BC Cancer Protocol Summary for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma Using Venetoclax and riTUXimab

Protocol Code	*LYVENETOR*
Tumour Group	*Lymphoma*
Contact Physicians	*Dr. Alina Gerrie, Dr. Laurie Sehn*
Contact Pharmacist	*Louisa Pang*

ELIGIBILITY:
- Relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma with or without chromosome 17p deletion, who have received at least one prior line of therapy
- Symptomatic disease requiring systemic therapy
- Patients who responded to anti-CD20 therapy (riTUXimab or oBINutuzumab) and with a treatment-free interval of 12 months or longer.
- Patients may be re-treated with LYVENETOR if they responded to and completed 2 years of LYVENETOR with at least 12 months of progression-free interval (remission).
- Patients currently receiving and responding to venetoclax monotherapy (ULYVENETO) but without achieving an adequate response. Venetoclax therapy is funded to a maximum of 2 years from the time when riTUXimab is added.

EXCLUSION:
- Creatinine clearance less than 30 mL/min (Cockcroft-Gault formula)*****
- Platelet count less than 30 x 10^9/L unless disease-related
- Absolute neutrophil count (ANC) less than 1.0 x 10^9/L may be considered a relative contraindication unless disease-related. Consider giving filgrastim.
- Bilirubin greater than 3 x upper limit of normal (ULN)
- AST and ALT greater than 3 x upper limit of normal (ULN)
- Active and uncontrolled autoimmune cytopenias
- Strong CYP3A4 inhibitors contraindicated during initiation and dose ramp-up phase of venetoclax

***In clinical trials, venetoclax was given to patients with a CrCl ≥ 50 mL/min. The Canadian product monograph decreases this threshold to ≥ 30 mL/min and mentions that a CrCl < 80 mL/min may be at an increased risk of tumour lysis syndrome (TLS).*

TESTS:
- **Baseline** (required within 72 h before first treatment): CBC and diff, potassium, calcium, magnesium, phosphate, uric acid, creatinine, bilirubin, ALT, LDH, albumin, pregnancy test prior to treatment in females of child-bearing potential
- **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
- **Prior to each dose increment during ramp-up phase (weeks 1 to 5)**: potassium, calcium, phosphate, uric acid, creatinine, LDH, albumin
- **Tumour lysis syndrome (TLS) monitoring:** potassium, calcium, phosphate, uric acid, creatinine, LDH, albumin based on tumour burden/TLS risk (See **Table 1** below). **TLS labs must be drawn STAT at a laboratory capable of rapid turnaround time (e.g. BC Cancer or hospital laboratory)**

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- **Post ramp-up phase (week 6 onwards), cycles 1 to 6:** CBC and diff, creatinine, bilirubin, ALT, prior to each cycle
- **Maintenance phase (cycle 7 onwards):** CBC and diff, creatinine, bilirubin, ALT, prior to each cycle but up to every 12 weeks at the physician's discretion

PREMEDICATIONS:

- Antiemetic protocol for Low emetogenic chemotherapy (see 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*
- 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.

Tumour lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has been reported in patients with medium or high tumour burden, but the incidence is reduced when the venetoclax dose is gradually increased. It is mandatory that electrolytes are monitored as recommended as TLS requires prompt management (**see Appendix I**). TLS can occur as early as 6-8 hours after the first dose and after each dose increase.

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Table 1: Recommended TLS monitoring and prophylaxis based on tumour burden:

Tumour Burden		Prophylaxis		Blood chemistry monitoring
		Hydration	**Anti-hyperuricemic**	**Setting and Frequency of Assessments**
Low	All LN* less than 5 cm **AND** ALC** less than 25 x 10^9/L	Oral: 1.5-2 L daily (8 glasses) Start 48 h prior to 1st dose and continue until the first week of venetoclax plus riTUXimab combination therapy is completed	allopurinol 300 mg PO daily until first week of venetoclax plus riTUXimab combination therapy completed and at physician discretion Start 72 h prior to 1st dose	**Outpatient:** • Pre-dose at each dose increment • 6 h and 24 h post first dose of 20 mg and 50 mg
Medium	Any LN* 5 cm to less than 10 cm **OR** ALC** greater than or equal to 25 x 10^9/L AND any LN less than 5 cm	Oral: 1.5-2 L daily (8 glasses) Start 48 h prior to 1st dose, and continue until first week of venetoclax plus riTUXimab combination therapy completed. Consider additional IV fluids as needed	allopurinol 300 mg PO daily until first week of venetoclax plus riTUXimab combination therapy completed and at physician discretion Start 72 h prior to 1st dose	**Outpatient:** • Pre-dose at each dose increment • 6h and 24 h post first dose of 20 mg and 50 mg • Consider hospitalization, if CrCl± 50-80 mL/min or if patient unable to drink 2 L of oral fluids at first dose of 20 mg and 50 mg (see High Risk category)

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Tumour Burden		Prophylaxis		Blood chemistry monitoring
		Hydration	**Anti-hyperuricemic**	**Setting and Frequency of Assessments**
High	Any LN* greater than or equal to 10 cm **OR** ALC** greater than or equal to 25 x 10^9/L AND any LN greater than or equal to 5 cm **OR** CrCl ± 30-50 mL/min	Oral: 1.5-2 L daily (8 glasses) Start 48 h prior to 1st dose, and continue until the first week of venetoclax plus riTUXimab combination therapy is completed IV NS (150 to 200 mL/h, as tolerated)	allopurinol 300 mg PO daily or TID until first week of venetoclax plus riTUXimab combination therapy completed and at physician discretion Start 72 h prior to 1st dose Consider rasburicase 3 mg IV x 1, may repeat Q24H prn **For patients on rasburicase, blood sample for uric acid must be placed on ice while awaiting assay**	**Inpatient:** First dose of 20 mg and 50 mg • Pre-dose, 4 h, 8 h, 12 h and 24 h post first dose of 20 mg and 50 mg **Outpatient:** Subsequent ramp-up doses • Pre-dose, 6 h and 24 h post dose

*LN= lymph node
**ALC= absolute lymphocyte count

±Cockcroft-Gault Equation:

$$\text{Estimated creatinine clearance: CrCl (mL/min)} = \frac{\text{N (140 - age) wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

N = 1.23 male
N = 1.04 female

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TREATMENT:

Phase	Timing	Drug	Dose	Route
Ramp-up (Monotherapy)	Week 1	venetoclax	20 mg daily	PO
	Week 2		50 mg daily	PO
	Week 3		100 mg daily	PO
	Week 4		200 mg daily	PO
	Week 5		400 mg daily	PO
Post ramp-up (Combination therapy)	Cycle* 1	venetoclax**	400 mg daily	PO
		riTUXimab	375 mg/m^2 Day 1	IV
	Cycles 2-6	venetoclax	400 mg daily	PO
		riTUXimab	500 mg/m^2 Day 1 *OR* 1600 mg Day 1	IV subcutaneous
Maintenance (Monotherapy)	Cycle 7 onwards	venetoclax	400 mg daily	PO

*Repeat every 28 days for 6 cycles.

**Ensure patient continues venetoclax therapy. Continue venetoclax 400 mg PO daily for a maximum of 2 years from the start of Cycle 1, Day 1 or until progressive disease, whichever occurs first.

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Ramp-up phase: Weeks 1-5 for low, medium, high risk TLS patients

Due to the risk of TLS, venetoclax dosing must be initiated carefully according to a 5 week ramp-up schedule up to the recommended dose of 400 mg PO once daily. Patients who show signs of TLS should have their dose held or if appropriate, kept the same for more than one week, until it is safe to dose escalate.

For low or medium risk TLS patients, the start date must be on a Thursday, and patients must pick up their venetoclax before Thursday.

For high risk TLS patients, start date is not restricted to a Thursday.

Week	Drug	Dose	BC Cancer Administration Guideline
1	venetoclax±	20 mg once daily	PO
2		50 mg once daily	
3		100 mg once daily	
4		200 mg once daily	
5		400 mg once daily	

± Lab results must be reviewed by pharmacist or MD, at the time points indicated below, before next dose can be authorized in person or by phone (**baseline labs** reviewed by **MD**, ramp-up and **TLS labs** reviewed by **pharmacist**):

- baseline, within 72 h of initiating treatment (day 1)
- before each dose increase at 50 mg, 100 mg, 200 mg and 400 mg (weeks 2 to 5)
- the day after the first 20 mg dose (24 h) and 50 mg dose (24 h) increase (weeks 1 and 2)
- for high risk patients only, 24 h after each additional dose increase (100 mg, 200 mg, and 400 mg, at weeks 3, 4 and 5)

For **low or medium risk TLS** patients, see **Appendix II, Table 1** for frequency of laboratory monitoring by pharmacist and patient follow-up schedule.

- If baseline labs adequate to proceed, patient to take first dose at **6 am on a Thursday in order for labs and RN phone call not to fall on a statutory holiday or weekend**
- Outpatient STAT **TLS labs** at **6 h** (12 noon) and at approximately **24 h** (8 am the second day)
- Results must be reviewed immediately by the pharmacist to assess for signs of TLS and determine whether prompt management or admission is required
- A pharmacist will contact the patient **after the 24 h lab results are reviewed** for instructions on whether to proceed with the next dose

For **high risk TLS** patients, see **Appendix II, Table 2** for frequency of laboratory monitoring by pharmacist and patient follow-up schedule.

- Treatment is not restricted to a Thursday start date. When patients are discharged home, supply enough tablets, so that the start day of a new dose occurs on a Thursday to ensure that labs will be monitored by pharmacy.

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Post ramp-up phase: Week 6 onwards for low, medium, high risk TLS patients

CYCLE 1:

Drug	Dose	BC Cancer Administration Guideline
venetoclax[T]	400 mg once daily	PO
riTUXimab**	375 mg/m^2 on day 1	IV in 250 to 500 mL NS over 1 hour 30 min to 8 hours*

[T] Ensure patient continues venetoclax therapy

*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 minutes). 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 with peripheral blood lymphocyte count is greater than 30 to 50 x 10^9/L. While there is no requirement to withhold riTUXimab based on the 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.

CYCLES 2 - 6:

Drug	Dose	BC Cancer Administration Guideline
venetoclax[T]	400 mg once daily	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

[T] Ensure patient continues venetoclax therapy

[†]Patients must receive first riTUXimab 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.

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DOSE INTERRUPTIONS AND MODIFICATIONS

For patients who require a dosing interruption of greater than 1 week during the first 5 weeks (dose ramp-up phase) or greater than 2 weeks after completing the dose ramp-up phase (combination therapy or maintenance phase), reassess risk of TLS to determine if re-initiation with a reduced dose (ie. all or some levels of dose ramp-up schedule) is necessary.

Table 1: Dose modifications during dose ramp-up phase

Venetoclax Dose at Interruption	Recommended Restarting Dose
20 mg once daily	10 mg once daily
50 mg once daily	20 mg once daily
100 mg once daily	50 mg once daily
200 mg once daily	100 mg once daily
300 mg once daily	200 mg once daily
400 mg once daily	300 mg once daily

- Once on maintenance dose, if a dose reduction to less than 100 mg is required for more than 2 weeks, discontinue venetoclax.
- Gradual dose increase following resolution of toxicity leading to a dose reduction may be considered if the patient is stable for 2 weeks on the lower dose; however, if the toxicity recurs, the patient may continue treatment on the lower dose
- riTUXimab should be discontinued if venetoclax is discontinued due to toxicity

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1. Tumour Lysis Syndrome (TLS)

- Changes in blood chemistries that require prompt management can occur as early as 6-8 hours after the first dose of venetoclax and after each dose increase
- Reduced renal function (CrCl ≤ 80mL/min) increases the risk for TLS
- Electrolytes must be corrected to within normal limits prior to proceeding with next dose of venetoclax or any dose increases during the 5-week ramp-up phase
- See **Appendix I** for TLS management strategies

Event	Action
Abnormal blood chemistry outside normal parameters for any of the following: • Elevated potassium • Low calcium (corrected for albumin*) • Elevated phosphate • Elevated uric acid • Serum creatinine increase of greater than 20 micromol/L from baseline	Hold venetoclax. Correct abnormalities. If resolved within 24-48h, resume at same dose.
Abnormal blood chemistry lasting more than 48 hours ***OR*** **Clinical TLS** (presence of **laboratory TLS**† plus any of the following): • cardiac arrhythmia, symptomatic hypocalcemia, seizures, increased creatinine level of 26.5 micromol/L or single value greater than 1.5 times ULN	Hold until resolved; then resume at a reduced dose (Refer to Table 1 above). Continue the reduced dose for 1 week before continuing with dose escalation.

* Corrected calcium (mmol/L) = total calcium (mmol/L) + (0.02 x [40 – albumin in g/L])

† **Laboratory TLS** (2 or more metabolic abnormalities during the same 24 hour period):
- Uric acid greater than or equal to 476 micromol/L
- Phosphate greater than or equal to 1.45 mmol/L
- Potassium greater than or equal to 6 mmol/L
- Corrected calcium less than or equal to 1.75 mmol/L

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2. Hematological and Non-Hematological Toxicities:

Toxicity	Venetoclax
ANC less than 1.0 x 10^9/L*†	Hold until ANC greater than or equal to 1.0 x 10^9/L, then resume at same dose
Platelets less than 30 x 10^9/L*	Hold until platelets greater than or equal to 50 x 10^9/L, then resume at same dose
Non-hematological toxicity grade 3* or 4*	Hold until improvement to grade 1 toxicity or baseline, then resume at same dose

*For 2nd and subsequent occurrences, resume treatment at a reduced dose following the above Dose Modification table.

- Consider discontinuing treatment for patients needing dose reduction to less than 100 mg once daily for more than 2 weeks.

† consider GCSF as clinically indicated

3. Hepatotoxicity

Hepatic Impairment	Dosing recommendation
Mild to moderate (total bilirubin greater than 1.5 to less than 3 x ULN)	No dose adjustment
Severe (total bilirubin greater than 3 x ULN)	Discontinue venetoclax and riTUXimab

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4. Drug Interactions

Venetoclax is a major CYP3A4 substrate and a substrate of P-glycoprotein. Concurrent administration of drugs which are **strong CYP 3A4 inhibitors are contraindicated at initiation and during the dose ramp-up phase** due to increased serum concentration of venetoclax and potential increased risk of TLS.

CYP3A4 inducers may decrease serum concentration of venetoclax.
P-glycoprotein inhibitors (P-gp) may increase serum concentration of venetoclax.

Agent Initiated	At initiation and dose ramp-up	After dose-ramp up is completed
Strong CYP3A4 inhibitors	Contraindicated	Reduce venetoclax dose by 75%. Resume standard venetoclax dosing 2 to 3 days after CYP3A4 inhibitor is discontinued.
Moderate CYP3A4 inhibitors	Avoid if possible, but if unavoidable, reduce venetoclax dose by at least 50%. Monitor patients more closely for signs of toxicities. Resume standard venetoclax dosing 2 to 3 days after CYP3A4 inhibitor is discontinued.	
Weak CYP3A4 inhibitors	No dose adjustment needed	
Strong and moderate CYP3A4 inducers	Avoid. Consider alternative treatments with less CYP3A4 induction.	
P-glycoprotein inhibitors	Avoid if possible, but if unavoidable, reduce venetoclax dose by at least 50%. Monitor patients more closely for signs of toxicities. Resume standard dosing one day after discontinuation of P-gp inhibitor. **Note:** an exception is made for **Azithromycin**, where dose adjustments of venetoclax are not required.	

PRECAUTIONS:

1. **Tumour lysis syndrome (TLS):** TLS has been reported and the risk is greatest during the dose ramp-up phase. Patients should be stratified as low, medium, or high risk based on their lymph node size (LN), absolute lymphocyte count (ALC), and comorbidities including renal dysfunction. All patients require prophylaxis for TLS using hydration beginning 48 hours and anti-hyperuricemic agents beginning 72 hours prior to initiation of therapy. Hospitalization is recommended for high risk patients, medium risk patients with abnormal CrCl and any risk patients with CrCl ≤ 50 mL/min. Hospitalization may be considered for those with additional risk factors for TLS (CrCl ≤ 80 ml/min, unable to drink 1.5-2 L per day, unsuitable for outpatient treatment and lab monitoring, or at physician discretion). It is mandatory that electrolytes are monitored as TLS requires prompt management (see **Appendix I** for management recommendations). **For outpatients, TLS labs must be**

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reviewed at 6 hours and 24 hours after the first 2 dose escalations (20 mg and 50 mg) for low or medium risk patients and after all dose escalations for high-risk patients (100 mg, 200 mg, and 400 mg). Patients must be instructed to wait to take the second dose until approval is given (by phone). See Appendix II, Tables 1 and 2 for frequency of laboratory monitoring and patient follow-up schedule.

2. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
3. **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 100 mg PO daily, for the entire 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. 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.
4. **Drug interactions:** Venetoclax is a major CYP3A4 substrate and a substrate of P-glycoprotein. Concurrent administration of drugs which are strong CYP 3A4 inhibitors is contraindicated at initiation and during the dose ramp-up phase, due to increased serum concentration of venetoclax and potential increased risk of TLS. See Drug Interactions in Dose Modification section above.
5. **Pregnancy:** Venetoclax is not recommended for use in pregnancy. Fetotoxicity is likely. Women of childbearing potential should undergo pregnancy testing before initiating treatment and use adequate contraception during treatment and for at least 30 days after the last dose
6. **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).
7. **Fatal Cytokine Release Syndrome** has been reported. 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.

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8. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, riTUXimab should be discontinued.
9. **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.
10. **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 or 1600mg/13.4mL ready-to-use solution which contains hyaluronidase to facilitate injection.
11. 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. Alina Gerrie, 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.

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APPENDIX I:

Manage Tumour Lysis Syndrome (TLS) according to institution guidelines. If no local guidelines, may use the following. Consider hospital admission, if needed for cardiac monitoring or IV medications/hydration.

Suggested Guide for Management of Tumour Lysis Syndrome (TLS) (adapted from MD Anderson TLS guidelines[10])

Electrolyte Abnormality	Management Recommendations
Hyperkalemia	

Mild
 	
(greater than upper limit of normal to less than 6 mmol/L)
	• Restrict potassium intake (avoid IV and PO potassium, limit dietary intake)
	• Sodium polystyrene (Kayexalate®)
	  ○ 15-30 grams PO
	  ○ Repeat as needed depending on follow-up potassium levels
	• Consider ECG and cardiac rhythm monitoring at physician discretion

Moderate
 	
(6-7 mmol/L) **and** asymptomatic
	• Restrict potassium intake (avoid IV and PO potassium, limit dietary intake)
	• ECG and cardiac rhythm monitoring
	• Sodium polystyrene (Kayexalate®)
	  ○ 15-30 grams PO
	  ○ Repeat every 4 to 6 hours depending on follow-up potassium levels

Severe
 	
(greater than 7 mmol/L **and/or** symptomatic)
	Same as moderate plan plus:
	• Concurrent ECG changes: calcium gluconate 1 g via slow IV infusion; may be repeated after 5-10 minutes if ECG changes persist
	• To temporarily shift potassium intracellularly:
	  • IV insulin and dextrose
	  ➢ Give 10 units of regular insulin in 500 mL of D10W infused IV over 60 minutes
	  ➢ Monitor blood glucose closely
	  • Sodium bicarbonate
	  ➢ Give 50 mEq via slow IV infusion
	  ➢ Can be used if patient is acidemic; however sodium bicarbonate and calcium should not be administered through the same lumen
	  • Salbutamol
	  ➢ Give 10-20 mg in 4 mL saline via nebulizer over 20 minutes or 10-20 puffs via inhaler over 10-20 minutes
	  ➢ Avoid in patients with acute coronary disease

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Electrolyte Abnormality	Management Recommendations
Hyperphosphatemia	

Moderate
(greater than or equal to 1.94 mmol/L)
	• Restrict phosphorus intake (avoid IV and PO phosphorus; limit dietary sources)
	• Administer phosphate binder:
	  ○ Sevelamer (Renagel®, Renvela®) 800-1600 mg PO three times a day with meals
	  ○ Lanthanum carbonate (Fosrenol®) 500-1000 mg PO three times a day with meals
	  ○ Aluminum hydroxide tablet 300 mg PO three times a day with meals, may increase dose to 600 mg PO three times a day (avoid in patients with renal dysfunction)
	  ○ Aluminum hydroxide 64 mg/mL suspension 15 mL PO three times a day with meals, may increase dose to 30 mL four times a day based on phosphate level (avoid in patients with renal dysfunction)

Severe	Dialysis may be needed in severe cases
Hypocalcemia (calcium less than or equal to 1.75 mmol/L or ionized calcium less than or equal to 0.8 mmol/L)	
Asymptomatic	• No therapy • To avoid calcium phosphate precipitation, asymptomatic patients with acute hypocalcemia and hyperphosphatemia should not be given calcium repletion until phosphorous level has normalized
Symptomatic	Calcium gluconate 1 g via slow IV infusion with ECG monitoring
Uremia (renal dysfunction)	
	• Fluid and electrolyte management • Uric acid and phosphate management • Adjust doses for renally excreted medications • Dialysis

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APPENDIX II.

Table 1. Monitoring for <u>Low or Medium Risk TLS Patients.</u> Pharmacist reviews labs and contacts patient to take venetoclax dose.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1 **20 mg** ▪ baseline lab	6 AM dose ▪ lab at 12 noon ▪ review bloodwork and notify MD if abnormal	▪ lab at 8 am ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 1 day 2 dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 2 day 1 dose (50 mg) the following day
Week 2 **50 mg**	6 AM dose ▪ lab at 12 noon ▪ review bloodwork and notify MD if abnormal	▪ lab at 8 am ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 2 day 2 dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 3 day 1 dose (100 mg) the following day
Week 3 **100 mg**	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 4 day 1 dose (200 mg) the following day
Week 4 **200 mg**	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 5 day 1 dose (400 mg) the following day
Week 5 onwards **400 mg**	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose

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Table 2. Monitoring for <u>High Risk TLS patients.</u> Unless otherwise specified, lab review is done by pharmacist and pharmacist contacts patient to take venetoclax dose.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1 **20 mg** ▪ baseline lab	Inpatient ▪ labs 4h, 8h, 12h and 24 h post dose (monitoring done by ward)	Inpatient for 2nd dose ▪ ward team to review 24h lab post 20 mg dose and notify MD if abnormal. If normal, give patient week 1 day 2 dose and may be discharged home or at MD discretion	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal.
Week 2 **50 mg**	Inpatient ▪ labs 4h, 8h, 12h and 24 h post dose (monitoring done by ward)	Inpatient for 2nd dose ▪ ward team to review 24h lab post 50 mg dose and notify MD if abnormal. If normal, give patient week 2 day 2 dose and may be discharged home or at MD discretion	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 3 day 1 dose (100 mg) the following day
Week 3 **100 mg**	6 AM dose ▪ lab at 12 noon ▪ review bloodwork and notify MD if abnormal	▪ lab at 8am ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 3 day 2 dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 4 day 1 dose (200 mg) the following day
Week 4 **200 mg**	6 AM dose ▪ lab at 12 noon ▪ review bloodwork and notify MD if abnormal	▪ lab at 8am ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 4 day 2 dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 5 day 1 dose (400 mg) the following day
Week 5 onwards **400 mg**	6 AM dose ▪ lab at 12 noon ▪ review bloodwork and notify MD if abnormal	▪ lab at 8am ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 5 day 2 dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose

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