efficacy with an ORR of 61% and a</td>
</tr>
<tr>
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<tr>
<td>Rituximab (2 years)</td>
<td></td>
<td>Yes</td>
<td><strong>Phase 3 (PRIMA), randomized, open-label</strong></td>
<td>Placebo</td>
<td>PFS</td>
<td>Maintenance after an initial response to rituximab (R-CHOP, R-CVP, R-FCM)</td>
<td>• 2 years of rituximab maintenance therapy after immunochemotherapy as first-line treatment for follicular lymphoma significantly improves PFS</td>
</tr>
<tr>
<td>Obinutuzumab + bendamustine, CHOP, or CVP, followed by obinutuzumab maintenance</td>
<td>2A</td>
<td>Yes</td>
<td><strong>Phase 3 (GALLIUM), randomized, open-label, multi-center</strong></td>
<td>Rituximab + bendamustine, CHOP, or CVP, followed by rituximab</td>
<td>PFS</td>
<td>First line</td>
<td>• Obinutuzumab-based immunochemotherapy and maintenance therapy resulted in longer progression-free survival than rituximab-based therapy. High-grade adverse events were</td>
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</table>
more common with obinutuzumab-based chemotherapy.

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</thead>
<tbody>
<tr>
<td>Bendamustine + obinutuzumab (BO), followed by maintenance obinutuzumab in non-progressing patients</td>
<td>2A preferred (in patients refractory to rituximab)</td>
<td>Yes</td>
<td>Phase 3 (GADOLIN), randomized, controlled, open-label, multi-center</td>
<td>Bendamustine (B)</td>
<td>PFS</td>
<td>Refractory to rituximab (no response to or progressed within 6 months of therapy with a rituximab-containing regimen)</td>
<td>• Obinutuzumab plus bendamustine followed by obinutuzumab maintenance has improved efficacy (PFS and OS) over bendamustine monotherapy in rituximab-refractory patients with indolent non-Hodgkin lymphoma, with manageable toxicity</td>
</tr>
<tr>
<td><strong>Gastric &amp; Non-Gastric MALT Lymphoma</strong></td>
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<tr>
<td>Rituximab</td>
<td>2A preferred</td>
<td>No</td>
<td>Prospective study</td>
<td>N/A</td>
<td>-----</td>
<td>Resistant to or not eligible for anti-H. pylori therapy</td>
<td>• 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%.</td>
</tr>
<tr>
<td>Rituximab</td>
<td>2A preferred</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>-----</td>
<td>Untreated and relapsed MALT lymphomas</td>
<td>• Rituximab demonstrated clinical activity in patients with non-gastric MALT lymphomas with an ORR of 80%.</td>
</tr>
<tr>
<td>Rituximab + cyclophosphamide + doxorubicin/ mitoxantrone + vincristine + prednisone (R-CHOP or R-CNOP)</td>
<td>2A preferred</td>
<td>No</td>
<td>Retrospective analysis</td>
<td>N/A</td>
<td>-----</td>
<td>Relapsed disease</td>
<td>• Data demonstrated R-CHOP/R-CNOP activity with a CR of 77% in relapsing MALT lymphoma.</td>
</tr>
<tr>
<td>Treatment</td>
<td>Phase</td>
<td>Rituximab</td>
<td>Phase</td>
<td>N/A</td>
<td>CR</td>
<td>First line</td>
<td>Details</td>
</tr>
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</tr>
<tr>
<td>Rituximab + fludarabine</td>
<td>None</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>-----</td>
<td>First line</td>
<td>Combination therapy with rituximab and fludarabine demonstrated a CR of 100% as first-line systemic treatment for patients with extranodal MALT lymphoma.</td>
</tr>
<tr>
<td>Rituximab + chlorambucil</td>
<td>2A</td>
<td>No</td>
<td>Phase 3 (IELSG-19), randomized</td>
<td>Chlorambucil</td>
<td>EFS</td>
<td>First line systemic therapy</td>
<td>Both treatments were active; the better response rate and EFS obtained with the addition of rituximab did not translate into improved OS</td>
</tr>
<tr>
<td>Bendamustine + rituximab (BR)</td>
<td>2A</td>
<td>No</td>
<td>Phase 3 (StiL), open-label, multi-center, randomized</td>
<td>R-CHOP</td>
<td>PFS</td>
<td>First line</td>
<td>Among the patients with marginal zone lymphoma, median PFS with BR was not significantly different from that with R-CHOP.</td>
</tr>
<tr>
<td>Bendamustine + rituximab (BR)</td>
<td>2A</td>
<td>No</td>
<td>Phase 3 (BRIGHT), randomized</td>
<td>R-CHOP or R-CVP</td>
<td>CR</td>
<td>First-line</td>
<td>Among the patients with marginal zone lymphoma, BR resulted in similar CR (20 versus 24 percent) and overall (92 versus 71 percent) response rates.</td>
</tr>
<tr>
<td>Bendamustine + rituximab (BR)</td>
<td>2A</td>
<td>No</td>
<td>Phase 2 (MALAT-2008-01)</td>
<td>N/A</td>
<td>-----</td>
<td>First-line</td>
<td>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%.</td>
</tr>
<tr>
<td>Rituximab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>-----</td>
<td>Untreated and relapsed MALT lymphomas</td>
<td>Rituximab demonstrated clinical activity in patients with non-gastric MALT lymphomas with an ORR of 80%.</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>2A (as a substitute for rituximab or obinutuzumab)</td>
<td>No</td>
<td>Phase 2 (O-MA 1)</td>
<td>N/A</td>
<td>-----</td>
<td>H. pylori refractory or extragastric MALT lymphoma</td>
<td>Ofatumumab is clinically active with an ORR of 81% for the treatment of MALT lymphoma</td>
</tr>
</tbody>
</table>

**Nodal Marginal Zone Lymphoma**
<table>
<thead>
<tr>
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<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine + rituximab (BR)</td>
<td>2A</td>
<td>No</td>
<td>See clinical trials above for Gastric MALT lymphomas</td>
<td></td>
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<tr>
<td>Ibrutinib</td>
<td>2A</td>
<td>Yes</td>
<td>Phase 2, single-arm, open-label</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed after ≥ 1 prior therapy with CD20 monoclonal antibody regimen</td>
<td>• Single-agent ibrutinib induced durable responses with an ORR of 48% and median PFS of 14 months.</td>
</tr>
<tr>
<td>Lenalidomide + rituximab</td>
<td>2A</td>
<td>No</td>
<td>Phase 3 (AUGMENT), multi-center, randomized</td>
<td>Rituximab + placebo</td>
<td>PFS</td>
<td>Relapsed or refractory disease</td>
<td>• 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.</td>
</tr>
<tr>
<td>Bendamustine + obinutuzumab</td>
<td>2A</td>
<td>No</td>
<td>See Follicular Lymphoma above</td>
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</table>

**Splenic Marginal Zone Lymphoma**

<table>
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<tr>
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<th>Comparator</th>
<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>2A preferred</td>
<td>No</td>
<td>Retrospective study</td>
<td>N/A</td>
<td>CR</td>
<td>Treatment naive and previously treated disease</td>
<td>• Rituximab was found to have major activity in patients with splenic MZL with an ORR of 88% and CR of 42%.</td>
</tr>
<tr>
<td>Rituximab ± chemotherapy</td>
<td>2A</td>
<td>No</td>
<td>Retrospective study</td>
<td>Chemotherapy</td>
<td>*****</td>
<td>Treatment naive and previously treated disease</td>
<td>• The CR and DFS rates after rituximab, given alone or with chemotherapy, were significantly better than after chemotherapy without rituximab.</td>
</tr>
</tbody>
</table>

**Hairy Cell Leukemia – Relapsed or Refractory Disease**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NCCN Category</th>
<th>FDA Approved</th>
<th>Trial Design</th>
<th>Comparator</th>
<th>Primary End-Point</th>
<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Stage</td>
<td>Repeatable</td>
<td>Study Design</td>
<td>CR Rate</td>
<td>Disease Type</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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</tr>
<tr>
<td>Cladribine followed by rituximab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>Untreated</td>
<td>• Cladribine followed by rituximab is highly effective even in patients with relapsed HCL with a CR rate of 100%.</td>
<td></td>
</tr>
<tr>
<td>Cladribine followed by rituximab</td>
<td>2A</td>
<td>No</td>
<td>Retrospective study</td>
<td>N/A</td>
<td>Relapsed HCL</td>
<td>• The combination of a purine analog with rituximab was effective for patients with recurrent HCL with a CR rate of 89%.</td>
<td></td>
</tr>
<tr>
<td>Rituximab + pentostatin or cladribine</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>Relapsed HCL</td>
<td>• Rituximab has only modest single-agent activity in cladribine-failed HCL with an ORR of 25% and CR of 13%.</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>Relapsed HCL</td>
<td>• Rituximab demonstrated clinical activity in refractory HCL with an ORR of 80% and CR of 32%.</td>
<td></td>
</tr>
<tr>
<td>Cladribine retreatment</td>
<td>2A</td>
<td>Yes</td>
<td>Extended follow-up</td>
<td>N/A</td>
<td>Relapsed disease</td>
<td>• Retreatment with cladribine is an effective treatment for relapsed HCL with a CR rate of 75% after first relapse and 60% after subsequent relapse.</td>
<td></td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>Treatment naïve and relapsed disease</td>
<td>• Ibrutinib can induce remission in HCL including heavily pre-treated patients with an ORR of 46%.</td>
<td></td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory disease after purine analogs</td>
<td>• High response rates with vemurafenib monotherapy in patients with relapsed or refractory HCL was confirmed with an ORR of 86% at a median 24-month follow up.</td>
</tr>
<tr>
<td>Vemurafenib + rituximab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory HCL</td>
<td>• Vemurafenib plus rituximab represents a regimen that produces deep and durable responses in heavily pre-treated</td>
</tr>
</tbody>
</table>
Moxetumomab pasudotox

<table>
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<tr>
<th>Regimen</th>
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</thead>
<tbody>
<tr>
<td>Rituximab + dexamethasone + cytarabine (RDHA) + platinum (carboplatin, cisplatin, or oxaliplatin), followed by maintenance rituximab</td>
<td>2A preferred</td>
<td>No</td>
<td>Phase 3, randomized</td>
<td>RDHA + platinum, followed by observation</td>
<td>EFS</td>
<td>Induction</td>
<td>• Induction therapy with RDHA plus platinum resulted in an ORR of 89%.</td>
</tr>
<tr>
<td>Alternating RCHOP and RDHAP</td>
<td>2A preferred</td>
<td>No</td>
<td>Phase 3</td>
<td>RCHOP</td>
<td>TTF</td>
<td>Induction</td>
<td>• Induction therapy with alternating RCHOP/RDHAP is associated with a higher time to treatment failure and complete response rates compared to RCHOP alone.</td>
</tr>
<tr>
<td>Rituximab + fractionated cyclophosphamide + vincristine + doxorubicin + dexamethasone (R-hyper-CVAD),</td>
<td>2A preferred</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>FFS</td>
<td>First line</td>
<td>• 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.</td>
</tr>
</tbody>
</table>

Mantle Cell Lymphoma – Induction Therapy

- Induction therapy with RDHA plus platinum resulted in an ORR of 89%.
- Induction therapy with alternating RCHOP/RDHAP is associated with a higher time to treatment failure and complete response rates compared to RCHOP alone.
- 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.
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<th>Line of Therapy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>alternating with rituximab + methotrexate + cytarabine</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP)</td>
<td>2A preferred</td>
<td>No</td>
<td>Phase 3</td>
<td>Cyclophosphamide + doxorubicin + vincristine + prednisone (CHOP)</td>
<td>ORR CR</td>
<td>First line</td>
<td>• The addition of rituximab to CHOP chemotherapy was associated with high response rates but did not translate to prolonged PFS or OS.</td>
</tr>
<tr>
<td>Rituximab + chemotherapy</td>
<td>2A preferred</td>
<td>No</td>
<td>Meta-analysis</td>
<td>N/A</td>
<td>ORR</td>
<td>Untreated and previously treated disease</td>
<td>• In patients with indolent or mantle cell lymphoma, R-chemo is superior to chemotherapy alone with respect to overall survival</td>
</tr>
<tr>
<td>Bendamustine ± ofatumumab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2</td>
<td>N/A</td>
<td>ORR</td>
<td>First line</td>
<td>• Ofatumumab-bendamustine is effective as first line treatment for older pts with MCL as demonstrated by an ORR of 92%.</td>
</tr>
<tr>
<td>Bendamustine + rituximab (BR)</td>
<td>2A preferred (less aggressive therapy)</td>
<td>No</td>
<td>Phase 3 (StiL), open-label, multi-center, randomized</td>
<td>R-CHOP</td>
<td>PFS</td>
<td>First line</td>
<td>• The primary endpoint of PFS was significantly longer with BR compared with R-CHOP however OS outcomes were not significantly different between treatment arms.</td>
</tr>
<tr>
<td>Bortezomib + rituximab + cyclophosphamide + doxorubicin + prednisone (VR-CAP)</td>
<td>2A preferred (less aggressive therapy)</td>
<td>Yes</td>
<td>Phase 3, randomized</td>
<td>R-CHOP</td>
<td>PFS</td>
<td>First line (not candidates for HDT/ASCR)</td>
<td>• 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.</td>
</tr>
</tbody>
</table>

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**Mantle Cell Lymphoma – Second-line Therapy**
<table>
<thead>
<tr>
<th>Drug</th>
<th>Preference</th>
<th>Response Duration to Prior Treatment</th>
<th>Study Design</th>
<th>ORR/Label</th>
<th>ORR/PFS</th>
<th>Disease Type</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acalabrutinib</td>
<td>2A preferred</td>
<td>Yes (after at least one prior therapy)</td>
<td>Phase 2, open-label</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory MCL</td>
<td>• Acalabrutinib treatment provided a high rate of durable responses and a favorable safety profile in patients with relapsed or refractory mantle cell lymphoma.</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>2A preferred</td>
<td>Yes (after at least one prior therapy)</td>
<td>Phase 3 (RAY), randomized, open-label</td>
<td>Tensirolimus</td>
<td>PFS</td>
<td>Relapsed or refractory MCL</td>
<td>• Ibrutinib demonstrated significant improvement in ORR and PFS over tensirolimus in patients with relapsed or refractory MCL.</td>
</tr>
<tr>
<td>Ibrutinib + rituximab</td>
<td>2A preferred</td>
<td>Yes (after at least one prior therapy)</td>
<td>Phase 2, single-center, single-arm, open-label</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory MCL</td>
<td>• Ibrutinib combined with rituximab demonstrated an ORR of 88%.</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>2A preferred</td>
<td>Yes (after two prior therapies, one of which included bortezomib)</td>
<td>Phase 2 (EMERGE), multi-center</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory MCL after prior bortezomib</td>
<td>• 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.</td>
</tr>
<tr>
<td>Lenalidomide + rituximab</td>
<td>2A preferred</td>
<td>Yes (after two prior therapies, one of which included bortezomib)</td>
<td>Phase 1/2</td>
<td>N/A</td>
<td>ORR</td>
<td>Relapsed or refractory MCL</td>
<td>• Lenalidomide plus rituximab is effective for patients with relapsed or refractory MCL with an ORR of 57%.</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>2A preferred</td>
<td>No</td>
<td>Phase 1</td>
<td>N/A</td>
<td>-----</td>
<td>Relapsed or refractory NHL</td>
<td>• Venetoclax resulted in responses across all NHL subtypes with higher ORR and median PFS in patients with MCL than other NHL subtypes.</td>
</tr>
<tr>
<td>Bendamustine + rituximab</td>
<td>2A preferred (extended response)</td>
<td>No</td>
<td>Phase 3, randomized, multi-center, Fludarabine + rituximab</td>
<td>Fludarabine + rituximab</td>
<td>PFS</td>
<td>Relapsed or refractory disease</td>
<td>• In combination with rituximab, bendamustine was more effective than</td>
</tr>
<tr>
<td>Regimen</td>
<td>duration to prior treatment</td>
<td>open-label, non-inferiority</td>
<td>N/A</td>
<td>Relapsed or refractory MCL after at least one prior therapy</td>
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</tr>
<tr>
<td>Bortezomib</td>
<td>2A preferred (extended response duration to prior treatment)</td>
<td>Yes</td>
<td>Phase 2 (PINNACLE)</td>
<td>-----</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib + rituximab</td>
<td>2A preferred (extended response duration to prior treatment)</td>
<td>Yes</td>
<td>Phase 2</td>
<td>-----</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>2A (as a substitute for rituximab or obinutuzumab)</td>
<td>No</td>
<td>Phase 2</td>
<td>-----</td>
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</tbody>
</table>

- Single agent bortezomib induced an ORR of 33% in patients with relapsed or refractory MCL.
- R-bortezomib had significant activity in patients with relapsed or refractory MCL with an ORR of 29%.
- In relapsed or refractory MCL patients, ofatumumab demonstrated a low ORR of 8.3%.

**Post-transplant lymphoproliferative disorder (PTLD)**

<table>
<thead>
<tr>
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<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>2A</td>
<td>No</td>
<td>Phase 2, prospective, multi-center</td>
<td>N/A</td>
<td>ORR</td>
<td>PTLD after solid organ transplant</td>
<td>Rituximab is an effective treatment in PTLD with an ORR of 44% and 1-year OS rate of 67%.</td>
</tr>
<tr>
<td>Rituximab</td>
<td>2A</td>
<td>No</td>
<td>Retrospective analysis, multi-center</td>
<td>N/A</td>
<td>-----</td>
<td>PTLD after solid organ transplant and initial reduced immunosuppression</td>
<td>This retrospective analysis suggests significantly improved PFS and OS associated with early rituximab-based treatment in PTLD.</td>
</tr>
<tr>
<td>Rituximab, followed by cyclophosphamide + doxorubicin +</td>
<td>2A</td>
<td>No</td>
<td>Phase 2, prospective, multi-center</td>
<td>N/A</td>
<td>ORR</td>
<td>Failure to initial reduced</td>
<td>Use of sequential immunochemotherapy with rituximab and CHOP demonstrated an ORR of 90%.</td>
</tr>
<tr>
<td>Regimen</td>
<td>NCCN Category</td>
<td>FDA Approved</td>
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</tr>
<tr>
<td>Rituximab + LMB chemotherapy regimen</td>
<td>2A</td>
<td>No</td>
<td>Phase 3, randomized</td>
<td>LMB chemotherapy regimen</td>
<td>EFS</td>
<td>---------------</td>
<td>• Rituximab in addition to standard LMB therapy improves EFS of children/adolescents with high risk B-cell non-Hodgkin lymphoma and mature acute leukemia.</td>
</tr>
</tbody>
</table>

**Primary Cutaneous B-Cell Lymphomas (PCBCL)**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Rituximab IV</td>
<td>2A</td>
<td>No</td>
<td>Retrospective analysis</td>
<td>N/A</td>
<td>-----</td>
<td>---------------</td>
<td>• Rituximab demonstrated to be effective for indolent PCBCL with an ORR of 87%.</td>
</tr>
<tr>
<td>Rituximab intralesional</td>
<td>2A</td>
<td>No</td>
<td>Observational multi-center study</td>
<td>N/A</td>
<td>-----</td>
<td>---------------</td>
<td>• Intralesional rituximab is an effective treatment for PCBCL with a CR rate of 71% and PR rate of 23%.</td>
</tr>
</tbody>
</table>

**Histiocytic Neoplasms**

**Rosai-Dorfman Disease**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>2A certain circumstances</td>
<td>No</td>
<td>Retrospective analysis</td>
<td>N/A</td>
<td>-----</td>
<td>All lines of therapy</td>
<td>• Of the 7 patients who were given rituximab, 64% remained progression free 24 months after the initial rituximab administration.</td>
</tr>
</tbody>
</table>

**Management of Immunotherapy-Related Toxicities**
### Non-viral encephalitis

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>2A</td>
<td>No</td>
<td>Retrospective case study</td>
<td>N/A</td>
<td>N/A</td>
<td>--------</td>
<td>• Treatment with rituximab resulted in improved neurologic symptoms in patients autoimmune encephalitis in patients receiving immune checkpoint blockade therapy</td>
</tr>
</tbody>
</table>