

BC Cancer Protocol Summary for the Treatment of ritUXImab-refractory Follicular Lymphoma with **bendamustine in Combination with oBINutuzumab**

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, **HBV viral load (see protocol [SCHBV](#))**

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 of oral medications)

Cycle 1 Day 1:

30 minutes prior to bendamustine:

- dexamethasone 20 mg IV

30 minutes prior to oBINutuzumab (give during bendamustine infusion):

- acetaminophen 650 mg to 975 mg PO
- diphenhydramine 50 mg PO

Cycle 1 Days 8 and 15:

60 minutes prior to oBINutuzumab, if reaction to previous oBINutuzumab was Grade 3, or if lymphocyte count greater than $25 \times 10^9/L$ before Cycle 1 Day 1:

- dexamethasone 20 mg IV

30 minutes prior to oBINutuzumab:

- acetaminophen 650 to 975 mg PO
- diphenhydramine 50 mg PO

Cycles 2 to 6 Day 1:

30 minutes prior to bendamustine, if reaction to previous oBINutuzumab was Grade 3, or if lymphocyte count greater than $25 \times 10^9/L$ before Day 1 of current cycle:

- dexamethasone 20 mg IV (if not giving PO)

30 minutes prior to oBINutuzumab (give during bendamustine infusion):

- acetaminophen 650 to 975 mg PO
- diphenhydramine 50 mg PO

Cycles 7 to 18:

60 minutes prior to oBINutuzumab, if reaction to previous oBINutuzumab was Grade 3, or if lymphocyte count greater than $25 \times 10^9/L$ before Day 1 of current cycle:

- dexamethasone 20 mg IV

30 minutes prior to oBINutuzumab:

- acetaminophen 650 to 975 mg PO
- diphenhydramine 50 mg PO

Note: Alternative glucocorticoids include 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, follow hepatitis B prophylaxis as per [SCHBV](#).

TREATMENT:

INDUCTION PHASE: bendamustine in combination with oBINutuzumab; induction phase cycle is every 28 days x 6 cycles

Cycle 1:

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

*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.
- For first dose, constant visual observation during dose increases and for 30 minutes 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. Refer to protocol appendix for oBINutuzumab infusion rate titration table.
- 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.

Cycles 2 to 6:

| Drug | Dose | BC Cancer Administration Guideline |
|--------------|--------------------------------------|------------------------------------|
| bendamustine | 90 mg/m ² on Days 1 and 2 | IV in 250 to 500 mL NS over 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.

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.

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.

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.

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 (mg/h) | Maximum infusion rate when resuming infusion (mg/h) |
|---|---|
| 25 | 10 |
| 50 | 25 |
| 100 | 50 |
| 150 | 50 |
| 200 | 100 |
| 250 | 100 |
| 300 | 150 |
| 350 | 150 |
| 400 | 200 |

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 bendamustine or oBINutuzumab. Patients greater than or equal to 65 years experienced more serious adverse events than younger patients.

PRECAUTIONS:

- 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 [SCDRUGRX](#).
- 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. Symptoms may include nausea, vomiting, chills, hypotension, pyrexia, dyspnea,

flushing, hypertension, headache, tachycardia, and diarrhea. Infusion reactions may require rate reduction, interruption of therapy, or treatment discontinuation. For first dose, patients are to be under constant visual observation during all dose increases and for 30 minutes after infusion is completed. For all subsequent doses, constant visual observation is not required. Vital signs are not required unless symptomatic. 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.

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 [bendamustine](#) and 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. 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 [bendamustine](#) and oBINutuzumab Drug Monographs 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 [bendamustine](#) and oBINutuzumab 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 [bendamustine](#) and 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.
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 mantle-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-refractory indolent 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. Bendamustine 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 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,**
- and**

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 |