

BC Cancer Protocol Summary for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Using Idelalisib and ritUXimab

Protocol Code	LYIDELAR
Tumour Group	Lymphoma
Contact Physician	Dr. Laurie Sehn Dr. Alina Gerrie

ELIGIBILITY:

- Relapsed/refractory CLL/SLL who have previously received at least one prior therapy
- Symptomatic disease requiring systemic therapy
- Not eligible for iBRUtinib, i.e., due to contraindications, side effects profile*

* Patients are eligible to receive either idelalisib with ritUXimab (LYIDELAR) OR iBRUtinib (LYIBRU) in the relapsed/refractory setting. LYIDELAR is not funded as a sequential treatment option for patients who have progressed on iBRUtinib, except as a bridge to allogeneic transplant in patients who have received first-line iBRUtinib for 17p deletion (ULYFIBRU) or high risk disease.

EXCLUSIONS:

- Active hepatitis or liver disease
- Evidence of ongoing systemic bacterial, fungal or viral infection
- Evidence of ongoing inflammatory bowel disease
- Caution in patients with baseline greater than 3 loose BM per day

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 cycle 2): HBsAg, HBcoreAb, Hepatitis C, and CMV-DNA by PCR
- CBC & diff, Platelets, bilirubin, ALT, CMV-DNA by PCR
 - First 3 months: every 2 weeks
 - Month 4-6: monthly
 - month 7 and subsequent: every 1 to 3 months, as clinically indicated

PREMEDICATIONS:

(Note: patients should bring their own supply)

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

For idelalisib portion:

- All patients should be advised to obtain an adequate supply of Loperamide (IMODIUM®) with explicit instructions for the management of diarrhea (see below).

SUPPORTIVE MEDICATIONS:

- If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive.
- Antibiotic prophylaxis for PCP/PJP (e.g., cotrimoxazole 1 SS tab daily) is required during treatment and for 2 to 6 months after discontinuation of treatment

TREATMENT:**Cycle 1**

Drug	Dose	BC Cancer Administration Guideline
idelalisib [‡]	150 mg twice daily continuously	PO
riTUXimab*	375 mg/m ² on day 1	IV in 250 to 500 mL NS over 1 hour 30 min to 8 hours**

Cycle 2, 3, 4, 5, 6, 7 and 8

Drug	Dose	BC Cancer Administration Guideline
idelalisib	150 mg twice daily continuously	PO
riTUXimab*, ***	500 mg/m ² on 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	
	1600 mg (fixed dose in 13.4 mL) on day 1	Subcutaneous over 7 minutes into abdominal wall [†] Observe for 15 minutes after administration

Repeat every 28 days. Maximum 8 cycles of riTUXimab. Discontinue rituximab or idelalisib if disease progression or unacceptable toxicity.

[‡]Idelalisib must be dispensed in the original container (i.e. 30 days supply)

*The risk of cytokine release syndrome is low but is increased when the peripheral blood lymphocyte count is greater than 30-50 x 10⁹/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.

**Start the riTUXimab (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 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 riTUXimab hypersensitivity below.

***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.

Cycle 9 and beyond

Drug	Dose	BC Cancer Administration Guideline
idelalisib	150 mg twice daily continuously	PO

Discontinue if disease progression or unacceptable toxicity.

DOSE MODIFICATIONS:

1. Hematological: idelalisib (for low counts due to treatment, not disease)

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	idelalisib Dose
greater than or equal to 1.0	and	greater than or equal to 50	150 mg BID
less than 1.0 and greater than or equal to 0.5*	or	less than 50 and greater than or equal to 25*	150 mg BID
less than 0.5**	or	less than 25**	delay until ANC greater than or equal to 0.5 and platelets greater than or equal to 25; then resume at 100 mg BID

*monitor CBC at least weekly until ANC is greater than or equal to 1 x 10⁹/L and platelets are greater than or equal to 50

**monitor CBC at least weekly until ANC is greater than or equal to 0.5 x 10⁹/L and platelets are greater than or equal to 25

2. Hepatic Impairment: idelalisib

Bilirubin (micromol/L)		AST or ALT	Dose
less than or equal to 3 x ULN*	or	less than or equal to 5 x ULN*	150 mg BID
greater than 3 - 10 x ULN*	or	greater than 5 to 20 x ULN*	Delay until less than or equal to 1 X ULN or less than or equal to baseline; then resume at 100 mg BID
greater than 10 x ULN	or	greater than 20 x ULN	Discontinue permanently

*monitor at least weekly until less than or equal to 1 X ULN

ULN = Upper Limit of Normal

3. Diarrhea/colitis: see Precautions

4. Pneumonitis: see Precautions

5. Dermatologic toxicity: see Precautions

6. **Renal impairment:** No adjustment recommended in mild or moderate renal impairment; no information found for severe renal impairment

PRECAUTIONS:

1. **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).
2. **Fatal Cytokine Release Syndrome** has been reported with riTUXimab. 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 $50 \times 10^9/L$. 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. Diarrhea/colitis with idelalisib:** Serious and/or fatal diarrhea and colitis has been reported. Time to onset of symptoms ranged from less than 1 month to 30 months after therapy initiation.

Grade	Description	Treatment
1	Increase of less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline	<ul style="list-style-type: none"> • May continue idelalisib • Start loperamide 4 mg po stat, followed by 2 mg q2h while awake and q4h during the night; maximum 16 mg/24 hours. • Continue around the clock until diarrhea free. • If diarrhea free greater than 12 h, stop loperamide • If new episode, retreat with loperamide
2	Increase of 4 to 6 stools per day over baseline; IV fluids indicated for less than 24 h; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living	Hold idelalisib and provide supportive care as above. Monitor at least weekly until resolved to grade 1 or less; resume idelalisib at same dose
3	Increase of greater than 6 stools per day over baseline; incontinence; IV fluids for greater than 24 h; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living.	Hold idelalisib and provide supportive care as above. If infection ruled out, consider addition of anti-inflammatory agent e.g., sulfasalazine, budesonide, prednisone; monitor at least weekly until resolved to grade 1 or less; resume idelalisib at 100 mg BID
4	Life-threatening consequences i.e., hemodynamic collapse	Discontinue idelalisib permanently

- 4. CMV-DNA by PCR positive:** Discontinue idelalisib treatment. Continue CMV-DNA by PCR testing until resolved and initiate CMV treatment and/or obtain infectious disease consult.
- 5. *Pneumocystis carinii/jirovecii* pneumonia (PCP/PJP) positive:** Discontinue idelalisib treatment and initiate appropriate treatment.

6. **Dermatologic toxicity:** Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) some fatal, have been reported. Monitor closely for dermatologic toxicity.

Grade	Description	Management
2		Hold idelalisib until resolved to Grade 1 or less, resume idelalisib at same dose
3	More extensive cutaneous/mucocutaneous reactions including exfoliative dermatitis, rash (generalized, erythematous, maculopapular, papular, pruritic, exfoliative) or requiring hospitalization and/or limiting self-care.	Hold idelalisib and monitor at least weekly until resolved to Grade 1 or less, resume idelalisib at 100 mg BID
	Severe cutaneous reaction or confirmed SJS/TEN (rare)	Discontinue idelalisib and riTUXimab and treat appropriately

7. **Pneumonitis:** Serious and/or fatal pneumonitis may occur. Monitor for pulmonary symptoms and bilateral interstitial infiltrates. May require therapy interruption or discontinuation. Symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates, or an oxygen saturation decrease of more than 5% should be promptly evaluated. Time to onset of symptoms ranged from less than 1 month to 15 months after therapy initiation. Interrupt therapy for suspected pneumonitis.
- If non-infectious etiology or association with idelalisib treatment is confirmed, discontinue idelalisib and administer corticosteroids as appropriate.
 - If infectious etiology is confirmed, treat infection per the facility's guidelines; monitor until resolved; then may resume idelalisib at 100 mg BID
8. **Infections:** Fatal and/or serious infection occurred in 21% to 36% of idelalisib-treated patients. These included atypical infections, such as CMV and PCP. Monitor for signs and symptoms of infection. Interrupt idelalisib if infection is suspected. Treat infection as per the facility's guidelines.
9. **Intestinal perforation:** Fatal and serious intestinal perforation has occurred in idelalisib-treated patients across clinical trials. Discontinue idelalisib for intestinal perforation.
10. **Gastrointestinal Obstruction or Perforation,** sometimes fatal, has also been reported rarely 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.
11. **Hepatotoxicity,** including fatal and/or serious occurred in 11% to 18% of idelalisib-treated patients. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue idelalisib as recommended, see dose modifications above.
12. **Drug Interactions:**
- Strong or moderate CYP 3A inhibitors may increase idelalisib concentration – avoid if possible
 - Strong CYP 3A inducers may decrease idelalisib concentration – avoid if possible
13. **Elderly Patients:** No specific dose adjustment is required for elderly patients (age 65 years or greater)
14. **Hepatitis B Reactivation:** All lymphoma patients should be tested for both HBsAg and HbCAb. If either test is positive, such patients should be treated with lamivudine during chemotherapy and for six months afterwards. 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 treatment.

- 15. Medication Safety:** ritUXimab IV is formulated differently for IV versus subcutaneous administration. Use caution during prescribing, product selection, preparation and administration.
- **The ritUXimab IV formulation** is supplied as **10 mg/mL solution** which must be diluted prior to administration.
 - **The ritUXimab subcutaneous formulation for CLL** is supplied as a fixed dose of **1600 mg/13.4 mL** ready-to-use solution which contains hyaluronidase to facilitate injection.
 - **The ritUXimab subcutaneous formulation for NHL** is supplied as a fixed dose of **1400 mg/11.7 mL** ready-to use solution which contains hyaluronidase to facilitate injection.
- 16. 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, Dr Alina Gerrie or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Brown JR, Byrd JC, Coutre SE, et al: Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110 δ , for relapsed/refractory chronic lymphocytic leukemia. *Blood* 2014;123:3390–3397.
2. Furman RR, Sharman JP, Coutre SE, et al: Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2014;370:997–1007.
3. Coutre SE, Furman RR, Sharman JP: Second interim analysis of a phase 3 study evaluating idelalisib and rituximab for relapsed CLL. *J Clin Oncol* 2014;32:5s:abstr 7012.
4. Ghia P, O'Brien SM, Hillmen P: Health-related quality of life (HRQL) impact of idelalisib (IDELA) in patients (pts) with relapsed chronic lymphocytic leukemia (CLL): Phase 3 results. *J Clin Oncol* 2014;32:5s:abstr 7099.
5. Coutre S, et al: Management of adverse events associated with idelalisib treatment: expert panel opinion. *Leuk Lymph* 2015;56(10):2779-2786.