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

Protocol Code	*LYPOLABR*
Tumour Group	*Lymphoma*
Contact Physician	*Dr Laurie H. Sehn*
Contact Pharmacist	*Louisa Pang*

ELIGIBILITY:

Patients must:

- Have relapsed or refractory diffuse large B-cell lymphoma (DLBCL),
  - including patients with DLBCL that has transformed from an underlying indolent lymphoma and patients with DLBCL histology and translocation of MYC and BCL2 and/or BCL6
- Not be eligible for transplant or have relapsed post-ASCT, and
- Have received at least one prior line of systemic therapy for DLBCL

Note:
For patients who have received prior bendamustine, response duration must have been more than 1 year

Patients should have:

- Adequate hematologic function (unless due to underlying disease):
- Hemoglobin greater than 90 g/L,
- ANC greater than or equal to 1.5 x 10^9/L, and
- Platelets greater than or equal to 75 x 10^9/L

EXCLUSIONS:

Patients must not:

- Have primary CNS lymphoma,
- Be eligible for autologous stem cell transplant,
- Have current peripheral neuropathy greater than grade 1, or
- Have a history of sensitivity to mannitol

CAUTION:

- Creatinine clearance less than 40 mL/min,
- AST or ALT greater than 2.5 x ULN, or
- Total bilirubin greater than 1.5 x ULN

TESTS:

- **Baseline**:
  - Required before first treatment: CBC and differential, platelets, creatinine, ALT, bilirubin, alkaline phosphatase
  - Required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2: HBsAg, HBcoreAb
- **Before Day 1 of each cycle**: CBC and differential, platelets, creatinine, total bilirubin, ALT, alkaline phosphatase
- **If clinically indicated**: sodium, potassium, calcium, albumin, phosphate, uric acid, direct bilirubin

PREMEDICATIONS:

Antiemetic protocol for moderately emetogenic chemotherapy (see protocol SCNAUSEA)

For riTUXimab portion:

- For intravenous infusion:
  diphenhydrAMINE 50 mg PO *prior to riTUXimab IV and then* q 4 h during the IV infusion, *if the infusion exceeds 4 h*
  acetaminophen 650 to 975 mg PO *prior to riTUXimab IV and then* q 4 h during the IV infusion, *if the infusion exceeds 4 h*

- For subcutaneous injection:
  diphenhydrAMINE 50 mg PO *prior to riTUXimab subcutaneous*
  acetaminophen 650 to 975 mg PO *prior to riTUXimab subcutaneous*

For polatuzumab vedotin portion:

Premedications are optional but if infusion-related reactions are observed in the absence of premedication, premedication must be administered before subsequent doses:
- diphenhydrAMINE 50 mg PO *prior to infusion*
- acetaminophen 650 to 975 mg PO *prior to infusion*

SUPPORTIVE MEDICATIONS:

- If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg PO daily for the duration of chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive.
- valACYClovir 500 mg PO daily and cotrimoxazole DS 1 tab PO 3 times each week (Monday, Wednesday and Friday) for the duration of chemotherapy and continue for 6 months after treatment completion

TREATMENT:

1 cycle= 21 days. Treat for 6 cycles. (May extend interval to every 28 days if required for better tolerance).

Discontinue if definite progression at any time.

Filgrastim is mandatory for primary prevention of neutropenia. Submit a special authority request to Pharmacare for filgrastim coverage.

CYCLE 1:

Drug	Dose	BC Cancer Administration Guideline
riTUXimab**†	375 mg/m^2 on Day 1	IV in 250 to 500 mL NS over 1 hour 30 min to 8 hours*
polatuzumab vedotin¥	1.8 mg/kg on Day 2	IV in 50 to 250 mL NS over 1 hour and 30 minutes (with 0.2 micron in-line filter)
bendamustine	90 mg/m^2 on Days 2 and 3	IV in 250 to 500 mL NS over 1 hour
filgrastim	5 mcg/kg daily for 5 days starting on Day 7. 300 mcg: up to 75 kg 480 mcg: 76kg to 110 kg 600 mcg: greater than 110kg	subcutaneous

CYCLES 2 to 6:

Drug	Dose	BC Cancer Administration Guideline
polatuzumab vedotin¥	1.8 mg/kg on Day 1	IV in 50 to 250 mL NS over 30 minutes (if no prior reaction) with 0.2 micron in-line filter
bendamustine	90 mg/m^2 on Days 1 and 2	IV in 250 to 500 mL NS over 1 hour
riTUXimab**†	375 mg/m^2 on Day 1 or 2 whenever possible but not later than 72 h after day 1 of polatuzumab vedotin	IV in 250 to 500 mL NS over 1 hour 30 min to 8 hours*
	If IV infusion tolerated (no severe reactions requiring early termination), subsequent doses can be given by subcutaneous administration	
	1400 mg (fixed dose in 11.7 mL) on Day 1 or 2 whenever possible but not later than 72 h after day 1 of polatuzumab vedotin	Subcutaneous over 5 minutes into abdominal wall‡ Observe for 15 minutes after administration
filgrastim	5 mcg/kg daily for 5 days starting on Day 7. 300 mcg: up to 75 kg 480 mcg: 76kg to 110 kg 600 mcg: greater than 110kg	subcutaneous

*Start the (first dose) initial infusion at 50 mg/h and, after 1 hour, increase by 50 mg/h every 30 minutes until a rate of 400 mg/h is reached. ***For all subsequent treatments***, infuse 50 mL (or 100 mL) of the dose over 30 minutes then infuse the remaining 200 mL (or 400 mL) (4/5) over 1 hour (total infusion time = 1 hour 30 min). Development of an allergic reaction may require a slower infusion rate. See hypersensitivity below.

**The risk of cytokine release syndrome is low but is increased when the peripheral blood lymphocyte count is greater than 30 to 50 x 10^9 /L. While there is no requirement to withhold riTUXimab based on lymphocyte count, clinicians may wish to pre-medicate patients with high tumour burden with steroids prior to riTUXimab infusion or omit the riTUXimab from the first cycle of treatment.

†Patients must receive first dose by IV infusion (using the IV formulation) because the risk of reactions is highest with the first infusion. IV administration allows for better management of reactions by slowing or stopping the infusion.

‡During treatment with subcutaneous riTUXimab, administer other subcutaneous drugs at alternative injection sites whenever possible.

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¥Monitor for infusion--related reactions with polatuzumab vedotin during the infusion and for at least 90 minutes following completion of the initial dose. Observe for 90 minutes for fever, chills, rigors, hypotension, nausea or other infusion associated symptoms. If prior infusion was well tolerated, subsequent doses may be administered over 30 minutes and patients should be monitored during the infusion and for at least 30 minutes after completion of infusion.

Vitals monitoring for polatuzumab vedotin:

For infusions on Cycle 1
Vital signs including temperature, blood pressure, respiratory rate, and pulse rate immediately before the start of infusion, every 30 minutes during the infusion, at the end of infusion and every 30 minutes for 90 minutes following completion of dosing at Cycle 1.

For subsequent infusions
Vital signs including temperature, blood pressure, respiratory rate, and pulse rate immediately before the start of infusion, at the end of infusion and as needed.

DOSE MODIFICATIONS:

Dose Levels for Toxicities

Drug	Dose Level 0 (Starting Dose)	Dose Level –1	Dose Level –2
bendamustine	90 mg/m^2	70 mg/m^2	50 mg/m^2

A. Dose Modifications for HEMATOLOGIC Toxicity

No dose modifications for polatuzumab vedotin or riTUXimab for hematologic toxicity

ANC (x10^9/L)	Bendamustine
Greater than or equal to 1.0	100%
Less than 1.0 **First occurrence** without infection or fever	• Delay until recovery • ↓ 1 dose level or consider increasing cycle interval to 28 days • If primary cause of neutropenia is thought to be lymphoma infiltration into the bone marrow, physician may elect not to reduce dose
Less 1.0 **Repeat occurrence***	• Delay until recovery • ↓ 1 dose level from previous level (maximum of 2 dose reductions allowed) or consider increasing interval to 28 days

*If persistent neutropenia (ANC less than 1.0 x 10^9/L) despite GCSF support and after 2 bendamustine dose reductions, consider discontinuing bendamustine or increasing the duration of filgrastim.

Platelets (x10^9/L)	Bendamustine
Greater than or equal to 50	100%
Less than 50 **First occurrence**	• Delay until platelets greater than 75 x 10^9/L • ↓ 1 dose level or consider increasing interval to 28 days • If thrombocytopenic at baseline and the primary cause of thrombocytopenia is thought to be lymphoma infiltration into the bone marrow, physician may elect not to reduce dose
Less than 50 **Repeat occurrence****	• Delay until platelets greater than 75 x 10^9/L • ↓ 1 dose level from previous level (maximum of 2 dose reductions allowed) or consider increasing interval to 28 days

** If platelets continue to be less than 50 x 10^9/L following two bendamustine dose reductions, consider discontinuing bendamustine.

B. Dose Modifications for NON-HEMATOLOGIC Toxicity

1. Peripheral Neuropathy

Grade	Peripheral neuropathy
1	Asymptomatic, loss of deep tendon reflexes or paresthesia
2	Moderate symptoms, limiting instrumental ADLs
3	Severe symptoms, limiting self care ADL
4	Life-threatening consequences eg. paralysis, urgent intervention indicated

No dose reductions for bendamustine or riTUXimab for peripheral neuropathy.

Prior to a Cycle (Day 1)	Dose delay	Polatuzumab vedotin only	
		Current dose (mg/kg)	Dose for subsequent cycles (mg/kg)
Grade 1	No delay	1.8	1.8
Grade 2 or 3 peripheral neuropathy¥ (PN)	Delay all drugs until recovered to less than or equal to Grade 1. If delay is prolonged, can consider proceeding with bendamustine and rituximab until recovery)	1.8	1.4 (permanent dose reduction).
		1.4	discontinue
Grade 4 peripheral neuropathy¥	Discontinue polatuzumab vedotin permanently Continue bendamustine and rituximab		

¥ Note: Polatuzumab vedotin should be permanently discontinued if any of the following occur:

- Grade 4 peripheral neuropathy
- Grade 3 peripheral neuropathy that leads to a treatment delay of 14 days or more and does not improve to less than or equal to grade 1 within 14 days
- Recurrence of greater than or equal to grade 2 peripheral neuropathy at the reduced dose

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Primary prophylaxis with filgrastim is required.
2. **Extravasation**: Polatuzumab vedotin causes pain and may, rarely, cause tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.

3. **Thrombocytopenia**: Support with platelet transfusion may be required.
4. **Peripheral neuropathy** including sensory and/or motor neuropathy may develop in patients receiving polatuzumab vedotin. They are generally reversible, but it is not known if full reversibility can be expected or predicted. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, gait disturbance, loss of balance or weakness and institute dose modifications accordingly
5. **Hepatitis B Reactivation**: All lymphoma patients should be tested for both HBsAg and HBcoreAb. If either test is positive, such patients should be treated with lamiVUDine during chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.
6. **Hepatotoxicity** has been observed in patients treated with polatuzumab vedotin, including elevations in transaminases and/or bilirubin. It should be avoided in patients with moderate or severe hepatic impairment (total bilirubin greater than 1.5 x ULN, AST/ ALT greater than 2.5 x ULN) as they are likely to have increased exposure to MMAE, potentially increasing their risk of adverse reactions. Any case involving an increase in hepatic transaminase greater than 3 x baseline AND an increase in direct bilirubin greater than 2 x ULN, WITHOUT any findings of cholestasis or jaundice or signs of hepatic dysfunction AND other contributing factors is suggestive of potential drug related toxicity and polatuzumab vedotin should be discontinued. Use of bendamustine in patients with moderate to severe impairment (AST/ALT 2.5 to 10x ULN and total bilirubin greater than 1.5 x ULN) is not recommended.
7. **Renal toxicity.** Elevations in creatinine has been observed in patients treated with polatuzumab vedotin. If creatinine rises to greater than 3 times baseline, delay polatuzumab vedotin until recovery to baseline Consider dose reduction at physician discretion.
8. **Infusion Reactions and Hypersensitivity** have been reported in patients receiving polatuzumab vedotin bendamustine and rituximab. Commonly experienced events include nausea, vomiting, chills, fever, pruritus, hypotension, flushing and other symptoms. Bendamustine can also cause allergic type reactions during the IV infusion such as fever, chills, pruritus and rash. Severe anaphylactic and anaphylactoid reactions have occurred rarely, particularly in the second and subsequent cycles of therapy. If an allergic reaction occurs, stop the infusion and the physician in charge should determine a safe time and rate to resume the infusion. Consider pre-treatment with antihistamines, antipyretics and corticosteroids for patients experiencing Grade 1 or 2 infusion reactions; consider discontinuing treatment for patients experiencing Grade 3 or 4 infusion reactions. See BC Cancer Hypersensitivity Guidelines and SCDRUGRX for management guidelines
9. **riTUXimab Hypersensitivity:** Refer to BC Cancer Hypersensitivity Guidelines. Rituximab can cause allergic type reactions during the IV infusion such as hypotension, wheezing, rash, flushing, alarm, pruritus, sneezing, cough, fever or faintness. For the first dose, patients are to be under constant visual observation during all dose increases and for 30 minutes after infusion is completed. For all subsequent doses, constant visual observation is not required. Vital signs are not required unless symptomatic. Because transient hypotension may occur during infusion, consider withholding antihypertensive medications 12 hours prior to riTUXimab infusion. If an allergic reaction occurs, stop the infusion and the physician in charge should determine a safe time and rate to resume the infusion. A reasonable guideline is as follows. After recovery of symptoms, restart riTUXimab infusion at

one infusion rate below the rate at which the reaction occurred and continue with escalation of infusion rates on the appropriate schedule above. If the infusion must be stopped a second time, restart after clearance of symptoms, at one infusion rate lower and continue at that rate without further escalation. Fatal cytokine release syndrome can occur (see below).

10. **Tumour Lysis Syndrome**: Tumor lysis syndrome has been associated with polatuzumab vedotin, bendamustine and rituximab, possibly leading to acute renal failure and death. Usual onset occurs during the first cycle. Maintain adequate volume status and monitor blood chemistry, including potassium and uric acid levels as required. Patients who are considered to have high tumour burden (e.g. lymphocyte count greater than or equal to 25 x 10^9/L or bulky lymphadenopathy) may be at a higher risk for tumour lysis and may require tumour lysis prophylaxis and monitoring, as per physician discretion. Allopurinol has been used, but the concomitant use of bendamustine and allopurinol can cause increased risk of severe skin toxicity.
11. **Infection,** including pneumonia and sepsis has been reported. Antiviral coverage for HSV, VZV and anti-pneumocystis prophylaxis are required during treatment and continue for at least 6 months after completion.
12. **Drug Interactions**: CYP1A2 inhibitors can potentially decrease plasma concentration of bendamustine. CYP1A2 inducers can potentially increase plasma concentration of bendamustine. Strong CYP3A4 inhibitors may increase unconjugated MMAE AUC which may increase polatuzumab vedotin toxicities. Strong CYP3A4 inducers may decrease the AUC of unconjugated MMAE; clinical significance unknown.
13. **Skin Reactions**: Rash, toxic skin reactions and bullous exanthema have been reported with bendamustine. They may be progressive and increase in severity with further treatment. Monitor closely. If skin reactions are severe or progressive, consider withholding or discontinuing bendamustine.
14. **Fatal Cytokine Release Syndrome** has been reported with riTUXimab. It usually occurs within 1-2 hours of initiating the first riTUXimab infusion. Initially, it is characterised by severe dyspnea (often with bronchospasm and hypoxia) in addition to fever, chills, rigors, urticaria and angioedema. Pulmonary interstitial infiltrates or edema visible on chest x-ray may accompany acute respiratory failure. There may be features of tumour lysis syndrome such as hyperuricemia, hypocalcemia, acute renal failure and elevated LDH. For severe reactions, stop the infusion immediately and evaluate for tumour lysis syndrome and pulmonary infiltration. Aggressive symptomatic treatment is required. The infusion can be resumed at no more than one-half the previous rate once all symptoms have resolved, and laboratory values and chest x-ray findings have normalized. The risk of cytokine release syndrome is low but is increased when the peripheral blood lymphocyte count is greater than 30-50 x 10^9/L. While there is no requirement to withhold riTUXimab based on lymphocyte count, clinicians may wish to pre-medicate patients with high tumour burden with steroids prior to riTUXimab infusion or omit the riTUXimab from the first cycle of treatment.
15. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported with riTUXimab. If such a reaction occurs, riTUXimab should be discontinued.
16. **Gastrointestinal Obstruction or Perforation:** There have been rare reports of gastrointestinal obstruction or perforation, sometimes fatal, when riTUXimab is given in combination with other chemotherapy, occurring 1 to 12 weeks after treatment. Symptoms possibly indicative of such complications should be carefully investigated and appropriately treated.

17. **Medication Safety:** riTUXimab is formulated differently for IV versus subcutaneous administration. Use caution during prescribing, product selection, preparation and administration. IV formulation is supplied as 10 mg/mL solution which must be diluted prior to administration. Subcutaneous formulation is supplied as a fixed dose of 1400 mg/11.7 mL ready-to-use solution which contains hyaluronidase to facilitate injection.
18. **Increased drug absorption by hyaluronidase:** other subcutaneous medications should not be injected at the same site as subcutaneous riTUXimab. Increased systemic effects are unlikely to be clinically significant with topical applications of EMLA, hydrocortisone, or diphenhydramine

Call Dr. Laurie H. Sehn or tumor group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Sehn LH, Herrera AF, Flowers CT, et al. Polatuzumab vedotin in relapsed or refractory diffuse Large B-cell Lymphoma. J Clin Oncol 2020; 38(2):155-65.
2. Hoffmann-La Roche Limited. POLIVY® product monograph. Mississauga, ON; July 2021