BC Cancer Protocol Summary for the Treatment of riTUXimab-refractory Follicular Lymphoma with Gemcitabine, Dexamethasone, Platinum and oBINutuzumab

Protocol Code	*LYGDPO*
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 discretion of treating oncologist (e.g., treatment with bendamustine in previous 2 years)

Note:

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

CAUTION:

- Creatinine clearance (CrCl) less than 45 mL/min (use CARBOplatin option)

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
- Baseline if clinically indicated: alkaline phosphatase, magnesium, calcium
- Before each treatment:
  - Day 1: CBC & Diff, creatinine
  - Day 8: CBC & Diff
    Creatinine (if cisplatin dose is given Day 1 and Day 8)
- Before each treatment cycle: Use calculated creatinine clearance and serum creatinine to determine CISplatin dose, see dose modifications below.

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)

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:** dexamethasone, gemcitabine, and platinum in combination with oBINutuzumab; induction phase cycle is every 21 days x 6 cycles

Cycle 1:

Drug	Dose†	BC Cancer Administration Guideline
dexamethasone	40 mg on Days 1 to 4	PO in am with food *(Note: The anti-emetic premedication is separate from the dexamethasone given as part of the protocol; both should be prescribed separately)*
gemcitabine	1000 mg/m^2 on Day 1 and Day 8	IV in 250 mL NS over 30 min*
CISplatin¥	75 mg/m^2 on Day 1	Prehydrate with 1000 mL NS over 1 hour, then CISplatin IV in 500 mL NS with 20 mEq potassium chloride, 1 g MgSO4, 30 g mannitol over 1 hour
oBINutuzumab	1000 mg on Days 2, 8 and 15	IV in 250 mL NS**

† Consider dose reduction to 75% for gemcitabine and CISplatin or CARBOplatin in patients greater than 70 years of age

* gemcitabine may be given during prehydration for CISplatin

***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.

¥ Alternatively CARBOplatin may be used instead of CISplatin. See Renal Dysfunction under Dose Modifications. Note: it is acceptable for physicians to substitute CARBOplatin for CISplatin for reasons other than reduced GFR (for example, concerns around ototoxicity with CISplatin).

Estimate calculated creatinine clearance (CrCl) with following formula:

$$\text{CrCl (mL/min)} = \frac{\text{N x (140-age in years) x wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

(N=1.04 for females, N=1.23 for males)

Borderline cases (CrCl 60 to 70 mL/min): perform nuclear renogram for GFR, if available

Cycles 2 to 6:

Drug	Dose†	BC Cancer Administration Guideline
dexamethasone	40 mg on Days 1 to 4	PO in am with food *(Note: The anti-emetic premedication is separate from the dexamethasone given as part of the protocol; both should be prescribed separately)*
gemcitabine	1000 mg/m^2 on Day 1 and Day 8	IV in 250 mL NS over 30 min*
CISplatin¥	75 mg/m^2 on Day 1	Prehydrate with 1000 mL NS over 1 hour, then CISplatin IV in 500 mL NS with 20 mEq potassium chloride, 1 g MgSO4, 30 g mannitol over 1 hour
oBINutuzumab	1000 mg on Day 1	IV in 250 mL NS**

† Consider dose reduction to 75% for gemcitabine and CISplatin or CARBOplatin in patients greater than 70 years of age

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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.

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Borderline cases (CrCl 60 to 70 mL/min): perform nuclear renogram for GFR, if available

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 dexamethasone, gemcitabine, and platinum with oBINutuzumab) should continue on 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:

- 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:

Cycles 1 to 6, Day 1 (and Day 2 of Cycle 1):

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose (dexamethasone, gemcitabine, and platinum)	oBINutuzumab Dose
Greater than or equal to 1.0	and	Greater than or equal to 75	100%	100%
Greater than or equal to 1.0	and	Less than 75	Delay 1 week*	Delay 1 week*
			If platelets greater than or equal to 75, give 100% dose of all drugs If platelets less than 75 but greater than 50, proceed at 100% and support with platelet transfusions	
Less than 1.0	and	Greater than or equal to 75	Delay 1 week*	
			If ANC greater than or equal to 1.0 give 100% If ANC less than 1.0 but greater than or equal to 0.5, proceed at 100% and start filgrastim**	
Less than 1.0	and	Less than 75	Delay 1 week*	
			If ANC greater than or equal to 0.5 and platelets greater than or equal to 50, proceed with 100% and start filgrastim with platelet transfusions If ANC less than 0.5 and/or platelets less than 50, delay and check counts every 7 days. When both ANC greater than or equal to 0.5 and platelets greater than or equal to 50, resume as above	

* if counts presumed to be low due to marrow involvement, treat after 1 week delay (i.e., at 4 weeks) despite counts

** filgrastim should be given prophylactically for all future cycles.

Cycles 1 to 6, Day 8 (and Day 15 of Cycle 1):

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose (dexamethasone, gemcitabine, and platinum)	oBINutuzumab Dose
Greater than or equal to 1.0	and	Greater than or equal to 75	100%	100%
Greater than or equal to 0.5 and less than 1.0	and	Greater than or equal to 75	Reduce gemcitabine (and CISplatin or CARBOplatin) dose to 75% of current cycle's Day 1 dose	Omit
Greater than or equal to 1.0	and	Less than 75 and greater than or equal to 50	Reduce gemcitabine (and CISplatin or CARBOplatin) dose to 75% of current cycle's Day 1 dose	
Greater than or equal to 0.5 and less than 1.0	and	Less than 75 and greater than or equal to 50	Reduce gemcitabine (and CISplatin or CARBOplatin) to 75% of current cycle's Day 1 dose	
Less than 0.5	or	Less than 50	Omit gemcitabine (and CISplatin or CARBOplatin) and start filgrastim**	

** filgrastim should be given prophylactically for all future cycles

Cycles 7 to 18:

ANC ($x10^9$/L)	Platelets ($x10^9$/L)	oBINutuzumab dose
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. Renal Dysfunction: gemcitabine and CISplatin

- Delay for one week if ***serum*** creatinine greater than 3 x ULN where ULN = local upper limit of normal range. If serum creatinine less than 3 x ULN adjust CISplatin dose as follows

Creatinine Clearance (mL/min)	CISplatin dose	Gemcitabine dose
Greater than or equal to 60	75 mg/m^2 on Day 1	100%
45 to 59	37.5 mg/m^2 on Days 1 and 8 or go to CARBOplatin¥ option	100%
Less than 45	***Delay*** (or use CARBOplatin¥ option)	***Delay/Omit**** (or use CARBOplatin¥ option)

****Delay if Day 1; if Day 8, omit if serum creatinine greater than 3 x ULN where ULN = local upper limit of normal range.***

¥ Alternatively CARBOplatin can be used instead of CISplatin per physician discretion for reasons other than reduced GFR (for example, concerns around ototoxicity).

Drug	Dose	BC Cancer Administration Guideline
CARBOplatin	AUC 5 on Day 1 only Dose= AUC x (GFR+25) (maximum 800 mg)	IV in 100 to 250 mL NS over 30 minutes

The lab reported GFR (MDRD formula) may be used as an alternative to the Cockcroft-Gault estimate of GFR. When a nuclear renogram is available, this clearance would take precedence. Maximum carboplatin dose is 800 mg.

Note: The same method of estimation should be used throughout the treatment course (i.e., if lab reported GFR was used initially, this should be used for dosing in all subsequent cycles and not the Cockcroft-Gault estimate).

Consider re-calculation of CARBOplatin dose if serum creatinine changes ± 20% from baseline.

Prehydration is not needed if CARBOplatin is given.

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. **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.
3. **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.
4. **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.
5. **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)
6. **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare) with gemcitabine. Use caution with pre-existing renal dysfunction.
7. **Pulmonary Toxicity**: Acute shortness of breath may occur. Discontinue treatment if drug-induced pneumonitis is suspected.
8. **Hepatitis B Reactivation**: See SCHBV protocol for more details.
9. **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