BC Cancer Protocol Summary for Treatment of Lymphoma using oBINutuzumab, Glofitamab, Gemcitabine and Oxaliplatin

Protocol Code	*ULYOGGEMOX*
Tumour Group	*Lymphoma*
Contact Physicians	*LY Systemic Therapy*

ELIGIBILITY:

Patients must:

- Have one of the following indications for use for relapsed or refractory disease:
  - Diffuse large B-cell lymphoma (DLBCL) not otherwise specified,
  - DLBCL transformed from indolent lymphoma,
  - High grade B-cell lymphoma,
  - Primary mediastinal B-cell lymphoma,
  - Follicular lymphoma Grade 3b
- Meet one of the following criteria:
  - Be ineligible for autologous stem cell transplant (ASCT) and have received at least one prior line of therapy,
  - Received two or more prior lines of systemic therapy, and unable to receive CAR T-cell therapy,
  - Have previously received CAR T-cell therapy
- Have access to a treatment center with expertise to manage cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)
- Have BC Cancer “Compassionate Access Program” request approval prior to treatment

Patients should have:

- No signs or symptoms of active infection
- Have good performance status

EXCLUSIONS:

Patient must not:

- Be a candidate for ASCT
- Have current or previous primary or secondary CNS lymphoma
- Have disease refractory to CD20 x CD3 bispecific antibody or to gemcitabine and oxaliplatin therapy

TESTS:

- Baseline: CBC & Diff, creatinine, total bilirubin, ALT
- Baseline, if clinically indicated: sodium, potassium, urea, uric acid, alkaline phosphatase, phosphate, calcium, albumin, LDH, random glucose, immunoglobulin panel (IgA, IgG, IgM)
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with Cycle 2): HCAb, HBsAg, HBsAb, HBcoreAb
- Cycle 1, prior to Days 8 and 15: CBC & Diff (may proceed with treatment regardless of hematologic counts)
- Cycle 2 and onward, prior to each Cycle: CBC & Diff, creatinine, total bilirubin, ALT, vital signs
- Cycle 1 Day 9, if clinically indicated (responsible provider to review labs, if ordered, drawn day after treatment prior to discharge): CBC & Diff, creatinine, sodium, potassium, phosphate, calcium, magnesium, total bilirubin, ALT, alkaline phosphatase, LDH
- If clinically indicated: sodium, potassium, phosphate, calcium, magnesium, uric acid, albumin, alkaline phosphatase, LDH, random glucose, GGT, immunoglobulin panel (IgA, IgG, IgM), HBV viral load (see protocol SCHBV)

SUPPORTIVE CARE MEDICATIONS:

- Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV
- Ensure antiviral prophylaxis against herpes virus infections is in place prior to initiation of treatment. Patients should take valACYclovir 500 mg PO daily while on treatment and for 3 months following completion of glofitamab treatment
- Pneumocystis jirovecii (PJP) prophylaxis: cotrimoxazole 1 DS tablet PO 3 times each week (Monday, Wednesday and Friday) and for 3 months following completion of glofitamab treatment
- For patients receiving Cycle 1 Day 15 and Cycle 2 doses in the outpatient setting: consider providing a prescription for one dexamethasone 12 mg dose, for use in the event of CRS occurrence.

PREMEDICATIONS:

Premedication for oBINutuzumab to prevent infusion-related reactions (IRRs):
Cycle 1 Day 1:

- 60 minutes prior to oBINutuzumab infusion:
  - dexamethasone 20 mg IV
- 30 minutes prior to oBINutuzumab infusion:
  - acetaminophen 650 to 975 mg PO
  - diphenhydrAMINE 50 mg PO/IV

Note: Alternative glucocorticoids include methylPREDNISolone 80 mg IV. *Hydrocortisone is ineffective and not recommended as a premedication for oBINutuzumab but may still be used for an infusion-related reaction.*

Premedication for glofitamab to prevent CRS and IRRs:

- Optional prehydration with 500 mL NS IV over 30 minutes prior to glofitamab can be considered, to minimize risk of hypotension related to CRS

Cycle 1 Days 8 and 15, Cycle 2, and Cycle 3:

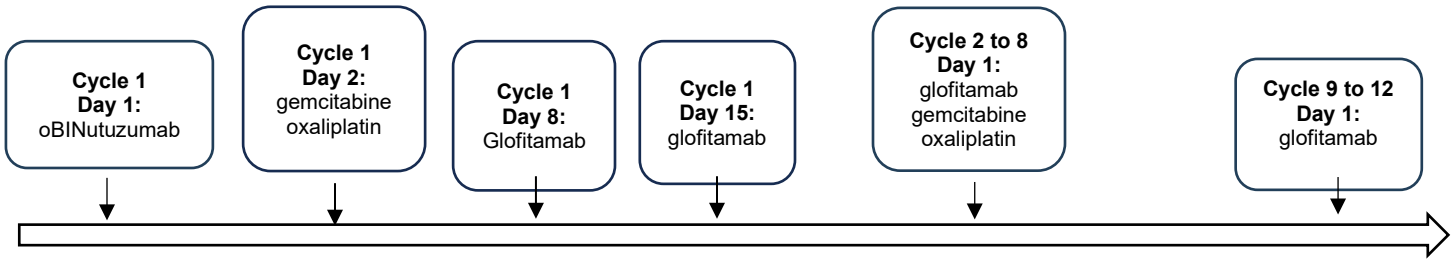
- 60 minutes prior to glofitamab:
  - dexamethasone 20 mg IV
- 30 minutes prior to glofitamab:
  - diphenhydrAMINE 50 mg PO/IV, and
  - acetaminophen 650 to 975 mg PO

Cycle 4 to 12:

- If patient experienced *any grade* CRS with previous dose, 60 minutes prior to glofitamab:
  - dexamethasone 20 mg IV
- All patients, regardless if prior CRS, 30 minutes prior to glofitamab:
  - acetaminophen 650 to 975 mg PO, and
  - diphenhydrAMINE 50 mg PO/IV

- For treatment days with gemcitabine and oxaliplatin: antiemetic protocol for moderately emetogenic chemotherapy. See SCNAUSEA protocol
- If Grade 1 or 2 oxaliplatin hypersensitivity reactions:
  - 45 minutes prior to oxaliplatin:
    - dexamethasone 20 mg IV in 50 mL NS over 15 minutes
  - 30 minutes prior to oxaliplatin:
    - diphenhydrAMINE 50 mg IV in 50 mL NS over 15 minutes and famotidine 20 mg IV in 100 mL NS over 15 minutes (Y-site compatible)
- Counsel patients to avoid cold drinks and exposure to cold air, especially for 3 to 5 days following oxaliplatin administration.
- Cryotherapy (ice chips) should NOT be used as may exacerbate oxaliplatin-induced pharyngo-laryngeal dysesthesias.

Treatment schema:



TREATMENT:

Cycle 1:

Drug	Treatment Day	Dose	BC Cancer Administration Guideline
oBINutuzumab	1	1000 mg	IV in 250 mL NS*
gemcitabine	2	1000 mg/m^2	IV in 250 mL NS over 30 minutes
oxaliplatin**		100 mg/m^2	IV in 250 to 500 mL D5W over 2 hours
glofitamab	8	Step-up Dose 1 2.5 mg	IV in 25 mL NS over 4 hours***
	15	Step-up Dose 2 10 mg	IV in 100 mL NS over 4 hours†

* Initiate oBINutuzumab 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.

** Oxaliplatin is not compatible with NS. Do not piggyback or flush lines with NS.

*** Additional line required to ensure minimum rate required to keep vein open (TKVO). Infuse NS IV at 20 mL/h continuous infusion during glofitamab administration via Y-site connector placed immediately before the injection site.

† If CRS of any grade with previous dose of glofitamab, duration of infusion may be extended up to 8 hours. If rate of glofitamab is below 20 mL/hour, infuse NS IV at 20 mL/h continuous infusion during glofitamab administration via Y-site connector placed immediately before the injection site.

If CRS occurs with any dose, do not initiate next glofitamab infusion until all CRS symptoms have been resolved for at least 72 hours.

Cycle 1 Day 1 (oBINutuzumab): ambulatory care treatment
- Vital signs as clinically indicated
- Due to the risk of infusion-related reactions, patients are to be under constant visual observation during all dose increases and for 30 minutes after infusion completed

Cycle 1 Day 2 (gemcitabine and oxaliplatin): ambulatory care treatment
- Vital signs as clinically indicated
- No observation required

Cycle 1 Day 8 (glofitamab): inpatient treatment
- In addition to IV for treatment, insert saline lock for emergency management
- Observation: All patients must be hospitalized for monitoring for treatment-related adverse events, in particular CRS and ICANS, during infusion and for at least 24 hours following completion of Cycle 1 Day 8 (Step-up Dose 1)
- Vital signs: (including blood pressure, heart rate, temperature and pulse oximetry) to be done prior to Cycle 1 Day 8, every hour during infusion, at the end of the infusion, and as clinically indicated
- If clinical evidence of CRS or ICANS, notify provider immediately. See Dose Modifications, below.

Cycle 1 Day 15 (glofitamab):

- **If no CRS of *any grade* and no treatment interruption with Cycle 1 Day 8:**
  - Treatment may be administered in ambulatory care setting
  - Vital signs prior to treatment, at the end of the infusion, and as clinically indicated
  - Patient to remain in proximity of treating facility for at least 24 hours after infusion completed. Patients must be counselled on the signs and symptoms of CRS and ICANS and to seek immediate medical attention should they occur. See Treatment Planning section, above
- **If *any grade* CRS or treatment interruption with Cycle 1 Day 8:**
  Patient to be admitted during Cycle 1 Day 15 infusion and for at least 24 hours following completion
  - In addition to IV for treatment, insert saline lock for emergency management
  - Observation and vital signs per Cycle 1 Day 8

Cycle 2 (to be given 7 days after Cycle 1 Day 15)**:**

Drug	Dose	BC Cancer Administration Guideline
glofitamab	30 mg on Day 1	IV in 100 mL NS over 4 hours*† Observe for 90 minutes after infusion
gemcitabine	1000 mg/m^2 on Day 1	IV in 250 mL NS over 30 minutes
oxaliplatin**	100 mg/m^2 on Day 1	IV in 250 to 500 mL D5W over 2 hours

* If rate of glofitamab is below 20 mL/hour, infuse NS IV at 20 mL/hour continuous infusion during glofitamab administration via Y-site connector placed immediately before the injection site

† If CRS of *any grade* with previous dose of glofitamab, duration of infusion may be extended up to 8 hours

** Oxaliplatin is not compatible with normal saline. Do not piggyback or flush lines with normal saline.

- **If no Grade 2 or higher CRS and no treatment interruption with previous glofitamab dose:**
  - Ambulatory care treatment
  - Vital signs prior to treatment, at the end of the infusion, and as clinically indicated.
  - Patient to remain in proximity of treating facility for at least 24 hours after infusion completed. Patients must be counselled on the signs and symptoms of CRS and ICANS and to seek immediate medical attention should they occur. See Treatment Planning section, above
- **If Grade 2 or higher CRS with previous glofitamab dose:**
  - Patient to be admitted to hospital during infusion and for at least 24 hours following completion
  - In addition to IV for treatment, insert saline lock for emergency management
  - Observation and vital signs per Cycle 1 Day 8

Cycles 3 to 8 (starts 21 days after Cycle 2):

Drug	Dose	BC Cancer Administration Guideline
glofitamab	30 mg on Day 1	IV in 100 mL NS over 2 hours† Observe for 90 minutes after infusion. If no CRS with 3 consecutive glofitamab doses with no reaction, may discontinue observation.
gemcitabine	1000 mg/m^2 on Day 1	IV in 250 mL NS over 30 minutes
oxaliplatin**	100 mg/m^2 on Day 1	IV in 250 to 500 mL D5W over 2 hours

† If CRS of *any grade* with previous dose of glofitamab, duration of infusion should be maintained at 4 hours

** Oxaliplatin is not compatible with normal saline. Do not piggyback or flush lines with normal saline.

Cycles 9 to 12: (starts 21 days after Cycle 8):

Drug	Dose	BC Cancer Administration Guideline
glofitamab	30 mg on Day 1	IV in 100 mL NS over 2 hours†

† If CRS of *any grade* with previous dose of glofitamab, duration of infusion should be maintained at 4 hours

For Cycles 3 to 12:

- **If no Grade 2 or higher CRS and no treatment interruption with previous glofitamab dose:**
  - Ambulatory care treatment
  - Vital signs prior to treatment, at the end of the infusion, and as clinically indicated
  - Post-treatment monitoring only if clinically indicated
- **If Grade 2 or higher CRS with previous dose:**
  - Patient to be admitted to hospital during infusion and for at least 24 hours following completion
  - In addition to IV for treatment, insert saline lock for emergency management
  - Observation and vital signs per Cycle 1 Day 8

Repeat every 21 days until disease progression or unacceptable toxicity up to a total of 12 cycles.

DOSE MODIFICATIONS:

- No dose reductions are recommended for oBINutuzumab, glofitamab or gemcitabine. The individual infusions may be discontinued, held or their rate reduced as appropriate.

1. Infusion- Related Reactions to oBINutuzumab:

- Refer to SCDRUGRX protocol for management guidelines

Infusion reactions	Management (oBINutuzumab)
Grades 1 or 2 (mild or moderate)	• Reduce infusion rate and treat symptoms • Once symptoms resolved, may resume infusion • Titrate infusion rate at appropriate increments – see Administration Guideline 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 appropriate increments – see Administration Guideline for oBINutuzumab, above
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 oBINutuzumab-related infusion reactions

Infusion rate when resuming oBINutuzumab infusion after Grade 3 symptoms are resolved:

oBINutuzumab Infusion Rate When Reactions Occur (mg/h)	Maximum oBINutuzumab 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. Cytokine Release Syndrome (CRS):

- See management of cytokine release syndrome protocol (SCCRS)
- Cycle 1 Day 15 (glofitamab Step-up Dose 2) to be given as inpatient if *any grade* CRS with Step-up Dose 1
- Cycle 2 onward: If patient experiences Grade 2 or greater CRS, subsequent dose to be given in inpatient setting

Grade	Management (glofitamab)
1	**If CRS symptoms during infusion:** • Hold until resolution • Manage per SCCRS (infusion should be interrupted) • Once symptoms resolve, restart infusion at 50% of rate at which symptoms occurred • If recurrent symptoms after restarting infusion, discontinue current infusion **Subsequent dose:** • Should not be given until CRS symptoms resolved for at least 72 hours • Given per Treatment Interruptions section, below • Administer at 50% rate of previous dose
2	**CRS symptoms during infusion:** • Discontinue current infusion and do not restart • Manage per SCCRS (infusion should not be restarted) **Subsequent dose:** • Should not be given until CRS symptoms resolved for at least 72 hours • Given per Treatment Interruptions section, below • Administer at 50% rate of previous dose
3	**If CRS symptoms during infusion:** • Manage per SCCRS **Subsequent dose:** • Should not be given until CRS symptoms resolved for at least 72 hours • Given per Treatment Interruptions section, below • Administer at 50% rate of previous dose • If recurrent Grade 3 or higher CRS with subsequent infusion, discontinue glofitamab treatment
4	**If CRS symptoms during infusion:** • Discontinue glofitamab treatment • Manage per SCCRS

3. Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS): see management of ICANS protocol (SCICANS)

Grade	Management (glofitamab)
1 or 2	▪ Manage per SCICANS
3	▪ Manage per SCICANS ▪ If resolution takes longer than 7 days, consider discontinuing glofitamab Subsequent dose: ▪ Should not be given until symptoms resolved for at least 7 days ▪ Given per Treatment Interruptions section, below
4	• Discontinue glofitamab treatment ▪ Manage per SCICANS

4. Hematological Toxicity:

- Proceed with Cycle 1 Day 1 oBINutuzumab regardless of hematologic counts
- Proceed with Cycle 1 Day 8 and Day 15 glofitamab doses regardless of hematologic counts

For Cycle 2 and onward:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Management
Greater than or equal to 1.0	and	Greater than or equal to 75	100%
Less than 1.0	and/or	Less than 75	▪ Delay until ANC recovers to greater than or equal to 1.0 and platelets recover to greater than or equal to 75 ▪ If recovery takes less than 14 days, resume treatment ▪ If recovery takes more than 14 days, discontinue gemcitabine and oxaliplatin. Restart glofitamab per Treatment Interruptions section, below ▪ If a patient has a subsequent delay of 14 days or longer while on single agent glofitamab, discontinue glofitamab

5. Treatment Interruptions:

- Treatment schedule and dose may be affected
- Give oBINutuzumab premedications per Cycle 1 Day 1 if repeating oBINutuzumab after treatment interruption
- Give glofitamab premedication per Cycles 1 to 3 if restarting glofitamab after treatment interruption
- Follow Administration Guideline for applicable dose, above, for appropriate rate of administration

Last Treatment Administered	Time from last dose administered	Action for Next Dose
oBINutuzumab	More than 1 week (First dose glofitamab is delayed)	Restart treatment; repeat oBINutuzumab per Cycle 1, Day 1, followed by glofitamab Step-up dosing schedule
glofitamab 2.5 mg (Step-up Dose 1)	Less than 2 weeks	• Administer 10 mg, • Then resume the recommended dosage schedule
	2 to 6 weeks	• Repeat 2.5 mg, then give10 mg the following week, followed by 30 mg one week later, • Then resume the recommended dosing schedule
	More than 6 weeks	• Restart treatment as per Cycle 1, beginning with oBINutuzumab on Day 1
glofitamab 10 mg (Step-up Dose 2)	Less than 2 weeks	• Administer 30 mg, • Then resume the recommended dosing schedule
	2 to 6 weeks	• Repeat 10 mg, then give 30 mg the following week, • Then resume the recommended dosing schedule
	More than 6 weeks	• Restart treatment as per Cycle 1, beginning with oBINutuzumab on Day 1
glofitamab 30 mg	6 weeks or less	• Administer 30 mg, • Then resume the recommended dosing schedule
	More than 6 weeks	• Restart treatment as per Cycle 1, beginning with oBINutuzumab on Day 1

6. Neuropathy: for oxaliplatin

Severity	Management
Acute pharyngolaryngeal dysesthesia	▪ Avoid ice during infusion. ▪ Limit exposure to cold temperature or cold objects. ▪ Consider extended infusion for up to 6 hours.
Grade 2 peripheral sensory neuropathy, paresthesia or gait disturbance	▪ If toxicity doesn't recover to Grade 1 by the time of next scheduled oxaliplatin treatment, reduce oxaliplatin dose to 75 mg/m^2. ▪ If patient has Grade 2 toxicity at time of subsequent dose, withhold oxaliplatin until recovery to Grade 1.
Grade 3 peripheral sensory neuropathy, paresthesia or gait disturbance	▪ If toxicity doesn't recover to at least Grade 1 by the time of the next scheduled oxaliplatin dose, reduce oxaliplatin to 75 mg/m^2. ▪ For persistent Grade 3 toxicity that does not recover to at least Grade 1 by the time of the next scheduled oxaliplatin dose, or for recurrent Grade 3 events, permanently discontinue oxaliplatin.
Grade 4 peripheral sensory neuropathy, paresthesia or gait disturbance	▪ Permanently discontinue oxaliplatin.

PRECAUTIONS:

1. **oBINutuzumab Infusion Reactions,** 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. Patients are to be under constant visual observation during all dose increases and for 30 minutes after infusion is completed. 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.

2. **Infusion-Related Reactions to glofitamab** can occur and may be clinically indistinguishable from CRS. **Treat as signs or symptoms of CRS** (See SCCRS).

3. **Cytokine release syndrome (CRS)** is reported in patients receiving glofitamab and can recur. Most patients experience Grade 1 or 2 reactions, but serious or life-threatening events can occur. Signs and symptoms of CRS may include fever, chills, hypoxia, hypotension, dyspnea, tachycardia, and elevated liver enzymes. Most events occur during Cycles 1 and 2. The incidence of CRS is highest after Step-up Dose 1 (glofitamab 2.5 mg) and decreases with each subsequent dose. Median time to onset after Step-up Dose 1 is 13 hours. See BC Cancer Drug Manual for details.

   To reduce the risk of CRS, pretreatment with oBINutuzumab is administered 7 days prior to the first dose of glofitamab to deplete the circulating and lymphoid B cells, and glofitamab is initiated with a Step-up dosing regimen. Premedication with antihistamine, antipyretic, and corticosteroid prior to glofitamab is recommended.

Closely monitor patients for signs and symptoms of CRS. At first sign of CRS, admit patient to hospital for further monitoring if not already admitted. CRS may be managed with acetaminophen, intravenous fluids, tocilizumab, corticosteroids, and other symptomatic measures – see management of cytokine release syndrome protocol SCCRS. Permanently discontinue glofitamab for recurrent Grade 3 and Grade 4 CRS.

Do not initiate the next glofitamab infusion until all CRS symptoms have been resolved for at least 72 hours. If patients present with symptoms suggestive of CRS after Cycle 3, especially after successful full dose free of CRS, other causes such as infection should be thoroughly investigated and ruled out prior to concluding CRS is the cause.

4. **Neurologic toxicity**, including **immune effector cell-associated neurotoxicity syndrome (ICANS)** can occur during treatment with glofitamab. The majority of neurological adverse events occur during Cycle 1 and 2. The onset varies depending on the dose. See BC Cancer Drug Manual for details. Most events are mild to moderate in severity, but serious or fatal neurologic toxicity such as **immune effector cell-associated neurotoxicity syndrome (ICANS)** can occur. Clinical manifestations of ICANS may include headache, confusion, disorientation, speech disturbances, altered levels of consciousness, seizures, muscle weakness, agitation, and tremor. Management of ICANS may include temporary dose interruption, corticosteroids, anti-seizure medications, and supportive care.

   If ICANS occurs, admit patient to hospital for further monitoring if not already admitted. Neurology consult may be required. Hold glofitamab until neurologic toxicity has resolved for at least 7 days. Symptoms are managed depending on their severity and whether they occur concurrently with CRS. Permanently discontinue glofitamab for Grade 4 ICANS. Consider discontinuation for Grade 3 ICANS that takes more than 7 days to resolve. Patients experiencing reduced consciousness or any symptoms that might affect their ability to drive or use machines, should refrain from driving or operating heavy machinery until symptoms resolve. See management of immune effector cell-associated neurotoxicity protocol, SCICANS.

5. **Infections,** including bacterial, fungal, and new or reactivated viral infections have been reported in patients treated with oBINutuzumab and glofitamab. These may be severe or life-threatening. Fatalities have been reported. oBINutuzumab and glofitamab should not be given to patients with an active infection; use cautiously in patients with recurring or chronic infections. Fever or other evidence of infection must be assessed promptly and treated aggressively. Prophylaxis against viral infections and PJP should be administered as per above. Consider IVIG prophylaxis in patients with recurrent infections and low immunoglobulin levels.

6. **Tumour Lysis Syndrome (TLS)** including acute renal failure can occur within 12 to 24 hours after the first infusion of oBINutuzumab. TLS has also been reported in patients treated with glofitamab. Patients considered to be at increased risk for TLS should receive hydration and prophylactic treatment with uric acid lowering agents. Patients should be monitored closely for signs and symptoms of TLS, especially patients with high tumour burden, rapidly proliferative tumours or reduced renal function. Monitor blood chemistries regularly and manage abnormalities promptly.

7. **Hepatitis B Reactivation:** See SCHBV protocol for more details.

8. **Vaccination:** Patients should not receive live or live attenuated vaccines within 4 weeks of starting treatment and at any point during treatment.

9. **Progressive Multifocal Leukoencephalopathy (PML)** may occur caused by reactivation of the JC virus during treatment with oBINutuzumab. 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.

10. **Cytomegalovirus (CMV) new infections and reactivations** have been reported during treatment with oBINutuzumab, glofitamab, gemcitabine and oxaliplatin. Consider CMV screening based on epidemiologic risk factors and initiate prophylaxis as clinically indicated.

11. **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.

12. **Tumour flare** has been reported with glofitamab, likely due to the activated immune response and T-cell influx towards tumour sites. Symptoms may include pain and swelling at lymphoma sites with tumour inflammation. Manage as indicated, using analgesics, corticosteroids, antihistamines and supportive care.

13. **Drug Interactions:** The initial release of cytokines associated with the start of glofitamab treatment could suppress CYP450 enzymes, resulting in increased exposure of CYP substrates. Possible interaction between gemcitabine and warfarin has been reported and may occur at any time. Close monitoring is recommended (monitor INR weekly during gemcitabine therapy and for 1 to 2 months after discontinuing gemcitabine treatment). See BC Cancer Drug Manual.

14. **Platinum hypersensitivity** can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, epinephrine and bronchodilators. Vasopressors may be required (see below). For Grade 1 or 2 acute hypersensitivity reactions no dose modification of oxaliplatin is required and the patient can continue treatment with standard hypersensitivity premedication. See Premedications.
    Reducing infusion rates (e.g., from the usual 2 hours to 4-6 hours) should also be considered since some patients may develop more severe reactions when rechallenged, despite premedications. The practice of rechallenging after severe life-threatening reactions is usually discouraged, although desensitization protocols have been successful in some patients. The benefit of continued treatment must be weighed against the risk of severe reactions recurring. The product monograph for oxaliplatin lists rechallenging patients with a history of severe HSR as a contraindication.

15. **Pharyngo-laryngeal dysesthesia** is an unusual dysesthesia characterized by an uncomfortable persistent sensation in the area of the laryngopharynx without any objective evidence of respiratory distress (i.e. absence of hypoxia, laryngospasm or bronchospasm). This may be exacerbated by exposure to cold air or foods/fluids. If this occurs during infusion, stop infusion immediately and observe patient. Rapid resolution is typical, within minutes to a few hours. Check oxygen saturation; if normal, an anxiolytic agent may be given. The infusion can then be restarted at a slower rate at the physician's discretion. In subsequent cycles, the duration of infusion should be prolonged (see Dose Modifications above in the Neurological Toxicity table).

Clinical Symptoms	Pharyngo-laryngeal Dysesthesia	Platinum Hypersensitivity
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O_2 saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritus	Absent	Present
Cold induced symptoms	Yes	No
Blood Pressure	Normal or Increased	Normal or Decreased
Treatment	Anxiolytics; observation in a controlled clinical setting until symptoms abate or at physician's discretion	Oxygen, steroids, epinephrine, bronchodilators; Fluids and vasopressors if appropriate

16. **QT prolongation and torsades de pointes** are reported with oxaliplatin: Use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Correct electrolyte disturbances prior to treatment and monitor periodically. Baseline and periodic ECG monitoring is suggested in patients with cardiac disease, arrhythmias, concurrent drugs known to cause QT prolongation, and electrolyte abnormalities. In case of QT prolongation, oxaliplatin treatment should be discontinued. QT effect of oxaliplatin with single dose ondansetron 8 mg prechemo has not been formally studied. However, single dose ondansetron 8 mg PO would be considered a lower risk for QT prolongation than multiple or higher doses of ondansetron, as long as patient does not have other contributing factors as listed above.

17. **Diarrhea:** Patients should report mild diarrhea that persists over 24 hours or moderate diarrhea (4 stools or more per day above normal, or a moderate increase in ostomy output). Mild diarrhea can be treated with loperamide (e.g. IMODIUM) following the manufacturer's directions or per the BC Cancer Guidelines for Management of Chemotherapy-Induced Diarrhea. Note that diarrhea may result in increased INR and the risk of bleeding in patients on warfarin.

18. Oxaliplatin therapy should be interrupted if symptoms indicative of **pulmonary fibrosis** develop – nonproductive cough, dyspnea, crackles, rales, hypoxia, tachypnea or radiological pulmonary infiltrates. If pulmonary fibrosis is confirmed oxaliplatin should be discontinued.

19. **Extravasation**: Oxaliplatin causes irritation if extravasated. Refer to BC Cancer Extravasation Guidelines.

20. Oxaliplatin therapy should be interrupted if **Hemolytic Uremic Syndrome (HUS)** is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.

21. **Renal Dysfunction:** Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare). Use caution with pre-existing renal dysfunction.

REFERENCES:

1. Abramson JS, Ku M, Hertzberg M et al. Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): a global phase 3 randomised, open label trial. Lancet 2024; 404; 1940-54.
2. Glofitamab (Columvi) CADTH [Canada's Drug Agency (CDA-AMC)] Reimbursement Recommendation. Canadian Journal of Health Technologies Oct 2025; 5(10): 1-26.

Appendix. oBINutuzumab infusion rate titration table

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