BC Cancer Protocol Summary for Maintenance riTUXimab for Indolent Lymphoma

Protocol Code	*LYRMTN*
Tumour Group	*Lymphoma*
Contact Physician	*Dr. Laurie Sehn*

ELIGIBILITY:

- Low grade or indolent B-cell lymphomas (e.g., follicular, marginal, lymphoplasmacytic), NOTE: Maintenance riTUXimab is not recommended for small lymphocytic lymphoma, which should be managed similarly to chronic lymphocytic leukemia or for follicular grade 3B lymphoma, which should be managed similarly to diffuse large B cell lymphoma.
  - After first line chemotherapy or chemotherapy for relapsed disease
  - Response status: At least a partial response must have occurred in response to the preceding chemotherapy
- Histology: Mantle Cell lymphoma, after first line chemotherapy only. NOTE: Maintenance riTUXimab is not recommended for relapsed Mantle Cell lymphoma.
  - Response status: At least a partial response must have occurred in response to the preceding chemotherapy

TESTS:
- Baseline (required before first treatment): CBC and diff, platelets, bilirubin, ALT
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with further treatment): hepatitis BsAg, hepatitis Bcore antibody, hepatitis C antibody (need not be repeated if tested previously).
- Before each treatment: CBC and diff, platelets

PREMEDICATIONS:

- 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 50 mg PO prior to riTUXimab (optional, to be used if previous maintenance doses of riTUXimab required more than 90 minutes to infuse)

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

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.

TREATMENT:

Note that the riTUXimab is given every 3 months, not weekly as is used when riTUXimab is used as single agent.

Drug	Dose	BC Cancer Administration Guideline
riTUXimab**†	375 mg/m^2	IV in 250 to 500 mL NS over 1 hour 30 min*
	If patient received IV riTUXimab in the past with no severe reactions requiring early termination, or if patient received subcutaneous riTUXimab in the past, maintenance 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

Repeat every 3 months for a total of 8 doses over 2 years

*Infuse the riTUXimab intravenously: initial 50 mL of 250 mL bag (or 100 mL of 500 mL bag) of the dose over 30 minutes then infuse the remaining 200 mL of 250 mL bag (or 400 mL of 500 mL bag) (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 and note optional use of prednisone for subsequent infusions.

**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.

† Please note, patients treated with maintenance riTUXimab have all received riTUXimab previously. If patient tolerated IV riTUXimab (no severe reactions requiring early termination) i.e., in active treatment or maintenance treatment or if patient tolerated subcutaneous riTUXimab previously i.e., active treatment or maintenance treatment, the patient can receive all subsequent treatment using subcutaneous riTUXimab.

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

DOSE MODIFICATIONS:

1. **Hematological**:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose Modification
less than 1.2	or	less than 75	delay x 1 week

PRECAUTIONS:

1. **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 maintenance dose # 1, patients are to be under constant visual observation during all dose increases and for 30 minutes after infusion completed. For all subsequent maintenance doses (# 2 to 8), 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 ½ the preceding infusion rate and continue with escalation of infusion rates every 30 minutes.
2. **Fatal Cytokine Release Syndrome.** Fatal cytokine release syndrome should be very rare or not seen at all in this patient population who lack circulating lymphoma cells and bulky disease. It usually occurs within 1 to 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 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.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively
4. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, riTUXimab should be discontinued.
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 riTUXimab maintenance 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 at least 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 riTUXimab maintenance.
6. **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.
7. **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 tumour group chair at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

REFERENCES:

1. Hochster HS, Weller E, Gascoyne RD, et al. Maintenance rituximab after CVP Results in superior clinical outcome in advanced follicular lymphoma (FL): Results of the E1496 Phase III Trial from the Eastern Cooperative Oncology Group and the Cancer and Leukemia Group B. Proc Am Soc Hematol 2005;106(11):abstract 349.
2. Van Oers MHJ, Van Glabbeke M, Teodorovic I, et al. Chimeric anti-CD20 monoclonal antibody (Rituximab;Mabthera) in remission induction and maintenance treatment of relapsed /resistant follicular non-hodgkin's lymphoma: final analysis of a Phase III Randomized Intergroup Clinical Trial. Proc Am Soc Hematol 2005;106(11):abstract 353.
3. Hiddemann W, Forstpointner R, Dreyling M, et al. Rituximab maintenance prolongs response duration after salvage therapy with R-FCM in patients with relapsed follicular lymphomas and mantle cell lymphomas: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). Proc Am Soc Hematol 2005;106(11):abstract 920.