BC Cancer Protocol Summary for Treatment of Previously Untreated Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma with oBINutuzumab and Chlorambucil

Protocol Code *LYOBCHLOR*

Tumour Group *Lymphoma*

Contact Physician *Dr Laurie Sehn*

ELIGIBILITY:

- Patients with previously untreated chronic lymphocytic leukemia/small lymphocytic lymphoma
- Patients not candidates for fludarabine-based therapy due to co-morbidities or renal insufficiency
- Patients with symptomatic disease requiring systemic treatment

TESTS:

- Baseline (required before first treatment): CBC & diff, platelets, creatinine, ALT, bilirubin, electrolytes, uric acid
- Required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2: HBsAg, HBcoreAb
- Day 1 of each Cycle: CBC & diff, platelets

PREMEDICATIONS:

Antiemetic protocol for rare emetogenic chemotherapy - see protocol SCNAUSEA

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

Cycle 1: Days 1 and 2:
60 minutes prior to infusion:

- dexamethasone IV 20 mg in 50 mL NS over 15 minutes

30 minutes prior to infusion:

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

Cycle 1: Days 8 and 15
30 minutes prior to infusion:

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

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

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

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

Note: Alternative corticosteroids include prednisoLONE PO 100 mg or methylPREDNIsolone IV 80 mg. *Hydrocortisone is ineffective and not recommended*.

SUPPORTIVE MEDICATIONS:
If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg PO daily for the duration of chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive.

TREATMENT

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)

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

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

Start cycle 2 on day 1 of 28 day cycle

Cycles 2 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)

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

Repeat every 28 days

chlorambucil:

Cycles 1 to 6

Drug	Dose	BC Cancer Administration Guideline
chlorambucil	0.5 mg/kg* on Day 1 and Day 15** Subsequently, if ANC greater than 3.5 x 10^9/L, increase dose by 0.1 mg/kg, adjusting dose to induce a therapeutic response but not cause a fall in neutrophil count below 1.2 x 10^9/L. MAXIMUM DOSE: 0.8 mg/kg every 2 weeks.	PO

*round to nearest 2 mg (2 mg tablet film-coated tablets)

**additional chlorambucil dosing options available, see BC Cancer Protocol LYCHLOR

Repeat every 28 days for 6 cycles unless disease progression or unacceptable toxicity occurs

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:

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

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

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 1.2	Greater than or equal to 80	100%
Less than 1.2	Less than 80	Delay until recovery

Missed doses may be administered later at clinician's discretion; the 28 day-interval should be maintained
If chlorambucil is discontinued due to related toxicity, may continue oBINutuzumab based on physician discretion

PRECAUTIONS:

1. **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. 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.
2. **Hepatitis B Virus (HBV) Reactivation** may occur and sometimes result in fulminant hepatitis, hepatic failure and death. **Do not administer to patients with an active hepatitis infection.** All patients should be tested for HBsAg and HBcoreAb prior to initiation of oBINutuzumab. If either test is positive, such patients should be treated with lamiVUDine during chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.
3. **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.
4. **Tumour Lysis Syndrome (TLS)** including acute renal failure, can occur within 12-24 hours after the first infusion. Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely. See BC Cancer Agency Cancer Drug Manual oBINutuzumab Drug Monograph for more information.
5. **Cardiovascular events,** such as myocardial infarction and dysrhythmias, including fatal cases can occur. Patients with pre-existing cardiac disease may develop worsening of the cardiovascular disease and should be monitored closely.
6. **Live or attenuated vaccines** are not recommended during treatment and until B-cell recovery has occurred after treatment (i.e., at least 3 months after treatment is discontinued)
7. **Bone Marrow Suppression** can occur when oBINutuzumab and Chlorambucil are used in combination and has resulted in grade 3 and 4 **neutropenia** and **thrombocytopenia**. Monitor for signs/symptoms of infection; antimicrobial prophylaxis is recommended in neutropenic patients. Antiviral and/or antifungal prophylaxis as well as filgrastim (G-CSF) should also be considered. Thrombocytopenia may require dose delays of oBINutuzumab and chlorambucil and/or dose reductions of chlorambucil. 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.
8. **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.** 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. Laurie 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, Dihuydy MS, et al. Obinutuzumab (GA 101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 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 (GA 101) in B-cell malignancies. 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 (GA 101) 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. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet 2010;376:1164-74.
7. Gerrie AS, Toze CL, Ramadan KM, et al. Fludarabine (F) and rituximab (R) (FR) as initial therapy for chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL): population-based experience matches clinical trials. Blood 2009;114;abstract 2363.
8. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2009;27:4378-84.
9. Leukemia/Bone Marrow Transplant Program of British Columbia. Leukemia/BMT Manual. E-Edition ed. Vancouver, British Columbia: Vancouver Hospital and Health Sciences/BC Cancer Agency;2013. 102-4.
10. Bosch F, Illmer T, Turgut M, et al. Preliminary safety results from the phase IIIb GREEN study of obinutuzumab (GA101) alone or in combination with chemotherapy for previously untreated of relapsed/refractory chronic lymphocytic leukemia (CLL). 56th ASH Annual Meeting and Exposition. Abstract 3345.

Appendix. 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