BC Cancer Protocol Summary for the Treatment of Non-Hodgkin Lymphoma with Lenalidomide and riTUXimab

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

ELIGIBILITY:

Patients must have:

- Relapsed or refractory Grade 1 to 3a follicular lymphoma or marginal zone lymphoma, and
- At least one prior line of treatment, and
- Registration of the prescribing physician and patient with the RevAid Program (www.RevAid.ca) is required

EXCLUSIONS:

Patients must not have:

- Clinical evidence of transformed lymphoma,
- Grade 3b follicular lymphoma,
- Pregnant or breastfeeding status, or
- riTUXimab-refractory status, defined as patients who did not respond to a prior riTUXimab-containing regimen or those who have previously relapsed within 6 months of the last riTUXimab dose.

CAUTIONS:

- Platelet count less than 50 x 10^9/L
- ANC less than 1.0 x 10^9/L. Consider giving filgrastim
- Calculated creatinine clearance less than 30 mL/minute

TESTS:

- Baseline (required before first treatment): CBC & Diff, creatinine, ALT, total bilirubin, uric acid, LDH. If female of child-bearing potential (FCBP): Confirm negative pregnancy test results via a quantitative beta-hCG blood test obtained 7 to 14 days and 24 hours prior to initial prescription.
- 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, TSH
- Every 4 weeks (required before treatment): CBC & Diff, creatinine, ALT, total bilirubin, LDH. If female of childbearing potential: quantitative beta-hCG blood test.
- Cycle 1 prior to Days 8, 15, 22: CBC & Diff
- Every three months (required, but results do not have to be available to proceed with treatment): TSH
- If female of childbearing potential: Every week for 4 weeks during cycle 1: quantitative beta-hCG blood test. Provider responsible for checking results.

- If clinically indicated during treatment: CBC & Diff weekly, HBV viral load (see protocol SCHBV)

PREMEDICATIONS:

- No premedication is required for lenalidomide.

For riTUXimab portion:
(Note: patients should bring their own supply)

- 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 hours*
  acetaminophen 650 to 975 mg PO *prior to riTUXimab IV and then* q 4 h during the IV infusion, *if the infusion exceeds 4 hours*

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

SUPPORTIVE MEDICATIONS:

- Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.
- Antiviral prophylaxis against reactivation of varicella-zoster virus (VZV) is recommended prior to initiating lenalidomide. Patients should take valACYclovir 500 mg PO daily.
- ASA (enteric coated), warfarin, direct oral anticoagulant (DOAC) or low molecular weight heparin (LMWH) subcutaneously daily continuing for the duration of treatment with lenalidomide.

TREATMENT (1 cycle = 28 days):

Cycles 1 to 5:

Drug	Dose	BC Cancer Administration Guideline
riTUXimab**†	**Cycle 1**: Weekly on Days 1, 8, 15 and 22 **Cycles 2 to 5**: Day 1 only	
	375 mg/m^2	IV in 250 to 500 mL NS over 90 minutes 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)	Subcutaneous over 5 minutes into abdominal wall‡ Observe for 15 minutes after administration
lenalidomide	20 mg¥ once daily for 21 days (Days 1 to 21)	PO, in the evening may be preferred

*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. The subsequent infusions may start at 100 mg/h and be increased by 100 mg/h every 30 minutes until a rate of 400 mg/h is reached. 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).

¥Lenalidomide 10 mg if eGFR or creatinine clearance is 30 to 59 mL/minute. May escalate to 15mg after 2 cycles if well tolerated and no Grade 3 or 4 toxicities (see Dose Modifications).

Repeat every 28 days for 5 cycles.

Cycles 6 to 12:

Drug	Dose	BC Cancer Administration Guideline
lenalidomide	20 mg* once daily for 21 days (Days 1 to 21)	PO, in the evening may be preferred

*Lenalidomide 10 mg if eGFR or creatinine clearance is 30 to 59 mL/minute. May escalate to 15mg after 2 cycles if well tolerated and no Grade 3 or 4 toxicities (see Dose Modifications).

Repeat every 28 days for 7 cycles (i.e. Cycles 6 to 12), unless disease progression or unacceptable toxicity.

DOSE MODIFICATIONS:

For rituximab: No dose reductions are recommended for riTUXimab.

For lenalidomide:

NB: Use one of the 20 mg, 15 mg, 10 mg, 5 mg, or 2.5 mg capsules for dosing. The use of two 5 mg capsules for a 10 mg dose etc., has significant budgetary implications.

Lenalidomide dose levels†:

Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3	Dose Level -4
20 mg	15 mg	10 mg	5 mg	2.5 mg*

*if starting dose was 10 mg

†dosing for 21 days (Days 1 to 21) of each 28-day cycle

1. Hematological: lenalidomide

ANC (x10^9/L)		Platelets (x10^9/L)	Lenalidomide Dose
Greater than or equal to 1.0	and	Greater than or equal to 50	Continue current dose
0.5 to 0.99† One isolated lab value only	and	Greater than or equal to 50	Notify provider. Continue current dose and monitor CBC & Diff weekly†
0.5 to 0.99† Sustained greater than or equal to 7 days OR febrile neutropenia (ANC less than 1.0 with oral temperature greater than or equal to 38.5° Celsius) OR Less than 0.5	or	Less than 50*	**Hold** (interrupt dose) and follow CDC & Diff weekly† until ANC greater than or equal to 1.0 and/or platelets greater than or equal to 50, then restart at next lower dose level

* follow CBC & Diff weekly.

† consider filgrastim if clinically indicated and filgrastim is available. Filgrastim is not covered as a benefit drug by BC Cancer.

2. Renal dysfunction: lenalidomide

Estimated GFR (eGFR)* or creatinine clearance (mL/min)	Lenalidomide Dose
Greater than or equal to 60	20 mg†
30 to 59	10 mg†‡

*as reported in patient's laboratory report

†dosing for 21 days (Days 1 to 21) of each 28-day cycle

‡dose can be escalated to 15 mg after 2 cycles if patient is tolerating the drug and no Grade 3 or 4 toxicities.

3. Tumour Flare Reaction (TFR): lenalidomide

Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy. The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.

Toxicity*	Lenalidomide Dose
Grade 1 to 2 Mild to moderate pain; pain interfering with function, but not interfering with ADL	▪ Continue current dose ▪ At the prescriber's discretion may initiate therapy with NSAIDs, limited duration corticosteroids, and/or narcotics
Grade 3 to 4 Severe pain; pain interfering with function and interfering with ADL, or disabling	▪ **Hold** (interrupt dose) and start therapy with NSAIDs, corticosteroids, and/or narcotics ▪ When symptoms resolve to Grade 1 or less, restart at same dose level for rest of current cycle.

4. Non-hematological/non-renal: lenalidomide

Toxicity	1st occurrence	2nd occurrence	3rd occurrence	4th or subsequent occurrence
Grade 3 or greater exfoliative rash, SJS, TEN	Discontinue			
Pneumonitis	For suspected pneumonitis, hold and investigate; discontinue if confirmed			
Grade 3-4 (any other toxicity)	Delay* then decrease by one dose level when dosing resumed at next cycle	Delay* then decrease by one dose level when dosing resumed at next cycle	Delay* then decrease by one dose level when dosing resumed at next cycle	Delay* then decrease by one dose level when dosing resumed at next cycle Do not dose below 2.5 mg

*stop treatment immediately and delay until toxicity resolved to Grade 0 to 2

PRECAUTIONS:

1. **Teratogenicity**: If lenalidomide is taken during pregnancy, it may cause severe birth defects or death to the fetus. Lenalidomide should never be used by females who are pregnant or who could become pregnant while taking the drug. Even a single dose taken by a pregnant woman may cause birth defects.
2. **Hepatotoxicity:** Hepatic failure, including fatal cases, have been reported in patients treated with lenalidomide in combination with dexamethasone during post-marketing. The mechanism of severe drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes and concomitant medications may be risk factors. Stop lenalidomide upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.
3. **Constipation**: Patients should be warned that constipation may occur in patients taking lenalidomide.
4. **Fatigue**: Patients should be warned that lenalidomide may cause fatigue.
5. **Hypothyroidism:** The use of lenalidomide may result in hypothyroidism. Treatment with thyroid replacement should be considered even for subclinical hypothyroidism. Lenalidomide can be continued if hypothyroidism can be easily managed.
6. **Venous thrombosis/embolism:** Lenalidomide with dexamethasone is known to increase the risk for thromboembolic disease. The risk is lower with lenalidomide monotherapy but ASA 81mg oral daily should be considered in all patients. For those with higher risk of thrombo-embolic disease full anti-coagulation should be considered.
7. **Skin Rashes**: Lenalidomide may cause skin rashes although in general it is not severe. Minor rashes can be treated with diphenhydrAMINE and/or steroid creams and lenalidomide can be continued. Moderate rashes may require holding lenalidomide until resolution of the rash. For more severe rashes (greater than or equal to Grade 3: severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering greater than or equal to 50% BSA) lenalidomide should be discontinued.
8. **Second Primary Malignancies (SPM):** SPM have been reported in the pivotal trial. The risk of occurrence of SPM must be taken into account before initiating treatment with lenalidomide. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.
9. **Hypersensitivity:** 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.

10. **Tumour Lysis Syndrome:** Tumor lysis syndrome has been associated with this treatment, 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. Allopurinol has been used, if clinically indicated.
11. **Fatal Cytokine Release Syndrome** has been reported. It usually occurs within 1 to 2 hours of initiating the first infusion. Initially, it is characterized 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.
12. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
13. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, riTUXimab should be discontinued.
14. **Hepatitis B Reactivation:** See SCHBV protocol for more details.
15. **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.
16. **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.
17. **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 the LY Systemic Therapy Chair with any problems or questions regarding this treatment program.

REFERENCES:

1. Leonard J, Trneny M, Izutsu K, et al; AUGMENT Trial Investigators. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. J Clin Oncol. 2019 May 10;37(14):1188-1199.
2. Leonard J, Trneny M, Offner F, et al. Five-Year Results and Overall Survival Update from the Phase 3 Randomized Study Augment: Lenalidomide Plus Rituximab (R^2) Vs Rituximab Plus Placebo in Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma. *Blood* 2022; 140 (Supplement 1): 561–563.
3. Lenalidomide Plus Rituximab Chemotherapy for Relapsed or Refractory Indolent B-Cell Non-Hodgkin Lymphomas. CADTH Health Technology Rapid Review. Nov 2021; 1(11): 1-58.