BC Cancer Protocol Summary for Treatment of Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma using Venetoclax and oBINutuzumab

Protocol Code	*LYVENOB*
Tumour Group	*Lymphoma*
Contact Physician	*Dr. Alina Gerrie*

ELIGIBILITY:

Patients must have chronic lymphocytic leukemia or small lymphocytic lymphoma with no prior therapy, and:

- With high-risk disease (eg. chromosome 17p deletion , *TP53* mutation and/or unmutated immunoglobulin heavy chain variable region [IGHV] status),or
- Ineligible for FCR, defined as patients 65 years of age or over, and/or a strong clinical reason that the patient is ineligible for FCR and
- Must have symptomatic disease requiring therapy

EXCLUSIONS:

Patients must not have:

- Inadequate renal function (creatinine clearance less than 30 mL/min per Cockcroft-Gault formula)***** or
- Taken strong CYP3A4 inhibitors within 7 days 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).*

CAUTION:

- Platelet count less than 30 x 10^9/L unless disease-related (platelets should be greater than or equal to 10 x 10^9/L if there is bone marrow involvement)
- Absolute neutrophil count (ANC) less than 1.0 x 10^9/L. Consider giving filgrastim.
- Total bilirubin greater than 3 x upper limit of normal (ULN)
- ALT or AST greater than 3 x upper limit of normal (ULN)
- Active and uncontrolled autoimmune cytopenias

TESTS:

- **Baseline** (required within 72 h before first treatment): CBC & Diff, potassium, calcium, magnesium, phosphate, uric acid, creatinine, total 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, HBsAb, HBcoreAb
- **Cycle 1 – Prior to Day 2:** CBC & Diff, potassium, calcium, phosphate, uric acid, creatinine, LDH, albumin

- **Cycle 2 – Prior to Day 1:** CBC & Diff, potassium, calcium, phosphate, uric acid, creatinine, LDH, albumin, total bilirubin, ALT
- **Cycle 2 – Prior to Days 8, 15, 22, and 29 (during venetoclax dose ramp up)**: CBC & Diff, 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)**
    - Note: if applicable, cycle 2 Day 8 labs may need to be drawn during oBINutuzumab infusion (see Appendix II)
- **Cycles 3 to 12 – Prior to each cycle:** CBC & Diff, creatinine, total bilirubin, ALT
- If clinically indicated: HBV viral load (see protocol SCHBV)

PREMEDICATIONS:

- Antiemetic protocol for low emetogenic chemotherapy (see SCNAUSEA)
- Optional prior to Cycle 1 Day 1 oBINutuzumab infusion:
    - dexamethasone 20 mg PO BID the day prior to infusion,
      OR
    - predniSONE 50 mg PO once daily for 3 days prior to infusion (for patients unable to tolerate high-dose dexamethasone)

Premedication to prevent oBINutuzumab infusion reactions:

Cycle 1: Days 1 and 2
60 minutes prior to infusion:
- dexamethasone 20 mg IV in 50 mL NS over 15 minutes

30 minutes prior to infusion:
- acetaminophen 650 mg to 975 mg PO
- diphenhydrAMINE 50 mg PO

Cycle 1: Days 8 and 15
30 minutes prior to infusion:
- acetaminophen 650 mg to 975 mg PO
- diphenhydrAMINE 50 mg PO

If previous reaction was grade 3 (refer to SCDRUGRX for definition) or if lymphocyte count greater than 25 x 10^9/L before treatment, add dexamethasone 20 mg IV 60 minutes prior to infusion

Cycles 2 to 6
30 minutes prior to infusion:
- acetaminophen 650 mg to 975 mg PO
- diphenhydrAMINE 50 mg PO

If previous reaction:
- dexamethasone 20 mg PO BID the day prior to infusion,

OR
- predniSONE 50 mg PO once daily for 3 days prior to infusion (for patients unable to tolerate high-dose dexamethasone),

and

If previous reaction was grade 3 or if lymphocyte count greater than 25 x 10^9/L before treatment, add dexamethasone 20 mg IV 60 minutes prior to infusion

Note: Alternative corticosteroids that may be considered on treatment days include prednisoLONE 100 mg PO or methylPREDNISolone 80 mg IV. *Hydrocortisone is ineffective and not recommended as a premedication but may still be used for an infusion-related reaction.*

SUPPORTIVE MEDICATIONS:

- Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, start hepatitis B prophylaxis as per current guidelines.
- Antihyperuricemic agents such as allopurinol 300mg PO daily should be started 72 hours prior to the first oBINutuzumab infusion and continued until the end of venetoclax dose ramp up to prevent **tumour lysis syndrome (TLS).**

TREATMENT:

Treatment summary (See further below for dosing and additional information for each drug):

Please note difference in cycle length between cycles 1, 2 and 3 plus. The differing cycle lengths for cycles 1 and 2 is to allow TLS re-assessment prior to initiation of venetoclax.

Cycle #	Day	oBINutuzumab IV	Venetoclax PO	Cycle length
1	1	100 mg		21 days (3 weeks)
	2	900 mg		
	8	1000 mg		
	15	1000 mg		
2	1		20 mg daily x 7 days	35 days (5 weeks)
	8	1000 mg	50 mg daily x 7 days	
	15		100 mg daily x 7 days	
	22		200 mg daily x 7 days	
	29		400 mg daily x 7 days	
3 to 6	1	1000 mg	400 mg daily x 28 days	28 days (4 weeks)
7 to 12	1		400 mg daily x 28 days	28 days (4 weeks)

Venetoclax dose ramp up occurs in cycle 2, starting 1 week prior to oBINutuzumab infusion.

TLS can occur within 12-24 hours after the first infusion of oBINUtuzumab. Inpatient admission for TLS monitoring prior to oBINutuzumab is at physician's discretion. Patients must be counselled to have adequate hydration (1.5 to 2 litres of fluids a day), starting 48 hours prior to the first oBINutuzumab to prevent TLS. TLS can also occur as early as 6 to 8 hours after the first dose of venetoclax and after each dose increase. Fatal events and renal failure requiring dialysis have been reported in patients with medium or high tumour burden when starting on venetoclax, but the incidence is reduced when the venetoclax dose is gradually increased. It is mandatory that

electrolytes are closely monitored as recommended since TLS requires prompt management (**see Appendix I**).

oBINutuzumab:

Cycle 1

Drug	Dose	BC Cancer Administration Guideline
oBINutuzumab	100 mg on Day 1	IV in 100 mL NS over 4 hours at 25 mg/h
	900 mg on Day 2	IV in 250 mL NS starting at 50 mg/h (maximum 400 mg/h)*

*increase by 50 mg/h every 30 minutes, as tolerated (see Titration Table in Appendix III)

Vital signs prior to start of infusion, at every increment of infusion rate, and as clinically indicated post infusion. For cycle 1 day 1, vital signs prior to start of infusion, at hour 2 and then post infusion.

Drug	Dose	BC Cancer Administration Guideline
oBINutuzumab	1000 mg on Days 8 and 15	IV in 250 NS starting at 100 mg/h (maximum 400 mg/h)**

**increase by 100 mg/h every 30 minutes, as tolerated (see Titration Table in Appendix III)

Vital signs prior to start of infusion, at every increment of infusion rate, and as clinically indicated post infusion.

Cycle 2

Drug	Dose	BC Cancer Administration Guideline
oBINutuzumab	1000 mg on Day 8	IV in 250 mL NS starting at 100 mg/h (maximum 400 mg/h)**

**increase by 100 mg/h every 30 minutes, as tolerated (see Titration Table in Appendix III)

Vitals signs prior to start of infusion, and as clinically indicated during and post infusion

Cycles 3 to 6

Drug	Dose	BC Cancer Administration Guideline
oBINutuzumab	1000 mg on Day 1	IV in 250 mL NS starting at 100 mg/h (maximum 400 mg/h)**

**increase by 100 mg/h every 30 minutes, as tolerated (see Titration Table in Appendix III)

Vitals signs prior to start of infusion, and as clinically indicated during and post infusion

Note: Cycle 2 starts 21 days after cycle 1 and lasts for 5 weeks (35 days).
For cycles 3 to 6, treatment interval is 4 weeks (every 28 days).

Venetoclax:

Due to the risk of TLS, venetoclax dosing must be initiated carefully according to a 5 week ramp-up schedule (starting from cycle 2 Day 1 to Day 35 inclusive = 5 weeks) 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.

Cycle #	Week	Dose	BC Cancer Administration Guideline
1		**No venetoclax**	
2	1	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	
3 to 12	1 to 4	400 mg once daily	PO

After cycle 6, when oBINutuzumab infusion is completed, physicians may order up to 3 cycles of venetoclax at a time, but pharmacy will dispense 1 cycle at a time so that labs will be monitored prior to each cycle.

Treatment of venetoclax will continue until the end of cycle 12, disease progression or unacceptable toxicity, whichever occurs first.

Note: **For low or medium TLS risk patients, venetoclax treatment must start on a Thursday in week 1 of Cycle 2 for TLS monitoring.** See venetoclax section below for explanation. **oBINutuzumab must also start on a Thursday for Cycles 1 and 2** to match the Thursday start date of venetoclax and for correct timing of bloodwork.

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

Table 1: Recommended TLS monitoring and prophylaxis based on tumour burden at time of venetoclax start (cycle 2, week 1):

***** Since it is possible that de-bulking from oBINutuzumab therapy before starting venetoclax may significantly reduce the risk of TLS, **re-assess TLS risk category at cycle 2, Day 1, prior to initiation of venetoclax. In clinical trials, the number of high-risk patients decreased from 22% to 8% after cycle 1, Day 15 of oBINutuzumab.**

If a patient is reassigned to a lower risk group, the prophylaxis guidance for the lower risk group can be followed. However, patients classified as high risk because of a lymph node with largest diameter greater than or equal to 10 cm should **NOT** have TLS risk reassessment and should follow the prophylaxis plan for high-risk patients throughout the venetoclax ramp-up period.

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 of oBINutuzumab and continue until end of ramp-up period with venetoclax is completed (Cycle 3 Day 1)	Allopurinol 300 mg PO daily until end of ramp-up period with venetoclax is completed (Cycle 3 Day 1) and at physician discretion Start 72 h prior to 1st dose of oBINutuzumab	**Outpatient:** • Pre-dose at each dose increment • 6 h and 24 h post first dose of 20 mg and 50 mg

Tumour Burden		Prophylaxis		Blood chemistry monitoring
		Hydration	**Anti-hyperuricemic**	**Setting and Frequency of Assessments**
Medium	Any LN***** 5 cm to less than 10 cm **<u>OR</u>** 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 of oBINutuzumab , and continue until end of ramp-up period with venetoclax is completed (Cycle 3 Day 1) Consider additional IV fluids as needed	Allopurinol 300 mg PO daily until end of ramp-up period with venetoclax is completed (Cycle 3 Day 1) and at physician discretion Start 72 h prior to 1st dose of oBINutuzumab	**<u>Outpatient:</u>** • 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)

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 of oBINutuzumab , and continue until end of ramp-up period with venetoclax is completed (Cycle 3 Day 1) IV NS (150 to 200 mL/h, as tolerated)	Allopurinol 300 mg PO daily until end of ramp-up period with venetoclax is completed (Cycle 3 Day 1) and at physician discretion Start 72 h prior to 1st dose of oBINutuzumab 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

TLS Monitoring:

Prior to Cycle 1 Day 2 oBINutuzumab and initiation of venetoclax at the following time points:

Lab results must be reviewed by pharmacist or MD, at the time points indicated below, before the next venetoclax dose can be authorized in person or by phone (**baseline labs and labs prior to Cycle 2 Day 1** reviewed by **MD**, ramp-up and **TLS labs** reviewed by **pharmacist**):

- Within 72 h of initiating venetoclax on Day 1 of Cycle 2
- 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 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 venetoclax so that the start day of a new dose occurs on a Thursday to ensure that labs will be monitored by pharmacy.

DOSE INTERRUPTIONS AND MODIFICATIONS

For patients who require a dosing interruption of greater than 1 week during the first 5 weeks of venetoclax (dose ramp-up phase) or greater than 2 weeks after completing the dose ramp-up 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 2: 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
- **OBINutuzumab should be discontinued if venetoclax is discontinued due to toxicity**

1. Tumour Lysis Syndrome (TLS)

- Changes in blood chemistries that require prompt management can occur as early as 12-24 hours after the first infusion of oBINutuzumab and 6-8 hours after the first dose of venetoclax and after each dose increase
- Reduced renal function (CrCl less than or equal to 80mL/min) increases the risk for TLS
- Electrolytes must be corrected to within normal limits prior to proceeding with oBINutuzumab or with the 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 and/or oBINutuzumab if applicable. • Correct abnormalities. • If resolved within 24-48h, resume both drugs 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 and/or oBINutuzumab until resolved. • Resume oBINutuzumab at same dose • Resume venetoclax at a reduced dose (Refer to Table 2 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]).
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 and Non-Hematological Toxicities:

No dose reductions are recommended for oBINutuzumab**. Hold oBINutuzumab if venetoclax is held**. The infusion may also be discontinued or its rate reduced as appropriate.

Toxicity	Action
ANC less than 1.0 x 10^9/L	• Delay venetoclax (and oBINutuzumab if neutropenia occurs during cycles 1 to 6) for 1 week • Consider GCSF as clinically indicated until ANC greater than or equal to 1.0 x 10^9/L • When ANC recovers to greater than or equal to 1.0 x 10^9/L, and/or platelets greater than or equal to 75 x 10^9/L • Restart oBINutuzumab at same dose (if applicable) • Resume venetoclax at 1 dose level reduction following Dose Modification table above
Platelets less than 25 x 10^9/L and/or severe symptomatic bleeding*	• Hold venetoclax (and oBINutuzumab if event occurs during cycles 1 to 6) until platelets greater than or equal to 50 x 10^9/L, then resume at same dose(s).
Non-hematological toxicity grade 3* or 4*	• Hold venetoclax (and oBINutuzumab if event occurs during cycles 1 to 6) until improvement to grade 1 toxicity or baseline for a maximum of 28 days, then resume at same dose.

*For 2nd and subsequent occurrences, resume at one dose level reduction following Dose Modification table above

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

3. Infusion reactions to oBINutuzumab:

Refer to SCDRUGRX protocol for management guidelines.

Infusion reactions	Management
Grade 1 (mild)	Reduce infusion rate and treat symptoms. Once symptoms resolved, may resume infusion. Titrate infusion rate at increments appropriate to the treatment dose – see BC Cancer Administration Guidelines for oBINutuzumab above.
Grades 2 or 3 (moderate or severe)	Hold infusion and treat symptoms. Once symptoms resolved, may resume infusion at no more than half of the rate when reactions occurred (see table below). Titrate infusion rate at increments appropriate to the treatment dose.
Grade 4 (life-threatening)	Stop infusion and discontinue oBINutuzumab therapy. May continue venetoclax.

Hydrocortisone may be used but more potent corticosteroids such as methylPREDNISolone may be required for infusion reactions.

Infusion rate when resuming infusion after grade 3 symptoms are resolved:

Infusion rate when reactions occur	Maximum infusion rate when resuming infusion
25 mg/h	10 mg/h
50 mg/h	25 mg/h
100 mg/h	50 mg/h
150 mg/h	50 mg/h
200 mg/h	100 mg/h
250 mg/h	100 mg/h
300 mg/h	150 mg/h
350 mg/h	150 mg/h
400 mg/h	200 mg/h

4. 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 oBINutuzumab

5. 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)** including acute renal failure, can occur within 12-24 hours after the first infusion of oBINutuzumab. Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely. See BC Cancer Drug Manual oBINutuzumab Drug Monograph for more information.TLS has been reported with venetoclax 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 less than or equal to 50 mL/min. Hospitalization may be considered for those with additional risk factors for TLS (CrCl less than or equal to 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 reviewed at 6 hours and 24 hours after the first 2 dose escalations of venetoclax (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. **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.
4. **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.
5. **Infusion Reactions (IR),** including anaphylaxis, may occur within 24 hours of oBINutuzumab infusion, usually with the first infusion and decreasing with subsequent infusions. Cycle 1 Day 1 infusion reactions have been most frequently reported at 1 to 2 hours from the start of infusion. Cycle 1 Day 2 infusion reactions were most commonly seen at greater than 5 hours from the start of infusion. Risk factors include a high tumour burden. Infusion reactions may require rate reduction, interruption of therapy, or treatment discontinuation. Monitor during the entire infusion; monitor patients with pre-existing cardiac or pulmonary conditions closely. Consider temporarily withholding antihypertensive therapies for 12 hours prior to, during, and for 1 hour after infusion.
6. **Hepatitis B Reactivation**: See SCHBV protocol for more details.
7. **Progressive Multifocal Leukoencephalopathy (PML)** may occur caused by reactivation of the JC virus. Patients should be evaluated for PML if presenting with new neurologic symptoms such as confusion, vision changes, changes in speech or walking, dizziness or vertigo.
8. **Cardiovascular events,** such as myocardial infarction and dysrhythmias, including fatal cases can occur with oBINutuzumab. Patients with pre-existing cardiac disease may develop worsening of the cardiovascular disease and should be monitored closely.
9. **Live or attenuated vaccines** are not recommended during treatment and until B-cell recovery has occurred after treatment (i.e., at least 6 months after treatment with anti-CD20 monoclonal antibody and at least 3 months after other treatment is discontinued)
10. **Bone Marrow Suppression** can occur when oBINutuzumab and venetoclax are used in combination and has resulted in grade 3 and 4 **neutropenia** and **thrombocytopenia**. Monitor for signs/symptoms of infection. If clinically indicated, anti-infective prophylaxis for viral, fungal, bacterial or Pneumocystis infections may be considered in neutropenic patients as well as filgrastim (G-CSF). Azoles may interact with venetoclax and should be used with caution. Although there is a potential for drug-drug interactions with cotrimoxazole, there is likely to be limited potential clinical effects; therefore, cotrimoxazole can be considered for PCP prophylaxis with close clinical monitoring. Thrombocytopenia may require dose delays of oBINutuzumab and venetoclax and/or dose reductions of venetoclax. Consider withholding platelet inhibitors, anticoagulants, or other medications which may increase bleeding risk (especially during the first 2 cycles). Monitor blood counts frequently throughout therapy.

11. **Infection,** bacterial, fungal, and new or reactivated viral infections may occur during and/or following therapy; fatal infections have been reported. **Do not administer to patients with an active infection**. Patients with a history of recurrent or chronic infections may be at increased risk; monitor closely for signs/symptoms of infection

Call 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. Fischer, K. Al-Sawaf O. Bahlo J. et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N. Engl. J. Med 2019; **380:** 2225–2236.
2. Al-Sawaf O, Zhang C, Tandon M. et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2020: 21(9): 1188–1200 .
3. Al-Sawaf O, Gentile B, Devine J . et al. Rapid improvement of patient reported outcomes with venetoclax plus obinutuzumab in patients with previously untreated CLL and co-existing conditions: A prospective analysis from the CLL14 trial. *Blood 2019: (ASH Annu. Meet. Abstr.* **134**, 4305.
4. AbbVieCorporation. VENCLEXTA® product monograph. St-Laurent, Quebec; 27 September 2016
5. AbbVie Inc. VENCLEXTA® product monograph. North Chicago, IL; November 2018
6. Howard et al. the Tumor Lysis Syndrome. NEJM 2011; 364(19): 1844-1854.
7. Coiffer et al. Guidelines for the Management of Pediatric and Adult Tumor Lysis Syndrome: An Evidence-Based Review. JCO 2008; 26(16): 2767-2778.
8. Tumor Lysis Syndrome (TLS) in Adult Patients from MD Anderson Centre. https://www.mdanderson.org/content/dam/mdanderson/documents/for-physicians/algorithms/clinical-management/clin-management-tumor-lysis-web-algorithm.pdf
9. Agarwal et al. Effect of Azithromycin on Venetoclax Pharmacokinetics in Health Volunteers: Implications for Dosing Venetoclax with P-gp Inhibitors. Advances in Therapy 2018; 35(11):2015-2023

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[8])

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. VENETOCLAX DOSE RAMP UP

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

Note: Venetoclax dose ramp-up starts on Cycle 2

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1 **20 mg** Cycle 2 Day1 lab monitored by MD. Notify patient to pick up venetoclax.	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

*Week 2 Day 1 labs to be drawn during oBINutuzumab infusion

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.
Note: Venetoclax dose ramp-up starts on Cycle 2

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1 **20 mg** ▪ Cycle 2 Day 1 lab monitored by MD/ward	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

APPENDIX III: oBINutuzumab infusion rate titration table

Cycle 1: Day 1

oBINutuzumab 100 mg IV in 100 mL NS Total Volume = 114 mL		
TITRATION	**INFUSION RATE**	**VOLUME TO BE INFUSED (VTBI)**
25 mg/h x 240 min	28 mL/h	114 mL

Cycle 1: Day 2

oBINutuzumab 900 mg IV in 250 mL NS Total volume = 311 mL		
TITRATION	**INFUSION RATE**	**VOLUME TO BE INFUSED (VTBI)**
50 mg/h x 30 min	17 mL/h	9 mL
100 mg/h x 30 min	34 mL/h	17 mL
150 mg/h x 30 min	52 mL/h	26 mL
200 mg/h x 30 min	69 mL/h	35 mL
250 mg/h x 30 min	86 mL/h	43 mL
300 mg/h x 30 min	104 mL/h	52 mL
350 mg/h x 30 min	121 mL/h	61 mL
400 mg/h x 30 min	138 mL/h	69 mL

Cycle 1: Day 8 and Day 15
Cycle 2 to Cycle 6: Day 1 only

oBINutuzumab 1000 mg IV in 250 mL NS Total volume = 315 mL		
TITRATION	**INFUSION RATE**	**VOLUME TO BE INFUSED (VTBI)**
100 mg/h x 30 min	32 mL/h	16 mL
200 mg/h x 30 min	63 mL/h	32 mL
300 mg/h x 30 min	94 mL/h	47 mL
400 mg/h x 105 min	126 mL/h	220 mL