BC Cancer Protocol Summary for the Treatment of riTUXimab-refractory Follicular Lymphoma with DOXOrubicin, Cyclophosphamide, vinCRIStine, predniSONE, and oBINutuzumab

Protocol Code	*LYCHOPO*
Tumour Group	*Lymphoma*
Contact Physician	*Dr. Diego Villa*

ELIGIBILITY:

Patients must have:

- Rituximab-refractory follicular lymphoma, defined as patients who did not respond to a prior rituximab-containing regimen or those who have previously relapsed within 6 months of the last dose of rituximab, and
- Symptomatic disease requiring systemic therapy

Patients should:

- Not be a candidate for oBINutuzumab in combination with bendamustine (LYBENDO) at the discretion of the treating oncologist (e.g., treatment with bendamustine in previous 2 years)

Note:

- Only one of either LYBENDO, LYCHOPO, LYCVPO, or LYGDPO will be funded in the same patient

CAUTIONS:

- Congestive cardiac failure requiring current treatment (LYCHOPO may be used but DOXOrubicin should be omitted, see cardiotoxicity below)

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, total bilirubin
- 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
- Before Day 1 of each treatment cycle: CBC & Diff
- If clinically indicated: creatinine, ALT, total bilirubin

PREMEDICATIONS:

- **Induction phase treatment** (Cycles 1 to 6): Antiemetic protocol for highly emetogenic chemotherapy
- **Maintenance phase treatment**: (Cycles 7 onwards): Antiemetic protocol for rare emetogenic chemotherapy (see protocol SCNAUSEA)
- hydrocortisone & diphenhydrAMINE for history of hypersensitivity to etoposide (if applicable)

Premedication for oBINutuzumab to prevent infusion reactions:
(Note: patient should bring own supply of oral premedications)

Cycle 1 Day 2:

60 minutes prior to infusion, repeat in 4 hours if infusion exceeds 4 hours:
- dexamethasone IV 20 mg in 50 mL NS over 15 minutes

30 minutes prior to infusion, repeat in 4 hours if infusion exceeds 4 hours:
- acetaminophen PO 650 mg to 975 mg
- diphenhydrAMINE PO 50 mg

All subsequent infusions*:

30 minutes prior to infusion, repeat in 4 hours if infusion exceeds 4 hours:
- acetaminophen PO 650 mg to 975 mg
- diphenhydrAMINE PO 50 mg

*If patients experienced a Grade 3 infusion-related reaction with previous infusion **or** have a lymphocyte count greater than 25 x 10^9/L prior to next treatment: add an IV glucocorticoid (e.g., dexamethasone 20 mg) at least 60 minutes prior to infusion, repeat in 4 hours if infusion exceeds 4 hours.

Note: Alternative glucocorticoids include methylPREDNISolone IV 80 mg. *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.

TREATMENT:
- **INDUCTION PHASE:** predniSONE**,** DOXOrubicin, vinCRIStine, and cyclophosphamide in combination with oBINutuzumab; induction phase cycle is every 21 days x 6 cycles

Cycle 1:

Drug	Dose	BC Cancer Administration Guideline
predniSONE	45 mg/m^2* on Days 1 to 5 (*round dose to nearest 25mg)	PO in am with food
DOXOrubicin	50 mg/m^2 on Day 1	IV push
vinCRIStine	1.4 mg/m^2** on Day 1 (** no cap on dose)	IV in 50 mL NS over 15 min
cyclophosphamide	750 mg/m^2 on Day 1	IV in 100 to 250 mL NS over 20 min to 1 hour
oBINutuzumab	1000 mg on Days 2, 8 and 15	IV in 250 mL NS***

****Cycle 1 (Day 2):* initiate infusion at **50 mg/hour**; after 30 minutes, increase by 50 mg/hour every 30 minutes until rate = 400 mg/hour unless toxicity occurs. Refer to protocol appendix for oBINutuzumab infusion rate titration table. Vital signs prior to start of infusion, at every increment of infusion rate, and as

clinically indicated post infusion. Patients are to be under constant visual observation during all dose increases and for 2 hours after infusion completed.

Cycle 1 (Days 8 and 15): If no reaction or Grade 1 reaction to previous infusion and the final infusion rate was 100 mg/hour or faster, initiate infusion at **100 mg/hour** for 30 minutes; if tolerated, may escalate rate in increments of 100 mg/hour every 30 minutes until rate = 400 mg/hour. If Grade 2 or higher infusion reaction occurred during previous infusion, initiate infusion at 50 mg/hour for 30 minutes; if tolerated, may escalate rate in increments of 50 mg/hour every 30 minutes until rate = 400 mg/hour. Refer to protocol appendix for oBINutuzumab infusion rate titration table. Vital signs prior to start of infusion, at every increment of infusion rate, and as clinically indicated post infusion Patients are to be under constant visual observation during all dose increases and for 30 minutes after infusion completed.

Cycles 2 to 6:

Drug	Dose	BC Cancer Administration Guideline
predniSONE	45 mg/m^2** on Days 1 to 5 (**round dose to nearest 25mg)	PO in am with food
DOXOrubicin	50 mg/m^2 on Day 1	IV push
vinCRIStine	1.4 mg/m^2* on Day 1 (*no cap on dose)	IV in 50 mL NS over 15 min
cyclophosphamide	750 mg/m^2 on Day 1	IV in 100 to 250 mL NS over 20 min to 1 hour
oBINutuzumab	1000 mg on Day 1	IV in 250 mL NS***

***If no reaction or Grade 1 reaction with previous infusion and the final infusion rate was 100 mg/hour or faster, initiate infusion at **100 mg/hour** for 30 minutes; if tolerated, may escalate rate in increments of 100 mg/hour every 30 minutes until rate = 400 mg/hour. Refer to protocol appendix for oBINutuzumab infusion rate titration table. Vital signs prior to start of infusion, and as clinically indicated during and post infusion. Patients are to be under constant visual observation during all dose increases and for 30 minutes after infusion completed.

If Grade 2 or higher infusion reaction occurred during previous infusion, initiate infusion at 50 mg/hour for 30 minutes; if tolerated, may escalate rate in increments of 50 mg/hour every 30 minutes until rate = 400 mg/hour. Patients are to be under constant visual observation during all dose increases and for 2 hours after infusion completed.

Repeat every 21 days for 5 cycles i.e., cycles 2 to 6

- **MAINTENANCE PHASE:** oBINutuzumab monotherapy**.** To start ~ 2 months after the last induction phase oBINutuzumab dose. Maintenance phase cycle is every 2 months.

- **Cycles 7 to 18**: Patients with stable disease, complete response, or partial response after 6 cycles of combination therapy (with predniSONE, DOXOrubicin, vinCRIStine and cyclophosphamide with oBINutuzumab) should continue oBINutuzumab monotherapy for up to 2 years.

Drug	Dose	BC Cancer Administration Guideline
oBINutuzumab	1000 mg on Day 1	IV in 250 NS*

*If no reaction or Grade 1 reaction with previous infusion and the final infusion rate was 100 mg/hour or faster, initiate infusion at **100 mg/hour** for 30 minutes; if tolerated, may escalate rate in increments of 100 mg/hour every 30 minutes to a maximum rate of 400 mg/hour. Refer to protocol appendix for oBINutuzumab infusion rate titration table. Vital signs prior to start of infusion, and as clinically indicated during and post infusion Patients are to be under constant visual observation during all dose increases and for 30 minutes after infusion completed.

If Grade 2 or higher infusion reaction occurred during previous infusion, initiate infusion at 50 mg/hour for 30 minutes; if tolerated, may escalate rate in increments of 50 mg/hour every 30 minutes to maximum rate of 400 mg/hour. Patients are to be under constant visual observation during all dose increases and for 2 hours after infusion completed.

Repeat every 2 months for 2 years (12 doses) i.e., cycles 7 to 18

DOSE MODIFICATIONS:

- No dose reductions are recommended for oBINutuzumab. The infusion may be discontinued, held or its rate reduced as appropriate.

1. Infusion reactions to oBINutuzumab:

Refer to SCDRUGRX protocol for management guidelines.

Infusion reactions	Management
Grades 1 or 2 (mild or moderate)	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.
Grade 3 (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.

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

Infusion rate when resuming oBINutuzumab 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

2. Elderly Patients (age greater than 75 years):

- Cycle 1 doses of cyclophosphamide and DOXOrubicin should be administered at 75% doses. Further treatment should be given at the maximum dose tolerated by the patient, trying to escalate up to full 100% doses, but using the baseline experience with the 75% doses to guide these decisions.
- No dose adjustment is required for oBINutuzumab. Patients greater than or equal to 65 years experienced more serious adverse events than younger patients.

3. Hematological, for low counts due to treatment, not disease:

ANC (x10^9/L)	Platelets (x10^9/L)	Dose (all drugs)
Greater than or equal to 0.8	Greater than or equal to 80	100%
Less than 0.8	Less than 80	Delay until recovery

4. Neurotoxicity: For vinCRIStine

Toxicity	Dose Modification
Dysesthesias, areflexia only	100 %
Abnormal buttoning, writing	67%
Motor neuropathy, moderate	50%
Motor neuropathy, severe	Omit

5. **Hepatotoxicity**: For DOXOrubicin

Total bilirubin (micromol/L)	Dose Modification
2 to 35	100%
36 to 85	50%
Greater than 85	Omit DOXOrubicin. ***ADD*** cyclophosphamide 350 mg/m^2 to the dose already planned.

Note: This adjustment is only necessary for the initial treatment. After the hyperbilirubinemia has resolved, adjustment is only necessary if overt jaundice re-occurs. Serum bilirubin does not need to be requested before each treatment.

Hepatotoxicity: For vinCRIStine

Total bilirubin (micromol/L)	Dose Modification
Less than or equal to 25	100%
26 to 50	50%
Greater than 50	25%

6. **Cardiotoxicity**: DOXOrubicin only:

- When DOXOrubicin cannot be used due to proven cardiac dysfunction, it can be replaced by etoposide 50 mg/m^2 IV on Day 1, and 100 mg/m^2 PO on Days 2 and 3. (Use non-DEHP equipment with in-line filter)

PRECAUTIONS:

1. **oBINutuzumab Infusion Reactions (IR),** including anaphylaxis, may occur within 24 hours of infusion, usually with the first infusion and decreasing with subsequent infusions. Cycle 1 Day 2 infusion reactions have been most frequently reported at 1 to 2 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.
2. **Extravasation**: DOXOrubicin and vinCRIStine cause pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
3. **Hypersensitivity**: If applicable, monitor etoposide infusion for the first 15 minutes for signs of hypotension. Refer to SCDRUGRX.
4. **Tumour Lysis Syndrome (TLS)** including acute renal failure can occur within 12 to 24 hours after the first infusion of oBINutuzumab. Patients at risk of TLS should have appropriate prophylaxis and be monitored closely. Maintain adequate volume status and monitor blood chemistry, including potassium and uric acid levels. See BC Cancer Drug Manual for the oBINutuzumab drug monograph for more information.
5. **Bone Marrow Suppression** can occur during oBINutuzumab treatment and has resulted in Grade 3 and 4 **neutropenia** and **thrombocytopenia**. Monitor for signs/symptoms of infection; antimicrobial prophylaxis may be considered in neutropenic patients. Antiviral and/or antifungal prophylaxis as well as filgrastim (G-CSF) can also be considered.

Thrombocytopenia may require dose delays of oBINutuzumab. Consider withholding platelet inhibitors, anticoagulants, or other medications which may increase bleeding risk (especially during the first cycle). Leukopenia and lymphopenia commonly occur. Monitor blood counts frequently throughout therapy.

6. **Cardiac Toxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction. Cardiac assessment is recommended if patient has received greater than or equal to 300 mg/m^2 of doxorubicin. (BC Cancer Drug Manual). Work-up may include an assessment of cardiac ejection fraction, and cardiac oncology referral if necessary.
7. **Cardiovascular events**, such as myocardial infarction and dysrhythmias have been reported with oBINutuzumab and are sometimes fatal; patients with pre-existing cardiac disease may experience worsening of their cardiovascular disease.
8. **Hepatitis B Virus (HBV) Reactivation:** See SCHBV protocol for more details.
9. **Live or attenuated vaccines** are not recommended during treatment and until B-cell recovery has occurred after treatment (i.e., at least months after treatment is discontinued)
10. **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.

Call Dr. Diego Villa or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol. 2016 Aug;17(8):1081-1093.
2. Radford J, Davies A, Cartron G, et al. Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). Blood. 2013 Aug 15;122(7):1137-43.
3. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med. 2017 Oct 5;377(14):1331-1344.
4. Obinutuzumab (Gazyva) CADTH reimbursement recommendation for the treatment of adults with follicular lymphoma who relapsed after, or are refractory to, a rituximab containing regimen. Canadian Journal of Health Technologies, 2 June 2017

Appendix. oBINutuzumab infusion rate titration table

Induction Phase
- **Cycle 1: Day 2.**

oBINutuzumab 1000 mg IV in 250 mL NS Total volume = 315 mL		
TITRATION	**INFUSION RATE**	**VOLUME TO BE INFUSED (VTBI)**
50 mg/h x 30 min	16 mL/h	8 mL
100 mg/h x 30 min	32 mL/h	16 mL
150 mg/h x 30 min	47 mL/h	24 mL
200 mg/h x 30 min	63 mL/h	32 mL
250 mg/h x 30 min	79 mL/h	39 mL
300 mg/h x 30 min	95 mL/h	47 mL
350 mg/h x 30 min	110 mL/h	55 mL
400 mg/h x 45 min	126 mL/h	95 mL

Induction Phase
- **Cycle 1: Days 8 and 15.**
- **Cycles 2 to 6: Day 1 only.**

Maintenance Phase Cycles 7 to 18: 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