BC Cancer Protocol Summary for Treatment of Lymphoma with DOXOrubicin, Cyclophosphamide, prednisone, riTUXimab and Polatuzumab Vedotin

Protocol Code	*LYPOLARCHP*
Tumour Group	*Lymphoma*
Contact Physician	*LY Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Previously untreated CD20-positive diffuse large B-cell lymphoma (DLBCL) classified as activated B cell-like (ABC) subtype confirmed with gene expression profiling (GEP) including:
  - DLBCL NOS,
  - High grade B-cell lymphoma,
  - Epstein-Barr virus (EBV)-positive DLBCL NOS
  - T-cell/histiocyte rich LBCL
  - Transformed DLBCL

Patients should have:

- International Prognostic Index (IPI) score of 2 to 5
- Good performance status

Note:

- Patients who started treatment with LYCHOPR prior to 1 Feb 2026, may switch to LYPOLARCHP to complete a total of 6 cycles provided that:
  - all LYPOLARCHP eligibility criteria are met, and
  - no more than 2 cycles of LYCHOPR have been administered, and
  - no progression has occurred
- Patients may receive 1 cycle of LYCHOPR while awaiting diagnostic testing, then switch to LYPOLARCHP upon confirmation of eligibility to complete a total of 6 cycles
- Patients with non germinal centre B cell-like (non-GCB) subtype by immunohistochemistry (IHC) may receive 1 cycle of LYPOLARCHP, while awaiting GEP results
- If GEP testing not feasible due to lack of tissue availability or test failure, then patients with non-GCB subtype by IHC may receive a total of 6 cycles

EXCLUSION:

Patient must not have:

- Diagnosis of large B-cell lymphoma not classified as ABC subtype (e.g. GCB or indeterminate)

CAUTIONS:

- Congestive cardiac failure requiring current treatment (LYPOLARCHP can be used but DOXOrubicin should be omitted, see cardiotoxicity below)

TESTS:

- Baseline (required before first treatment): CBC & Diff, total bilirubin, ALT
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): HBsAg, HBsAb, HBcoreAb
- Baseline, if clinically indicated: LDH, alkaline phosphatase, creatinine
- Before each treatment: CBC & Diff, total bilirubin, ALT
- If clinically indicated: LDH, alkaline phosphatase, creatinine, HBV viral load (see protocol SCHBV)

PREMEDICATIONS:

- Antiemetic protocol for highly 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 650-975 mg PO *prior to riTUXimab IV and then* q 4 h during the IV infusion, *if the infusion exceeds 4 h*
  predniSONE as ordered for the LYPOLARCHP protocol

- For subcutaneous injection:
  diphenhydrAMINE 50 mg PO *prior to riTUXimab subcutaneous*
  acetaminophen 650-975 mg PO *prior to riTUXimab subcutaneous*
  predniSONE as ordered for the LYPOLARCHP protocol

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 30 minutes prior to infusion
  - acetaminophen 650 to 975 mg PO 30 minutes prior to infusion

SUPPORTIVE MEDICATIONS:
Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.

TREATMENT:

Cycle 1:

Drug	Dose	BC Cancer Administration Guideline
predniSONE	100 mg on Days 1 to 5	PO in the morning with food (the predniSONE dose for that day should be taken on the morning of the riTUXimab and polatuzumab vedotin infusions)
DOXOrubicin	50 mg/m^2 on Day 1	IV push
cyclophosphamide	750 mg/m^2 on Day 1	IV in 100 to 250 mL NS over 20 min to 1 hour
polatuzumab vedotin¥	1.8 mg/kg on Day 1	IV in 50 to 250 mL NS over 1 hour and 30 minutes (with 0.2 micron in-line filter)
riTUXimab**†	375 mg/m^2 on Day 2 whenever possible but no later than 72 hours after Day 1.	IV in 250 to 500 mL NS over 1 hour 30 min to 8 hours*
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
predniSONE	100 mg on Days 1 to 5	PO in the morning with food (the predniSONE dose for that day should be taken on the morning of the riTUXimab and polatuzumab vedotin infusions)
DOXOrubicin	50 mg/m^2 on Day 1	IV push
cyclophosphamide	750 mg/m^2 on Day 1	IV in 100 to 250 mL NS over 20 min to 1 hour
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
riTUXimab**†	375 mg/m^2 on Day 1 whenever possible but no later than 72 hours after Day 1	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 whenever possible but no later than 72 hours after Day 1.	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. IV first dose should also be given to patients previously treated more than 6 months ago.

‡During treatment with subcutaneous riTUXimab, administer other subcutaneous drugs at alternative injection sites whenever possible. If restarting more than 6 months from prior subcutaneous rituximab, give first dose by IV infusion (using the IV formulation).

¥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 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 immediately before the start of infusion, at the end of infusion and as needed.

Repeat every 21 days for 6 cycles.

DOSE MODIFICATIONS:

There are no dose modifications for riTUXimab. Toxicity is managed by treatment delay or other measures.

Polatuzumab Vedotin Dose Reductions:

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
1.8 mg/kg	1.4 mg/kg	1.0 mg/kg	Discontinue

DOXOrubicin and Cyclophosphamide Dose Reductions:

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
100%	75%	50% or discontinue	Discontinue

1. **Elderly Patients (age greater than 75 years)**:

Cycle 1 doses of cyclophosphamide and DOXOrubicin should be administered at 75% doses. Further treatment should be given at the maximum dose tolerated by the patient, trying to escalate up to full 100% doses, but using the baseline experience with the 75% doses to guide these decisions.

2. **Hematological**:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Management
Greater than or equal to 1.0	and	Greater than or equal to 50	▪ Continue with current dose
Less than 1.0, with or without infection or fever	and /or	Less than 50	▪ Delay treatment until ANC improves to 1.0 or higher and platelets improve to 75 or higher ▪ If improvement occurs on or before Day 7, resume all treatment without any dose reductions ▪ If improvement occurs after Day 7, resume all treatment and consider dose reduction of cyclophosphamide and/or DOXOrubicin to next lower dose level

3. **Hepatotoxicity**:

For DOXOrubicin:

Total bilirubin (micromol/L)	Dose Modification
2-35	100%
35-85	50%
Greater than 85	Omit DOXOrubicin. ***ADD*** cyclophosphamide 350 mg/m^2 to the dose already planned.

Note: This adjustment is only necessary for the initial treatment. After the hyperbilirubinemia has resolved, adjustment is only necessary if overt jaundice re-occurs. Serum bilirubin does not need to be requested before each treatment.

For polatuzumab vedotin:
Avoid use in moderate to severe hepatic impairment (total bilirubin greater than 1.5 x ULN).

4. **Peripheral Neuropathy:** for polatuzumab vedotin

Grade	Symptoms
1	Asymptomatic, loss of deep tendon reflexes or paresthesia (if sensory neuropathy), clinical or diagnostic observations only (if motor neuropathy)
2	Moderate symptoms, limiting instrumental ADLs
3	Severe symptoms, limiting self care ADL, assistive device indicated (if motor neuropathy)
4	Life-threatening consequences e.g. paralysis, urgent intervention indicated

Prior to a Cycle (Day 1)	Management
Grade 1	▪ Continue with current dose
Grade 2	▪ Sensory neuropathy: o Reduce polatuzumab vedotin by one dose level. o If Grade 2 persists or recurs at the start of a future cycle, reduce polatuzumab vedotin dose by another dose level. o If already at 1.0 mg/kg and Grade 2 occurs at Day 1 of a future cycle, discontinue polatuzumab vedotin ▪ Motor neuropathy: o Withhold polatuzumab vedotin until improvement to Grade 1, then reduce dose by one dose level o If already at 1.0 mg/kg and Grade 2 occurs at Day 1 of a future cycle, discontinue polatuzumab vedotin
Grade 3	▪ Sensory neuropathy: o Withhold polatuzumab vedotin until improvement to Grade 2, then reduce polatuzumab vedotin dose by one dose level o If already at 1.0 mg/kg, discontinue polatuzumab vedotin ▪ Motor neuropathy: o Withhold polatuzumab vedotin until improvement to Grade 1, then restart at next lower dose level o If already at 1.0 mg/kg and Grade 2 to 3 recurs, discontinue polatuzumab vedotin
Grade 4	Discontinue polatuzumab vedotin permanently

5. **Cardiotoxicity**: DOXOrubicin only:

When DOXOrubicin cannot be used due to proven cardiac dysfunction, it can be replaced by etoposide 50 mg/m^2 IV on day 1 (Use non-DEHP Equipment with in-line filter), 100 mg/m^2 PO on day 2 and 3.
NOTE: When doxorubicin is replaced with etoposide, administer etoposide IV in place of doxorubicin (follow same sequence).

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **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.
3. **Cardiac Toxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction. Cardiac assessment is recommended if patient has received greater than or equal to 300 mg/m^2 of doxorubicin. (BC Cancer Cancer Drug Manual). Work-up may include an assessment of cardiac ejection fraction, and cardiac oncology referral if necessary.
4. **Extravasation**: DOXOrubicin causes pain and tissue necrosis if extravasated. Polatuzumab vedotin causes pain and may, rarely, cause tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
5. **Peripheral neuropathy** including sensory and/or motor neuropathy may develop in patients receiving polatuzumab vedotin. Peripheral neuropathy is 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
6. **Infusion Reactions and Hypersensitivity** have been reported in patients receiving polatuzumab vedotin and rituximab. If applicable, monitor etoposide infusion for the first 15 minutes for signs of hypotension. 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 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). See BC Cancer Hypersensitivity Guidelines.
7. **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.

8. **Fatal Cytokine Release Syndrome** has been reported. It usually occurs within 1-2 hours of initiating the first 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 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.
9. **Tumour Lysis Syndrome**: Tumor lysis syndrome has been associated with polatuzumab vedotin and rituximab. 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 may be at a higher risk for tumour lysis and may require tumour lysis prophylaxis and monitoring, as per physician discretion.
10. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, riTUXimab should be discontinued.
11. **Hepatitis B Reactivation:** See SCHBV protocol for more details.
12. **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.
13. **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.
14. **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.

Contact the LY Systemic Therapy physician at your regional cancer centre or LY Systemic Therapy Chair with any problems or questions regarding this treatment program.

References:

1. Tilly H, Morschhauser F, Sehn et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-cell Lymphoma. N Engl J Med 2022;386: 351-363.
2. Polatuzumab Vedotin (Polivy) Canada's Drug Agency (CDA-AMC) Reimbursement Recommendation. Canadian Journal of Health Technologies. July 2025; 5(7): 1-29.