BC Cancer Protocol Summary for the Treatment of Lymphoma with Single Agent riTUXimab

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

ELIGIBILITY:

- Follicular lymphoma progressive despite alkylating agents and purine analogues (fludarabine or cladribine)
- Newly diagnosed (within 6 months) asymptomatic advanced stage follicular lymphoma not requiring systemic chemotherapy
- Post-transplant lymphoproliferative disease
- Thrombocytopenia secondary to proven lymphocytic neoplasm
- Documented monoclonal IgM in the peripheral blood AND:
  1. Stocking-glove, gradually worsening, peripheral polyneuropathy;
  2. No documentable lymphoma in the marrow or lymph nodes.
  3. Prior assessment by a consultant neurologist with experience managing this syndrome who asserts that there is no alternative explanation for the polyneuropathy.
- First line treatment of autoimmune hemolytic anemia secondary to a lymphocytic neoplasm, including cold agglutinin disease
  - May retreat for disease relapsing greater than 12 months from first line treatment
- Four treatments with riTUXimab will be reimbursed by BC Cancer. For further treatments, a "CAP Request" must be approved.

TESTS:

- Baseline (required before first treatment): CBC & diff, platelets, creatinine, bilirubin, ALT, alkaline phosphatase, LDH
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with further treatment): HBsAg, HBcoreAb
- Before treatment #1 and #4: CBC & diff, platelets

PREMEDICATIONS:
(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 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*

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

Transfuse as needed to keep hemoglobin greater than 90 g/L, platelets greater than 20 x 10^9/L

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:

<table>
<tr><th>Drug</th><th>Dose</th><th>BC Cancer Administration Standard</th></tr>
<tr><td rowspan="3">riTUXimab**†</td><td>375 mg/m^2
See precautions below</td><td>IV in 250 to 500 mL NS (to maintain concentration range between 1 to 4 mg/mL) over 3 to 8 hours*
(dose may be divided equally into 2 x 250 mL NS)</td></tr>
<tr><td colspan="2">If IV infusion tolerated (no severe reactions requiring early termination), subsequent doses can be given by subcutaneous administration</td></tr>
<tr><td>1400 mg (fixed dose in 11.7 mL)
See precautions below</td><td>Subcutaneous over 5 minutes into abdominal wall‡
Observe for 15 minutes after administration</td></tr>
</table>

Repeat weekly x 4 doses.

*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.

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

DOSE MODIFICATIONS:

None.

PRECAUTIONS:

2. **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 (#2 to 4), 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.

3. **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.
4. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, riTUXimab should be discontinued.
6. **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 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 chemotherapy.
7. **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.
8. **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.
9. **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 Sehn or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.