# BC Cancer Protocol Summary for the Treatment of riTUXimab-refractory Follicular Lymphoma (FL) with oBINutuzumab in combination with Bendamustine

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|---|---|
| ***Protocol Code*** | *LYBENDO* |
| ***Tumour Group*** | *Lymphoma* |
| ***Contact Physician*** | *Dr. Laurie H. Sehn* |

**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 a last dose of rituximab and
- Symptomatic disease requiring systemic therapy.

Patients should:

- Be appropriate candidates for bendamustine.

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

**CAUTION:**

- Creatinine clearance (CrCl) less than 40 mL/min, and
- AST or ALT greater than 2.5 x upper limit of normal and total bilirubin greater than 1.5 x upper limit of normal

**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 (cycle 1 to 6)**: Antiemetic protocol for moderate emetogenic chemotherapy (see protocol SCNAUSEA)

**Maintenance phase treatment**: Antiemetic protocol for rare emetogenic chemotherapy (see protocol SCNAUSEA)

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

*Cycle 1 Day 1:*
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: oBINutuzumab in combination with bendamustine; induction phase cycle is every 28 days x 6 cycles**

**Cycle 1**

| Drug | Dose | BC Cancer Administration Guideline |
|---|---|---|
| oBINutuzumab | 1000 mg on Days 1, 8 and 15 | IV in 250 mL NS* |
| bendamustine | 90 mg/m$^2$ on Days 1 and 2 | IV in 250 to 500 mL NS over 1 hour |

**Cycle 1 (Day 1):* 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 |
|---|---|---|
| oBINutuzumab | 1000 mg on Day 1 | IV in 250 mL NS* |
| bendamustine | 90 mg/m$^2$ on Days 1 and 2 | IV in 250 to 500 mL NS over 1 hour |

*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 28 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 bendamustine) 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.<br>Once symptoms resolved, may resume infusion.<br>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.<br>Once symptoms resolved, may resume infusion at no more than half of the rate when reactions occurred (see table below).<br>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. 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 |

**3. Dosage in the elderly**

No dose adjustment is required for either obinutuzumab or bendamustine. Patients greater than or equal to 65 years experienced more serious adverse events than younger patients.

**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 1 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. **Bendamustine Infusion Reactions (IR) and Hypersensitivity**: Bendamustine can cause allergic type reactions during the IV infusion such as fever, chills, pruritus and rash. Severe anaphylactic and anaphylactoid reactions have occurred rarely, particularly in the second and subsequent cycles of therapy. If an allergic reaction occurs, stop the infusion and the physician in charge should determine a safe time and rate to resume the infusion. Consider pre-treatment with antihistamines, antipyretics and corticosteroids for patients experiencing Grade 1 or 2 infusion reactions; consider discontinuing bendamustine treatment for patients experiencing Grade 3 or 4 infusion reactions. See BC Cancer Hypersensitivity Guidelines.
3. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Thrombocytopenia:** Support with platelet transfusion may be required.
5. **Hepatitis B Virus (HBV) Reactivation** See SCHBV protocol for more details.
6. **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.
7. **Tumour Lysis Syndrome (TLS)** including acute renal failure can occur within 12-24 hours after the first infusion for both oBINutuzumab and bendamustine. 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. Allopurinol has been used, but the concomitant use of bendamustine and allopurinol can cause increased risk of severe skin toxicity. See BC Cancer Drug Manual for the oBINutuzumab Drug Monograph and bendamustine Drug Monograph for more information.
8. 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.
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. **Bone Marrow Suppression** can occur when oBINutuzumab and bendamustine are used in combination 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 and bendamustine. 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.

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.
12. **Drug Interactions**: CYP1A2 inhibitors can potentially decrease plasma concentration of bendamustine. CYP1A2 inducers can potentially increase plasma concentration of bendamustine.
13. **Skin Reactions**: Rash, toxic skin reactions and bullous exanthema have been reported with bendamustine. They may be progressive and increase in severity with further treatment. Monitor closely. If skin reactions are severe or progressive, consider withholding or discontinuing bendamustine.

**Call Dr. Laurie H. Sehn or tumor group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.**

**References**:


1. Cartron G, de Guibert S, Dilhuydy MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase ½ GAUGUIN study. Blood 2014;124:2196-202.
2. Salles G, Morschhauser F, Lamy T, et al. Phase 1 study results of the type II glycoengineered humanized anti-CD20 monoclonal antibody obinutuzumab (GA101) in B-cell lymphoma patients. Blood 2012.
3. Sehn LH, Assouline SE, Stewart DA, et al. A phase 1 study of obinutuzumab induction followed by 2 years of maintenance in patients with relapsed CD20-positive B-cell malignancies. Blood 2012;119:5118-25.
4. Sehn LH, Goy A, Offner FC, et al. Randomized Phase II Trial Comparing Obinutuzumab (GA101) with Rituximab in Patients with Relapsed CD20+ Indolent B-Cell Non-Hodgkin Lymphoma: Final Analysis of the GAUSS Study. J Clin Oncol 2015;33:3467-74.
5. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 2014;370:1101-10.
6. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203-10.
7. Rummel M, Kaiser U, Balser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantel-cell lymphomas: a multicentre. Randomised, open-label, non-inferiority phase 3 trial. Lancet Oncol 2016;17:57-66.
8. Friedberg JW, Cohen P, Chen L, et al. Bendamustine in patients with rituximab-refractoryindolent and transformed non-Hodgkin lymphoma: results from a phase II multicentre, single-agent study. J Clin Oncol 2008;26:204-10.
9. Kahl BS, Bartlett NL, Leonard JP, et al. Bendamusitne is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a multicentre study. Cancer 2010;116:106-14.
10. 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 2 trial. Lancet Oncol 2016;1081-93.

## Appendix. oBINutuzumab infusion rate titration table

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

| **oBINutuzumab 1000 mg IV in 250 mL NS<br>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<br>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 |