BEND+RITU Regimen
Bendamustine-riTUXimab

Disease Site
Hematologic - Lymphoma - Non-Hodgkin's Low Grade (indolent)

Intent
Palliative

Regimen Category
Evidence-Informed:
Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses
Treatment of symptomatic indolent histology CD20-positive non-Hodgkin's B-cell or mantle cell lymphoma (excluding small lymphocytic lymphoma, SLL) in:

- "Rituximab-naïve" patients: treatment of initial or relapsed/refractory disease patients (BEND+RITU followed by maintenance RITU in responding patients)
- “Rituximab retreatment” (relapsed/refractory) patients who have responded to prior rituximab (as combination, single agent and/or maintenance therapy) and who had not required therapy for at least one year (BEND+RITU only; maintenance RITU is not funded)

Refer to the NDFP eligibility forms for detailed funding criteria.
**Supplementary Public Funding**

**bendamustine**  
New Drug Funding Program (Bendamustine - First Line - Indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma)

**bendamustine**  
New Drug Funding Program (Bendamustine - Relapsed_Refractory - Indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma)

**riTUXimab**  
New Drug Funding Program (Rituximab in Combination with Chemotherapy - Indolent B-cell Lymphoma)

**riTUXimab**  
New Drug Funding Program (Rituximab - Maintenance Treatment - Lymphoma)

**riTUXimab**  
New Drug Funding Program (Rituximab - Retreatment - Indolent Lymphoma)  
(with combination chemotherapy)

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**B - Drug Regimen**

**Treatment (“rituximab-naïve” or “rituximab retreatment” patients):**

<table>
<thead>
<tr>
<th><strong>riTUXimab</strong></th>
<th>375 mg /m²</th>
<th>IV</th>
<th>Day 1 ONLY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>bendamustine</strong></td>
<td>90 mg /m²</td>
<td>IV</td>
<td>Days 1 and 2</td>
</tr>
</tbody>
</table>

**Maintenance rituximab (responding “rituximab-naïve” patients only):**

<table>
<thead>
<tr>
<th><strong>riTUXimab</strong></th>
<th>375 mg /m²</th>
<th>IV</th>
<th>Day 1</th>
</tr>
</thead>
</table>

Should be started within 8 weeks of completion of the induction regimen (2015 guidelines). Maintenance rituximab is funded by NDFP if it is started within 6 months of the last dose of induction therapy.
C - Cycle Frequency

Treatment (“rituximab-naïve” or “rituximab retreatment” patients):
REPEAT EVERY 28 DAYS
For a maximum of 6 cycles in the absence of unacceptable toxicity or disease progression

Maintenance rituximab (responding “rituximab-naïve” patients only):
REPEAT EVERY 3 MONTHS
For maximum 2 years (8 doses total) of rituximab maintenance treatment in the absence of unacceptable toxicity or disease progression. (Refer to DSG guidelines and NDFP form for details*)

D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:

Also refer to CCO Antiemetic Summary

Bendamustine pre-medication (only for patients with Grade 1 or 2 reactions with prior infusion): • Analgesic/antipyretic (e.g. acetaminophen), corticosteroid and an antihistamine (e.g. diphenhydramine) should be considered in subsequent cycles.

Hypertension should be controlled prior to starting treatment.

Rituximab premedication:

• Acetaminophen 650mg PO

• Diphenhydramine 50mg PO/IV

• If high volume disease, consider steroids and prophylaxis for tumour lysis

HBsAg positive patients should receive antiviral prophylaxis during and after rituximab. HBsAg negative, but HBcAb positive patients should be considered for antiviral prophylaxis and be closely monitored for viral reactivation by a HBV expert.
E - Dose Modifications

See premedication and monitoring sections for supportive care, screening and monitoring recommendations.

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered.

**Dosage with toxicity**

Dose levels for bendamustine: 90 mg/m², 60 mg/m². Do not re-escalate after reduction for toxicity.

Rituximab: No dosage reduction recommendation. Dose is either delayed or discontinued due to toxicity.

<table>
<thead>
<tr>
<th>Toxicity / Counts (x 10⁹/L)</th>
<th>Rituximab Dose / Infusion Rate</th>
<th>Bendamustine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 neutropenia or platelets; thrombocytopenic bleeding</td>
<td>Hold*</td>
<td>Hold* then ↓ 1 dose level</td>
</tr>
<tr>
<td>Grade 1-2 Infusion-related</td>
<td>• Stop or slow infusion; exclude respiratory symptoms; treat symptomatically. • Restart at 50% previous rate after resolution of symptoms.</td>
<td>• Hold or slow infusion; premedicate with antipyretic, antihistamine, and corticosteroid before re-challenge and subsequent cycles.</td>
</tr>
<tr>
<td>≥ Grade 3 Infusion-related or pulmonary</td>
<td>• Discontinue • Manage appropriately; monitor patient until complete resolution.</td>
<td></td>
</tr>
<tr>
<td>Other ≥ grade 3 non-hematological/organ toxicity</td>
<td>Hold until ≤ grade 1; considering discontinuing if grade 4</td>
<td>Hold until ≤ grade 1 then reduce by 1 dose level; considering discontinuing if grade 4</td>
</tr>
<tr>
<td>• Severe mucocutaneous toxicity • Serious/life-</td>
<td>Discontinue</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>
threatening cardio-pulmonary events
• Reactivation of tuberculosis or hepatitis B; evidence of active hepatitis
• PML / RPLS

*Do not start new cycle until toxicities have recovered to ≤ grade 1, platelets ≥ 75-100 x 10⁹/L, and ANC ≥ 1 x 10⁹/L.

**Hepatic Impairment**

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>AST or ALT or ALP</th>
<th>Bendamustine Dose</th>
<th>Rituximab Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.5 x ULN</td>
<td>≤ 2.5 x ULN</td>
<td>Caution</td>
<td>No adjustment required; discontinue if evidence of hepatitis</td>
</tr>
<tr>
<td>&gt; 1.5 x ULN</td>
<td>&gt; 2.5 x ULN</td>
<td>Do not use</td>
<td></td>
</tr>
</tbody>
</table>

**Renal Impairment**

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Bendamustine Dose</th>
<th>Rituximab Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>100%</td>
<td>No adjustment required</td>
</tr>
<tr>
<td>40 - 80</td>
<td>Caution</td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>Do not use</td>
<td></td>
</tr>
</tbody>
</table>

**Dosage in the Elderly**

No dose adjustment required for either drug. Exercise caution as older patients are more likely to experience serious adverse events (including cardiac, pulmonary, or other grade 3/4 toxicity) with rituximab.
# F - Adverse Effects

Refer to [riTUXimab](#), [bendamustine](#) drug monograph(s) for additional details of adverse effects

<table>
<thead>
<tr>
<th>Very common (≥ 50%)</th>
<th>Common (25-49%)</th>
<th>Less common (10-24%)</th>
<th>Uncommon (&lt; 10%), but may be severe or life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity (may be severe)</td>
<td>Diarrhea</td>
<td>Anorexia, weight loss</td>
<td>Arterial / venous thromboembolism</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>Flu-like symptoms</td>
<td>Headache</td>
<td>Arrhythmia, prolonged QTc</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Constipation</td>
<td>Mucositis</td>
<td>Cardiotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cough, dyspnea</td>
<td>Increased LFTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dizziness</td>
<td>Tumour lysis syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insomnia</td>
<td>Renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rash (may be severe)</td>
<td>Pneumonitis, ARDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abdominal pain</td>
<td>GI obstruction / perforation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyspepsia</td>
<td>PRES</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dysgeusia</td>
<td>Hemolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Edema</td>
<td>Vasculitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunosuppression, atypical infections, viral/TB re-activation</td>
<td>Secondary malignancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormal electrolytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myelosuppression</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotension (transient)</td>
<td></td>
</tr>
</tbody>
</table>

# G - Interactions

Refer to [riTUXimab](#), [bendamustine](#) drug monograph(s) for additional details

- Additive hypotensive effects may occur with anti-hypertensive agents and rituximab. Consider withholding anti-hypertensives 12 hours before and during rituximab infusions.
- CYP1A2 inhibitors may increase bendamustine concentration and toxicity; use with caution
- CYP1A2 inducers (including cigarette smoking) may reduce bendamustine concentration
H - Drug Administration and Special Precautions

Refer to riTUXimab, bendamustine drug monograph(s) for additional details

Administration: rituximab

- Rituximab infusions should be administered in a setting where full resuscitation facilities are immediately available, and under the close supervision of someone experienced and capable of dealing with severe infusion-related reactions.
- DO NOT administer as an IV push or bolus.
- Dilute to a final concentration of 1-4 mg/mL in normal saline or D5W.
- To avoid foaming, gently invert the bag to mix the solution.
- Do not admix with other drugs.
- Administer rituximab through a dedicated line.
- Compatible with PVC or polyethylene bags.
- Keep vials refrigerated; do not freeze. Protect from light.
- **Infusion rates:**
  - Consider a slower infusion rate or split dosing over days 1-2 for any cycle where bulky disease present or WBC > 25 x 10^9/L.
  - First infusion: initial rate of 50 mg/h, then escalate rate in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h.
- **Subsequent infusions:**
  - Initial rate of 100 mg/h, then escalate rate in 100 mg/h increments every 30 minutes, to a maximum of 400 mg/h as tolerated.
  - Published data suggest that a 90 minute infusion (20% of the dose in the first 30 min then the remaining 80% over 60 min) can be used for second and subsequent infusions if no reaction occurred with the first infusion.

Administration: bendamustine

- **NHL** - infuse over 60 minutes
- Bendamustine infusions should be administered in a setting where full resuscitation facilities are immediately available, and under the close supervision of someone experienced and capable of dealing with severe infusion-related reactions.
- DO NOT administer as an IV push or bolus.
- **Dilute** to a final concentration of 0.2 - 0.6 mg/mL in 500 mL infusion bag of 0.9% sodium chloride or 2.5% dextrose/0.45% sodium chloride.
- Reconstituted solution must be transferred to infusion bag within 30 minutes of reconstitution.
- Administer bendamustine through a dedicated line.
- Compatible with PVC or polyethylene bags.
- Do not admix with other drugs.
Contraindications:

- Patients with known hypersensitivity and anaphylactic reactions to proteins of similar mouse or human origin, to Chinese Hamster Ovary (CHO) cell proteins or to any component of rituximab, bendamustine or mannitol
- Patients who have or have had PML, have active and/or severe infections, active hepatitis B, or severely immunocompromised (e.g. AIDS patients with very low CD4 or CD8 counts).
- Avoid the use of live vaccines
- Patients with CrCl < 40 mls/min or moderate/severe hepatic impairment

Warnings/precautions:

- Exercise caution in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection.
- Prior to starting rituximab in HBV seropositive patients, consultation with a liver disease expert is recommended to determine ongoing monitoring of HBV reactivation and its management.
- Exercise caution in patients with neutrophil counts < 1.5 x 10^9/L and/or platelets < 75 x 10^9/L due to limited experience in this patient group.
- Use with extreme caution in patients with pre-existing cardiovascular disease or in patients with high tumour burden. Consider steroids ± slow infusions or infusions split over 2 days for patients with bulky disease or > 25 x 10^9/L circulating malignant cells.
- Use with caution in patients with pulmonary insufficiency or lung tumour infiltration, and in patients with myelosuppression.
- Avoid in patients with relapsed indolent NHL who did not tolerate prior therapies (including other alkylating agents)
- Use with caution in patients with hypertension and patients with mild renal and hepatic impairment

Pregnancy & lactation:

- Bendamustine is not recommended for use in pregnancy. Adequate contraception should be used by both sexes 2 weeks before, during treatment, and for at least 4 weeks after the last dose.
- Rituximab should not be used during pregnancy. IgGs are known to pass the placental barrier. There have been reports of infants with transient B-cell depletion and lymphocytopenia. Adequate contraception is recommended for both sexes with childbearing potential, during rituximab treatment and up to 12 months after the last dose.
- Breastfeeding is not recommended during treatment with either drug.
I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- Blood pressure; baseline and before each dose
- CBC; baseline and before each cycle
- Electrolytes, including sodium, potassium, magnesium and uric acid; baseline and before each cycle
- Liver function tests; baseline and regular
- Renal function tests; baseline and regular
- The Hematology Disease Site group recommends screening patients for hepatitis B surface antigen (HBsAg) and core antibody (HBcAb) prior to starting treatment. If seropositive, consult with an expert in HBV and monitor closely.
- Clinical assessment of hypersensitivity reactions, tumour lysis syndrome, hypotension, infection (including viral, opportunistic), bleeding, GI, pulmonary, skin, CNS and cardiovascular side effects; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Monitor closely for cardiovascular symptoms for patients who have cardiac conditions or recurrent cardiac events with rituximab
- ECG; as clinically indicated; periodic in the setting of cardiac disorders and electrolyte imbalances
- Blood glucose; baseline and periodic
- CMV testing in febrile patients; as clinically indicated
- HIV status; baseline

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J - Administrative Information

Approximate Patient Visit

BEND+RITU – 6 hours (first cycle); 4 hours
### Pharmacy Workload (average time per visit)
- 24.073 minutes

### Nursing Workload (average time per visit)
- 55.417 minutes

#### K - References

Bendamustine and rituximab drug monographs, Cancer Care Ontario.


#### PEBC Advice Documents or Guidelines

- [Rituximab in Lymphoma and Chronic Lymphocytic Leukemia](#)

April 2017 updated adverse effects; added interactions, drug admin, precautions and missing references
information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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