Regimen Monograph

A - Regimen Name

BEND+POLA+RITU Regimen

Bendamustine-Polatuzumab-Rituximab

Disease Site

Hematologic
Lymphoma - Non-Hodgkin's High Grade

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

For the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, who are not eligible for autologous stem cell transplant (ASCT) and have received at least 1 prior therapy.

Eligible patients should have good performance status and a life expectancy ≥ 24 weeks.

Supplementary Public Funding

riTUXimab
New Drug Funding Program (Polatuzumab Vedotin with Bendamustine and Rituximab (Biosimilar) - Relapsed or Refractory Diffuse Large B-cell Lymphoma) (NDFP Website)

polatuzumab vedotin
New Drug Funding Program (Polatuzumab Vedotin with Bendamustine and Rituximab (Biosimilar) - Relapsed or Refractory Diffuse Large B-cell Lymphoma) (NDFP Website)

bendamustine
New Drug Funding Program (Polatuzumab Vedotin with Bendamustine and Rituximab (Biosimilar) - Relapsed or Refractory Diffuse Large B-cell Lymphoma) (NDFP Website)

back to top

B - Drug Regimen

Note: Different rituximab products are NOT INTERCHANGEABLE.

Cycle 1:

riTUXimab	375 mg /m²	IV	Day 1
polatuzumab vedotin	1.8 mg /kg	IV	Day 2
bendamustine	90 mg /m²	IV	Days 2 and 3

Cycle 2+[*]:

riTUXimab	375 mg /m²	IV	Day 1
polatuzumab vedotin	1.8 mg /kg	IV	Day 1
bendamustine	90 mg /m²	IV	Days 1 and 2

[*]Polatuzumab vedotin, bendamustine, and rituximab can be administered in any order on Day 1 of each cycle.

back to top

C - Cycle Frequency

REPEAT EVERY 21 DAYS

For a usual total of up to 6 cycles unless disease progression or unacceptable toxicity occurs

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal (Cycle 1 day 1)
Moderate (Cycle 1 days 2-3, Cycle 2+)

- Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Pre-medication (prophylaxis for infusion reactions):

Pre-medications for rituximab
Administer the following at least 30 minutes prior to rituximab:

- Oral antipyretic (e.g. acetaminophen)
- H1-receptor antagonist / antihistamine (e.g. diphenhydramine)
- Corticosteroid (e.g. methylprednisolone 80 mg IV) in patients with high bulk disease or pulmonary involvement if no corticosteroids are already being given as part of the chemotherapy regimen.

Pre-medications for polatuzumab vedotin:
If not already pre-medicated, administer an antihistamine and anti-pyretic at least 30 to 60 minutes prior to polatuzumab vedotin administration.

Other supportive care:

- Prophylaxis for tumour lysis (high bulk disease)
- Consider anti-infective prophylaxis. (e.g., PJP, herpes virus)
- Consider prophylactic G-CSF administration for neutropenia.

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Hypertension should be controlled prior to starting bendamustine.

Correct for hypokalemia and other electrolyte abnormalities prior to and during treatment, especially in patients with pre-existing cardiac disorders.

Since transient hypotension may occur during rituximab infusion, consideration should be given to withhold antihypertensive medication 12 hours prior to and throughout the rituximab infusion.

Dosage with toxicity

Dose levels

Dose level	Rituximab Dose[1] (mg/m^2)	Bendamustine Dose[2] (mg/m^2)	Polatuzumab vedotin Dose[2] (mg/kg)
0	375	90	1.8
-1	375	70	1.4
-2	375	50	Discontinue
-3	Discontinue	Discontinue	Not applicable

[1]No dosage reduction recommendation. Dose is either delayed or discontinued due to toxicity.

[2]Do not re-escalate once dose is decreased.

Hematological Toxicities

Toxicity	Grade	Rituximab Dose	Bendamustine Dose	Polatuzumab vedotin Dose
Neutropenia	≥ Grade 3	Hold* Consider G-CSF for subsequent cycles. Resume at same dose level†	Hold* Consider G-CSF for subsequent cycles. If recovery occurs in ≤7 days: • Resume at same dose level If recovery in >7 days: • Resume at 1 dose level ↓	Hold* Consider G-CSF for subsequent cycles. Resume at same dose level†
Thrombocytopenia	≥ Grade 3	Hold* Resume at same dose level†	Hold* If recovery occurs in ≤7 days: • Resume at same dose level If recovery in >7 days: • Resume at 1 dose level ↓	Hold* Resume at same dose level†

*Do not start new cycle until non-hematologic toxicities have recovered to ≤ grade 1, ANC ≥ 1 x 10^9/L and platelets ≥ 75 x 10^9/L

†If bendamustine is discontinued, discontinue polatuzumab and rituximab

Peripheral Neuropathy

Toxicity on Day 1 of any cycle	Polatuzumab vedotin Dose
Grade 2 and 3	Hold* If recovery in ≤14 days: • Resume (with the next cycle) at 1 dose level ↓ • If recurs, discontinue If recovery in >14 days: • Discontinue
Grade 4	Discontinue

*Do not start new cycle until non-hematologic toxicities have recovered to ≤grade 1, ANC ≥1 x 10^9/L and platelets ≥75 x 10^9/L

Bendamustine - Non-Hematological Toxicities

Toxicity	Grade	Bendamustine Dose
Skin reactions	Severe or progressive	Hold*, then ↓ by 1 dose level OR Consider discontinuing
Other related non-hematological/organ toxicity	Grade 2	Hold*, restart at the same dose
	Grade 3	Hold*, then ↓ by 1 dose level
	Grade 4	Hold*, then ↓ by 1 dose level OR Consider discontinuing

*Do not start new cycle until non-hematologic toxicities have recovered to ≤ grade 1, ANC ≥ 1 x 10^9/L and platelets ≥ 75 x 10^9/L

Other Non-Hematological Toxicities

Toxicity on Day 1 of any cycle	Grade	Rituximab Dose	Bendamustine Dose	Polatuzumab vedotin Dose
Progressive multifocal leukoencephalopathy (PML)	Any	Discontinue		
Pulmonary toxicity				
Severe mucocutaneous toxicity				
Serious/life-threatening cardio-pulmonary events				
Reactivation of tuberculosis or hepatitis B				
Evidence of active hepatitis				
Serious infections				

Management of Infusion-related Reactions:

Also refer to the CCO guideline for information on Management of Cancer Medication-Related Infusion Reactions.

Rituximab:

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion. • Manage the symptoms. Restart: • Once symptoms have resolved, restart at 50% of the rate at which the IR occurred.	• Re-challenge at 50% of the administration rate at which the IR occurred and with pre-medications. • Consider adding oral montelukast ± oral acetylsalicylic acid.

3 or 4	• Stop the infusion. • Aggressively manage symptoms.	• Consider clinical benefit and risks of further treatment. Consider patient factors, severity and nature of the IR and availability of suitable alternative treatment. • Consider desensitization for patients with recurrent reactions despite pre-medications and a slower infusion rate.

Polatuzumab vedotin:

Grade	Management	Re-challenge

1-3	• Stop the infusion.
	• Manage the symptoms.
	
	Restart:
	
	• Once symptoms have resolved, restart (if applicable) at 50% of the rate achieved prior to interruption.
	• If no reaction occurs, escalate the rate at no more than 50 mg/hour every 30 minutes.
	• Discontinue for:
	  ◦ Grade 3 wheezing, bronchospasm, or generalized urticarial
	  ◦ Recurrent grade 2 wheezing or urticaria, or recurrence of any grade 3 symptoms
		• Infuse polatuzumab vedotin over 90 minutes; if no infusion-related reaction occurs, infuse subsequent infusions over 30 minutes. Administer pre-medication for all cycles.

4	• Stop treatment. • Aggressively manage symptoms.	• Discontinue (do not re-challenge).

Bendamustine:

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. Restart: • Once symptoms have resolved, the infusion may be restarted with close monitoring.	• Re-challenge with close monitoring and pre-medications (e.g. antipyretic, corticosteroid and an antihistamine).
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Do not re-challenge. Consider discontinuation

Hepatic Impairment

Bilirubin		AST or ALT	Rituximab Dose	Bendamustine Dose	Polatuzumab vedotin Dose
≤ 1.5 x ULN	Or	≤2.5 x ULN	No dose adjustment required; discontinue if evidence of hepatitis	Caution	No dose adjustment required
> 1.5 x ULN	Or	>2.5 x ULN		Do not use	Avoid use. MMAE exposure may be increased and may lead to an increased incidence of adverse events.

Renal Impairment

Creatinine Clearance (mL/min)	Rituximab Dose	Bendamustine Dose	Polatuzumab vedotin Dose
>80	No dose adjustment required	100%	No dose adjustment required
40 - 80	No dose adjustment required	Caution	No dose adjustment required
30 - 39	No dose adjustment required	Do not use	No dose adjustment required
< 30 or ESRD	No dose adjustment required	Do not use	Has not been studied

Dosage in the Elderly

No dose adjustment required for polatuzumab vedotin, bendamustine or rituximab. Patients ≥ 65 of age had a higher incidence of adverse events ≥ grade 3 and discontinuation compared with younger patients with polatuzumab vedotin. Exercise caution as older patients are more likely to experience serious adverse events (including cardiac, pulmonary, or other grade 3/4 toxicity) with rituximab.

back to top

F - Adverse Effects

Refer to riTUXimab, polatuzumab vedotin, bendamustine drug monograph(s) for additional details of adverse effects.

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Myelosuppression ± infection (or viral reactivation), bleeding (may be severe) • Fatigue • Diarrhea • Nausea, vomiting • Infusion reactions (may be severe) • Anorexia, weight loss	• Peripheral neuropathy • Constipation • Abnormal electrolytes • Cough, dyspnea • Dizziness • Rash, pruritus • Abdominal pain • Headache	• Arterial / venous thromboembolism • Arrhythmia, prolonged QTc • Cardiotoxicity • Hypertension / hypotension • Hepatotoxicity • Tumour lysis syndrome • Nephrotoxicity • Pneumonitis, ARDS • GI obstruction / perforation • PRES, PML • Optical and cranial nerve disorder • SJS, TEN, DRESS • Hemolysis • Vasculitis • Hyperviscosity • Secondary malignancy

back to top

G - Interactions

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

- Consider withholding antihypertensive medication 12 hours prior to and during rituximab administration.
- Ingestion of grapefruit, starfruit, Seville oranges, their juices or products while on polatuzumab therapy may increase MMAE plasma concentrations as these products have CYP3A4 inhibitory activity; monitor closely for signs of toxicity.

back to top

H - Drug Administration and Special Precautions

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

Administration

Rituximab

Note: Different rituximab products are NOT INTERCHANGEABLE.

Rituximab IV and Subcutaneous formulations are not interchangeable. The dosing and concentrations of these products are different.

- **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.
- Monitor patients during and for at least 15 minutes after each rituximab dose, longer in patients at higher risk of hypersensitivity reactions
- 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:

First infusion:

- Recommended to be administered over a graduated rate: initial rate of 50 mg/h, then escalate rate in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h (about 4.25 hours in total).

Subsequent infusions:

- If no severe infusion reaction (grade 3 or 4) occurred with the first cycle, a rapid infusion of IV rituximab over a total of 90 minutes can be initiated with cycle 2 (20% of the dose in the first 30 min then the remaining 80% over 60 min).
- OR 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 (about 3.25 hours in total).

When bulky disease present or WBC > 25-50 x 10^9/L, consider:

- A slower infusion rate, or
- Split dosing over days 1-2, or
- Delaying rituximab treatment until chemotherapy has reduced the lymphocyte count

Polatuzumab vedotin

- **DO NOT** administer as an IV push or bolus.
- Reconstitute using sterile water for injection, immediately before dilution.
- Dilute into 0.9% sodium chloride, 0.45% sodium chloride or 5% dextrose IV infusion bag with a minimum volume of 50mL. Final concentration must be 0.72-2.7 mg/mL.
- Do not shake vial or IV bag. Agitation can result in aggregation.
- Infuse via dedicated line equipped with a sterile, non-pyrogenic, low-protein binding in-line or addon filter (0.2 or 0.22 µm size) and catheter.
- Administration of polatuzumab vedotin, bendamustine, and rituximab can occur any order on Day 1 of each cycle.
- Initial dose should be administered over 90 minutes. If well tolerated, the subsequent doses may be administered over 30 minutes.
- Patients should be monitored for infusion-related reactions during and for at least 90 minutes following the first infusion, and for at least 30 minutes following subsequent infusions.

- If a polatuzumab vedotin dose is missed, administer as soon as possible. Adjust cycle schedule in order to maintain a 21-day interval between doses.
- No incompatibilities have been observed between polatuzumab vedotin and:
    - IV infusion bags with polyvinyl chloride (PVC), or polyolefins (PO) such as polyethylene (PE) and polypropylene (PP).
    - Infusion sets or infusion aids with PVC, PE, polyurethane (PU), polybutadiene (PBD), acrylonitrile butadiene styrene (ABS), polycarbonate (PC), polyetherurethane (PEU), or fluorinated ethylene propylene (FEP), or polytetrafluorethylene (PTFE).
    - Filter membranes composed of polyether sulfone (PES) or polysulfone (PSU).
- Store unopened vials at 2-8°C in the original carton to protect from light.

Bendamustine:

- **DO NOT** administer as an IV push or bolus.
- Reconstituted solution must be transferred to infusion bag within 30 minutes of reconstitution.
- Infuse over 30-60 minutes.
- 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.
- Administer bendamustine through a dedicated line.
- Compatible with PVC or polyethylene lined PVC infusion bags.
- Do not admix with other drugs.
- Store unopened vials at 2-25°C, in original package protected from light.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications:

- Patients who have a hypersensitivity to polatuzumab vedotin, bendamustine or rituximab or any components of the formulation.
- 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 mannitol.

Other Warnings/Precautions:

- Exercise caution in patients:
    - with ≥ grade 2 peripheral neuropathy or prior allogeneic hematopoietic stem cell transplantation (HSCT) as they were excluded from polatuzumab vedotin clinical trials.
    - with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Patients may have increased risk of infection following treatment.
    - with pulmonary insufficiency or lung tumour infiltration, and in patients with myelosuppression.
    - who have or 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).
    - with CrCl < 40 mL/min or moderate/severe hepatic impairment
    - with hypertension and and mild renal impairment
- 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.
- Use rituximab with *extreme caution* in patients with pre-existing cardiovascular disease or in patients with high tumour burden. Consider steroids ± slow rituximab infusions or infusions split over 2 days for patients with bulky disease or > 25 x 10^9/L circulating malignant cells.
- Reduced immunogenicity may occur with the use of inactivated vaccines.
- Avoid live or live-attenuated vaccines, since they may result in serious or fatal infections in immunocompromised patients.
- An increased risk of severe skin toxicity (including Stevens-Johnson syndrome and toxic epidermal necrolysis) was noted when allopurinol was used concurrently with bendamustine.
- Caution with driving or using machinery as peripheral neuropathy, fatigue, and dizziness may occur with polatuzumab vedotin treatment.

Pregnancy/lactation:

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility Effects: Yes

back to top

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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; Baseline and before each cycle; consider more frequently for patients with Grade 3 or 4 neutropenia or thrombocytopenia
- Liver function tests; Baseline, before each cycle and as clinically indicated
- Renal functions tests; Baseline, before each cycle and as clinically indicated
- Blood pressure; Baseline and before each dose
- Electrolytes, including sodium, potassium, magnesium and uric acid; Baseline and before each cycle
- Clinical toxicity assessment for infusion-related reactions, neuropathy, TLS, PML, infections (including viral, opportunistic), bleeding, fatigue, secondary malignancies and pulmonary, cardiovascular, nervous system, GI or skin effects; At each visit

back to top

J - Administrative Information

Approximate Patient Visit	4 to 5 hours; Bendamustine only - 0.5 to 1 hour
Pharmacy Workload (average time per visit)	28.381 minutes
Nursing Workload (average time per visit)	63.583 minutes

back to top

K - References

BC Cancer Protocol Summary for Treatment of Relapsed or Refractory Diffuse Large B-Cell Lymphoma and Not Eligible for Transplant using Polatuzumab Vedotin, Bendamustine and rituximab; April 2022.

Bendamustine Drug Monograph, Ontario Health (Cancer Care Ontario).

Polatuzumab Drug Monograph, Ontario Health (Cancer Care Ontario).

Rituximab Drug Monograph, Ontario Health (Cancer Care Ontario).

Sehn L, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2019; 37. https://doi.org/10.1200/JCO.19.00172.

November 2024 Updated Pregnancy/breastfeeding section

back to top

M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management 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.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top