BC Cancer Protocol Summary for Treatment of Relapsed/Refractory Mantle Cell Lymphoma Using Venetoclax and iBRUtinib

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

ELIGIBILITY:
Patients must have:
- Relapsed or refractory mantle cell lymphoma
- Received at least 1 prior line of therapy

Patient should have:
- Adequate hematologic, hepatic and renal function
- Good performance status

Note:
- Patients who initiated treatment with iBRUtinib monotherapy between 1 Jan 2026 and 1 Jul 2026 may switch to LYMCIV, provided no progression has occurred.

EXCLUSION:
Patients must not:
- Have progression on or within 6 months of treatment with venetoclax and/or BTK inhibitors
- Be taking strong CYP3A4 inhibitors within 7 days prior to initiation and during the dose ramp-up phase of venetoclax

CAUTIONS:
- Cardiac risk factors including uncontrolled hypertension, diabetes mellitus, cardiac arrhythmia, cardiac failure
- Patients at high risk for bleeding complications
- Platelet count less than 30 x 10^9/L unless disease-related
- Absolute neutrophil count (ANC) less than 1.0 x 10^9/L unless disease-related.
- Total bilirubin greater than 3 x upper limit of normal (ULN)
- Active and uncontrolled autoimmune cytopenias

TESTS:

- Baseline (required, within 72 hours of first treatment): CBC & Diff, potassium, calcium, magnesium, phosphate, uric acid, creatinine, urea, total bilirubin, ALT, LDH, albumin, PTT, INR
- 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
- Baseline, if clinically indicated: ECG, MUGA scan or echocardiogram
- Prior to each dose increment during ramp-up phase (Cycle 1, Weeks 1 to 5): potassium, calcium, phosphate, uric acid, creatinine, LDH, albumin
- Tumour lysis syndrome (TLS) monitoring (Cycle 1, Weeks 1 to 5): potassium, calcium, phosphate, uric acid, creatinine, LDH and 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)
- Cycles 2 to 23, prior to each cycle: CBC & Diff, creatinine, total bilirubin, ALT**,** blood pressure
- Cycles 24 and onward, prior to each visit: CBC & Diff, creatinine, total bilirubin, ALT**,** blood pressure
- If clinically indicated: PTT, INR, ECG, MUGA scan or echocardiogram, HBV viral load (see protocol SCHBV)

PREMEDICATIONS:

- Antiemetic protocol for low emetogenic chemotherapy (see SCNAUSEA)

SUPPORTIVE MEDICATIONS:

- Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, start hepatitis B prophylaxis as per SCHBV.
- Consider antimicrobial prophylaxis for patients at increased risk of opportunistic infections:
    - valACYclovir 500 mg PO BID
    - cotrimoxazole 1 DS tab PO 3 times each week (Monday, Wednesday and Friday)

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 venetoclax dose and after each venetoclax dose increase.

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	CrCl± greater than or equal to 60 mL/min **AND one of the following:** All lesions less than or equal to 5 cm **OR** ALC** less than or equal to 25 x 10^9/L	Oral: 1.5 to 2 L daily (8 glasses) Start 48 h prior to 1st dose and continue throughout the first 5 weeks of therapy	Allopurinol 300 mg PO daily until dose escalation is complete and at physician discretion Start 72 h prior to 1st dose	**Outpatient:** • Pre-dose at each dose increment • 6 h and 24h post first dose of 20 mg and 50 mg
High	CrCl± less than 60 mL/min **OR** Any lesions greater than to 10 cm **OR** At least one lesion greater than 5 cm with ALC** less than or equal to 25 x 10^9/L	Oral: 1.5 to 2 L daily (8 glasses) Start 48 h prior to 1st dose, and continue throughout the first 5 weeks of therapy **AND** IV NS (150 to 200 mL/hr, as tolerated)	Allopurinol 300 mg PO daily until dose escalation complete and at physician discretion Start 72 h prior to 1st dose Consider rasburicase 3 mg IV x 1 if baseline uric acid is elevated, 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, 4h, 8h, 12h and 24h post first dose of 20 mg and 50 mg **Outpatient:** Subsequent ramp-up doses • Pre-dose, 6h, and 24h post dose

**ALC = absolute lymphocyte count

±Cockcroft-Gault Equation:

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

N = 1.23 male
N = 1.04 female

TREATMENT:
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 risk TLS patients, the start date must be on a Thursday, and patients must pick up their venetoclax before Thursday (unless an alternate date is agreed upon by provider and pharmacy/team for monitoring venetoclax ramp up labs).

For high-risk TLS patients, start date is not restricted to a Thursday as treatment is initiated in an inpatient setting.

Cycle 1:

Week	iBRUtinib PO	venetoclax± PO	Cycle length
1	560 mg once daily	20 mg once daily x 7 days	35 days (5 weeks)
2		50 mg once daily x 7 days	
3		100 mg once daily x 7 days	
4		200 mg once daily x 7 days	
5		400 mg once daily x 7 days	

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

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

For **low 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 a.m. on a Thursday in order for labs and RN phone call to not fall on a statutory holiday or weekend.**
- Outpatient STAT **TLS labs** at **6h** (noon) and at approximately **24h** (8 a.m. 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 24h 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.

Cycles 2 to 24:

Drug	Dose	BC Cancer Administration Guideline
iBRUtinib	560 mg once daily	PO
venetoclax	400mg once daily	PO

- Repeat every 28 days for 23 cycles (i.e. Cycles 2 to 24).

Cycles 25 and onward:

Drug	Dose	BC Cancer Administration Guideline
iBRUtinib	560 mg once daily	PO

- Treat until disease progression or intolerable toxicity.

DOSE MODIFICATIONS:

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 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 venetoclax until resolved; then resume at a reduced dose (see Dose Modification table below). 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]).
Note: Use this formula to correct for calcium only when albumin is low.

† **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

2. Hematological Toxicity:

Toxicity Grade	Occurrence	Doses
ANC less than 1.0 x 10^9/L with infection or fever OR Platelets less than 50 x 10^9/L with evidence of bleeding OR ANC less than 0.5 x 10^9/L OR Platelets less than 25 x 10^9/L	1st	Hold until improvement to ANC greater than or equal to 1.5 x 10^9/L and platelets greater than or equal to 75 x 10^9/L or baseline. Consider filgrastim (G-CSF) if clinically indicated. Resume both drugs at same dose.
	2nd and subsequent	Hold until improvement to ANC greater than or equal to 1.5 x 10^9/L and platelets greater than or equal to 75 x 10^9/L or baseline. Consider filgrastim (G-CSF) if clinically indicated. Resume both drugs per Dose Modifications tables below.

Dose Modifications for Second or Subsequent Toxicity Recurrence:

iBRUtinib Dose at Interruption	iBRUtinib Recommended Restarting Dose
560 mg	420 mg
420 mg	280 mg
280 mg	Discontinue

Venetoclax Dose at Interruption	Venetoclax Recommended Restarting Dose[a,b]
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

[a]Continue the reduced dose for one week before increasing the dose

[b]Consider discontinuing venetoclax for patients who require dose reductions to less than 100 mg for more than 2 weeks

2. Cardiac Toxicities:

Toxicity	Recommended iBRUtinib dose
Grade 2 cardiac failure	First occurrence: Hold until improvement to Grade 1 or baseline. Restart at 420 mg PO daily
	Second occurrence: Hold until improvement to Grade 1 or baseline. Restart at 280 mg PO daily
	Third occurrence: Discontinue iBRUtinib
Grade 3 cardiac arrhythmias	First occurrence: Hold until improvement to Grade 1 or baseline. Restart at 420 mg PO daily
	Second occurrence: Discontinue iBRUtinib
Grade 3 or 4 cardiac failure OR Grade 4 cardiac arrhythmias	Discontinue iBRUtinib

3. Hepatic Impairment:

Severity	Management
Mild (Child-Pugh Class A)	**iBRUtinib**: reduce dose to 140 mg PO daily; monitor patient for signs of toxicity **venetoclax:** no dose adjustment
Moderate or severe (Child-Pugh Class B or C)	Do not use

4. Other Non-Hematological Toxicities:

For any other Grade 3 or 4 non-hematological toxicity:

- For first occurrence: hold iBRUtinib, venetoclax, or both (depending on cause) until recovery to Grade 1 or baseline, then restart at same dose.
- For second or subsequent occurrence: hold iBRUtinib, venetoclax, or both (depending on cause) until recovery to Grade 1 or baseline, then restart as per dose modification guidelines in Hematological Toxicity section above.

5. Renal Impairment:

For iBRUtinib: No dose adjustment recommended if creatinine clearance is 30 mL/min. No information found for creatinine clearance less than 30 mL/min.

For venetoclax: No dose adjustment required if creatinine clearance is 30 mL/min or greater, but renal impairment increases TLS risk. No information found for creatinine clearance less than 30 mL/min.

6. Drug Interactions

For iBRUtinib:
iBRUtinib is a CYP3A4 substrate and concomitant therapy with strong or moderate CYP 3A inhibitors may increase iBRUtinib exposure; avoid if possible. iBRUtinib dose reduction for concurrent use may be necessary. Concomitant use of iBRUtinib with strong CYP 3A inducer may decrease iBRUtinib exposure; avoid if possible. Refer to BCCA Cancer Drug Manual for more details.

For venetoclax:
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 with venetoclax and the risk is greatest during the dose ramp-up phase. Patients should be stratified as lower high risk based on their lesion size, 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. Hospitalization may be considered for those with additional risk factors for TLS (reduced renal function, 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 reviewed at 6 hours and 24 hours after the first 2 dose escalations (20 mg and 50 mg)**

for low 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:** See SCHBV protocol for more details.
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. iBRUtinib is also a CYP3A4 substrate and concomitant therapy with strong or moderate CYP 3A inhibitors may increase iBRUtinib exposure; avoid if possible. iBRUtinib dose reduction for concurrent use may be necessary. Concomitant use of iBRUtinib with strong CYP 3A inducer may decrease iBRUtinib exposure; avoid if possible.
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. **Hemorrhagic events:** Minor hemorrhagic events including bruising, epistaxis and petechiae occur in approximately half of the patients treated with iBRUtinib. Major hemorrhagic events including subdural hematoma, gastrointestinal bleeding, hematuria and post-procedural bleeding occur in 3% of patients**.** Use with caution in patients taking anticoagulants or medications that inhibit platelet function. Hold treatment for 3-7 days pre- and post-surgery; reinitiate post-surgery based on the risk of bleeding.
7. **Elderly Patients:** patients over 65 years of age treated with iBRUtinib experience more cardiac events (atrial fibrillation, hypertension), infection (pneumonia, cellulitis), gastrointestinal events (diarrhea, dehydration), as well as a higher frequency of grade 3 or greater adverse effects.
8. **Cardiac failure:** evaluate cardiac risk at baseline and monitor for signs of deterioration during treatment with iBRUtinib. Hold iBRUtinib as indicated in dose modifications above, and evaluate with echocardiogram for new onset or worsening cardiac failure. Consider risk vs benefit prior to restarting at reduced dose.
9. **Hypertension** has been reported in patients taking Bruton's tyrosine kinase (BTK) inhibitors. Blood pressure should be checked at each visit and treated if it develops. Hypertension increases the risk of cardiac complications with BTK inhibitor treatment.
10. **Cardiac arrhythmias including atrial fibrillation**: baseline ECG recommended for patients with cardiac risk factors. ECG is recommended in patients who develop arrhythmic symptoms including palpitations and lightheadedness or a new onset of dyspnea. If atrial fibrillation persists, evaluate the risk vs. benefit of continuing treatment. iBRUtinib dose reduction is recommended for patients who develop cardiac arrhythmias or who have worsening symptoms while taking iBRUtinib.
11. **Lymphocytosis:** Has been reported with iBRUtinib, usually occurring within the first few weeks of therapy. Lymphocytosis may be possibly related to the inhibition of BTK-mediated cellular homing and adhesion.

Contact the Systemic Therapy physician at your regional cancer centre or LY Systemic Therapy Chair with any problems or questions regarding this treatment program.

References:

1. Wang M, Jurczak W, Trneny M et al. Ibrutinib Plus Venetoclax in Relapsed or Refractory Mantle Cell Lymphoma (SYMPATICO): a Multicentre Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study. Lancel Oncol 2025; 26: 200-13.
2. Venetoclax (VENCLEXTA) Canada's Drug Agency (CDA-AMC) Reimbursement Recommendation. Canadian Journal of Health Technologies Oct 2025; 5(10): 1-26.

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

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

APPENDIX II.

Table 1. Monitoring for <u>Low Risk TLS Patients.</u> Pharmacist reviews labs in Cycle 4 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

Table 2. Monitoring for <u>High Risk TLS patients.</u> Unless otherwise specified, Cycle 4 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