Regimen Monograph

A - Regimen Name

BEND+OBIN Regimen

Bendamustine-oBINutuzumab

Disease Site	Hematologic - Lymphoma - Non-Hodgkin's Low Grade
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	For the treatment of patients with follicular lymphoma† whose disease is refractory* to a rituximab-containing regimen and has a good performance status † indolent lymphoma histologies other than follicular lymphoma (excluding CLL and mantle cell lymphoma) may be eligible for obinutuzumab funding (refer to NDFP form) * no response to OR progression during or within 6 months after rituximab or a rituximab-containing regimen
Supplementary Public Funding	**oBINutuzumab** New Drug Funding Program (Obinutuzumab - In Combination with Chemotherapy for Refractory Follicular Lymphoma)

bendamustine
New Drug Funding Program (Bendamustine - Relapsed_Refractory - Indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma)

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B - Drug Regimen

Induction (BEND+OBIN):

Cycle 1:

oBINutuzumab	1000* mg	IV	Days 1, 8 and 15
bendamustine	90 mg /m²	IV	Days 1 & 2

Cycles 2-6:

oBINutuzumab	1000* mg	IV	Day 1
bendamustine	90 mg /m²	IV	Days 1 & 2

*For obinutuzumab maintenance use, report as regimen OBIN(MNT) after BEND+OBIN induction.

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C - Cycle Frequency

Induction: REPEAT EVERY 28 DAYS for up to 6 cycles unless disease progression or unacceptable toxicity (see NDFP form)

For patients who responded to or have stable disease after induction therapy, refer to maintenance obinutuzumab regimen - OBIN(MNT).

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Obinutuzumab:

Hepatitis B screening should be performed prior to treatment for all patients.

Patients at risk for tumour lysis syndrome should receive adequate hydration and uricostatics or alternative starting 12 to 24 hours prior to infusion.

Consider withholding antihypertensives (if applicable) 12 hours prior to infusion, during infusion and for the first hour after drug administration, and withholding concomitant medications that increase bleeding risk, especially in the first cycle.

Patients with neutropenia should receive antimicrobial prophylaxis; consider use of G-CSF, antiviral and antifungal prophylaxis.

Premedication recommendations:

Treatment cycle, day	Patients	Premedication
Cycle 1, Day 1	All	IV corticosteroid* completed at least 1 hr prior to infusion & PO analgesic/antipyretic** & antihistamine*** at least 30 min prior to infusion

Subsequent infusions	Patients with no prior IR during previous infusion	PO analgesic/antipyretic** at least 30 min prior to infusion
	Patients with grade 1 or 2 IR with previous infusion	PO analgesic/antipyretic** & antihistamine*** at least 30 min prior to infusion
	Patients with grade 3 IR with previous infusion OR patients with lymphocyte counts > 25 x 10^9/L prior to next treatment	IV corticosteroid* completed at least 1 hr prior to infusion & PO analgesic/antipyretic** & antihistamine*** at least 30 min prior to infusion

*e.g. 100 mg prednisone or 20 mg dexamethasone. Hydrocortisone should not be used as it has not been effective in reducing IR rates.

**e.g. 1000 mg acetaminophen

***e.g. 50 mg diphenhydramine

Bendamustine-only days:

- Consider pre-medication for patients with Grade 1 or 2 reactions with prior infusion
- Analgesic/antipyretic (e.g. acetaminophen), corticosteroid and an antihistamine (e.g. diphenhydramine) should be considered in subsequent cycles.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and may be considered.

Dosage with toxicity

No dose reductions are recommended for obinutuzumab. The infusion may be discontinued, held or its rate reduced as described in the table below.

Dose levels for bendamustine: 90 mg/m^2, 60 mg/m^2. Do not re-escalate after reduction for toxicity.

Do not treat until ANC and hemoglobin ≤ grade 2, platelets and non-hematologic toxicity ≤ grade 1.

Toxicity	Obinutuzumab dose	Bendamustine dose
Grade 4 hematologic, febrile neutropenia, bleeding	Hold* until ≤ grade 2, restart at usual dose. Discontinue if no recovery within 4 weeks.	Hold* until ≤ grade 2, consider G-CSF and prophylactic antibiotics. Consider dose modification. Discontinue if no recovery within 4 weeks.
Grade 2 or 3 related organ/non-hematologic toxicity	Hold* until ≤ grade 1. Discontinue if no recovery within 4 weeks.	Hold* until ≤ grade 1, then restart at 1 dose level reduction for grade 3. Discontinue if no recovery within 4 weeks.
Grade 4 related organ/non-hematologic toxicity	Discontinue	
Viral hepatitis or other serious infections; reactivation of hepatitis B	Discontinue	
Suspected PML	Hold and refer to neurologist for diagnosis and treatment. Discontinue if confirmed.	
Grade 1-2 infusion reaction (IR)	Reduce infusion rate and treat symptoms. Restart once resolved. Escalate infusion rate as tolerated at increments appropriate for treatment dose (see administration section).	If related to bendamustine, hold or slow infusion; premedicate before re-challenge and subsequent cycles.
Grade 3 IR	Hold infusion and treat symptoms. Restart once resolved at no more than half the previous rate. Escalate infusion rate as tolerated at increments appropriate for treatment dose (see administration section).	If related to bendamustine, discontinue.

Grade 4 IR, 2nd episode of grade 3 IR (during same or subsequent infusion), acute life-threatening respiratory symptoms OR Anaphylaxis or serum sickness	Discontinue	Discontinue

*Hold up to 4 weeks until major organ toxicities recover to ≤ grade 1 (or as specified in table), platelets ≥ 75 x 10^9/L and ANC ≥ 1 x 10^9/L

Hepatic Impairment

For obinutuzumab, safety and efficacy have not been established in patients with hepatic impairment.

For bendamustine:

Bilirubin	**AST or ALT or ALP**	**Bendamustine dose**
< 1.5 x ULN	2.5 x ULN	Caution
> 1.5 x ULN	> 2.5 x ULN	Do not use

Renal Impairment

For obinutuzumab, patients who have a creatinine clearance < 50mL/min in the pivotal study experienced more serious adverse events, including fatal ones, than those with creatinine ≥ 50 mL/min.

Creatinine clearance (mL/min)	**Obinutuzumab dose**	**Bendamustine dose**
> 50	No dose adjustment	Use with caution
30-50	No dose adjustment; use with caution	Use with caution
<30	No data	Do not use

Dosage in the Elderly

No dose adjustment is required for either obinutuzumab or bendamustine. Patients ≥ 65 years experienced more serious adverse events than younger patients. No efficacy differences were observed between older and younger patients.

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F - Adverse Effects

Refer to oBINutuzumab, bendamustine drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Nausea, vomiting • Infusion-related reaction (immediate or delayed; may be severe) • Fatigue	• Diarrhea • Myelosuppression +/- infection (including atypical, viral reactivation), bleeding (may be severe) • Fever • Constipation • Increased LFTs (may be severe) • Increased creatinine (may be severe)	• Anorexia • Mucositis • Dyspepsia • Cough, dyspnea • Rash (may be severe) • Edema • Musculoskeletal pain • Headache • Dizziness • Insomnia • Abdominal pain • Dysgeusia • Fever	• Arterial / venous thromboembolism • Cardiotoxicity • Arrhythmia • QTc prolongation • Hypertension • Tumour lysis syndrome • Secondary malignancy • Hemolysis • Capillary leak syndrome • Pancreatitis • Pneumonitis, ARDS • PML • GI perforation • Anaphylaxis, serum sickness

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G - Interactions

Refer to oBINutuzumab, bendamustine, drug monograph(s) for additional details

- No clinical drug interaction studies have been conducted with obinutuzumab or bendamustine
- Use with caution with CYP1A2 inhibitors and inducers (may alter bendamustine metabolism)
- Use with caution and monitor closely for infections when given with other immunosuppressive drugs.

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H - Drug Administration and Special Precautions

Refer to oBINutuzumab, bendamustine drug monograph(s) for additional details

Administration: obinutuzumab

Treatment cycle	Obinutuzumab dose	Infusion rate*
Cycle 1, day 1	1000 mg	50 mg/hr. May escalate as tolerated by 50 mg/hr q30 min to max of 400 mg/hr.
Cycle 1, days 8 & 15; Cycles 2-6, day 1	1000 mg	100 mg/hr if IR ≤ grade 1 at rates ≥ 100mg/hr on day 1. May escalate as tolerated by 100 mg/hr q30 min to max of 400 mg/hr. 50 mg/hr if previous grade grade 2 or 3 IR. May escalate as tolerated by 50 mg/hr q30 min to max of 400 mg/hr.

*For infusion rate modifications in the case of IR, see dosage with toxicity section

- Obinutuzumab should be administered only as an IV infusion through a dedicated line. **Do not administer as an IV push or bolus.**
- Withdraw required amount of diluent from vial and dilute in 250 ml PVC or non-PVC polyolefin

bags containing 0.9% sodium chloride. See product monograph for details.
- Gently invert the IV bag to mix. Do not shake.
- If a planned dose is missed, it should be administered as soon as possible; do not wait until the next planned dose. The planned treatment interval should then be maintained between doses.
- Compatible with sodium chloride 0.9%. Do not mix with other IV solutions.
- Also compatible with the following IV bags and sets:
    - polyethylene, polypropylene bags
    - PVC, polyurethane or polyethylene infusion sets
    - polyetherurethane catheters
    - optional inline filters with polyethersulfon product contact surfaces
    - 3-way stopcock infusion aid made from polycarbonate

Administration: bendamustine

- Infuse over 60 minutes
- Bendamustine infusions should be administered in a setting where full resuscitation facilities are immediately available, and under the close supervision of someone experienced and capable of dealing with severe infusion-related reactions.
- **DO NOT** administer as an IV push or bolus.
- **Dilute** to a final concentration of 0.2 - 0.6 mg/mL in 500 mL infusion bag of 0.9% sodium chloride or 2.5% dextrose/0.45% sodium chloride.
- Reconstituted solution must be transferred to infusion bag within 30 minutes of reconstitution.
- Administer bendamustine through a dedicated line.
- Compatible with PVC or polyethylene bags.
- Do not admix with other drugs.

Contraindications:

- Patients who have a hypersensitivity to these drugs or any of their components, including mannitol
- Patients with serious infections

Warnings/precautions:

- Do not give to patients who have an active infection.
- Avoid live and live-attenuated vaccines during treatment and until B-cell recovery. Following vaccination, do not start treatment until protective antibody titres have been reached.
- Use with extreme caution in patients who are positive for hepatitis.
- Use with caution in patients with a history of recurring or chronic infections.
- Patients with a history of cardiovascular or respiratory disease should be monitored closely during and after infusions. Use caution when hydrating patients with history of cardiovascular disease, to prevent fluid overload.
- Use with caution in patients with hypertension. Patients at acute risk of hypertensive crisis should be assessed for the risk vs benefit of withholding anti-hypertensives
- Use bendamustine with caution in patients with mild renal and hepatic impairment.

Pregnancy & lactation:

- These drugs are not recommended for use in pregnancy.
- Adequate contraception should be used by both sexes 2 weeks before, during treatment, and for at least 18 months after the last dose. In case of exposure during pregnancy, newborns should be monitored for B-cell depletion and live vaccines postponed until B-cell recovery.
- Breastfeeding is not recommended until at least 18 months after the last dose.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- Cardiac tests for all patients with cardiac risk factors; Baseline and as clinically indicated
- CBC; Baseline, before each dose and as clinically indicated following treatment completion
- Hepatitis B screening prior to treatment for all patients. Monitor for signs and symptoms of hepatitis B during treatment. Seropositive patients should see hepatologist and be closely monitored for several months after the last infusion.
- Liver and renal function tests; Baseline and prior to each cycle
- Blood pressure; Baseline and regular
- Electrolytes, including sodium, potassium, magnesium and uric acid; Baseline and regular
- Infusion-related reactions; during and after the infusion
- Clinical toxicity assessment for tumour lysis syndrome, hypersensitivity, infection, bleeding, thromboembolism, respiratory, neurologic, GI, skin and cardiac effects; At each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Blood glucose; Baseline and periodic
- CMV testing in febrile patients; As clinically indicated
- HIV status; Baseline

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J - Administrative Information

Approximate Patient Visit	6 hours
Pharmacy Workload (average time per visit)	28.224 minutes
Nursing Workload (average time per visit)	54.917 minutes

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K - References

Obinutuzumab and bendamustine drug monographs, Cancer Care Ontario

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):1081-93.

Cheson BD, Chua N, Mayer J, et al. Overall survival benefit in patients with rituximab-refractory indolent non-Hodgkin lymphoma who received obinutuzumab plus bendamustine induction and obinutuzumab maintenance in the GADOLIN study. J Clin Oncol. 2018 Aug 1;36(22):2259-66.

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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