BC Cancer Protocol Summary for Palliative Therapy for Urothelial Carcinoma using Enfortumab Vedotin

Protocol Code	*GUAVEV*
Tumour Group	*Genitourinary*
Contact Physicians	*Dr. Jean-Michel Lavoie*

ELIGIBILITY:

Patients must have:

- Unresectable locally advanced or metastatic urothelial cancer,
- Previous treatment with platinum-containing chemotherapy in either the neoadjuvant, adjuvant, locally advanced or metastatic setting, and
- Progression during or following treatment with programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor

Patients should have:

- ECOG performance status 0 to 2
- Adequate bone marrow and hepatic function

Note: the use of enfortumab vedotin (in GUAVEV protocol) precludes the use of pembrolizumab as any subsequent line of therapy.

EXCLUSIONS:

Patients must not have:

- Greater than or equal to grade 2 sensory or motor neuropathy
- Active central nervous system metastases (unless asymptomatic and/or stable)
- Leptomeningeal disease
- Uncontrolled diabetes
- Active keratitis or corneal ulcerations

TESTS:

- Baseline: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, bilirubin, sodium, potassium, phosphate, random glucose, uric acid, lipase, hemoglobin A1C (HbA1c). If clinically indicated: ophthalmologic consult
- Prior to Day 1 of each cycle: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, bilirubin, sodium, potassium, phosphate, random glucose
  - If clinically indicated: uric acid, lipase, HbA1c, ophthalmologic consult
- Prior to Day 8 and 15 of cycle 1: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, bilirubin, sodium, potassium, random glucose

PREMEDICATIONS:

- Antiemetic protocol for low emetogenic chemotherapy protocols (see protocol SCNAUSEA).
- If prior infusion reaction to enfortumab vedotin: diphenhydrAMINE 50 mg PO, acetaminophen 325 to 975 mg PO, and hydrocortisone 100mg IV 30 minutes prior to treatment

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
enfortumab vedotin	1.25 mg/kg on Days 1, 8 and 15 (maximum 125 mg)	IV in 50 mL NS over 30 minutes Observe for 60 minutes post infusion for cycle 1*

* observation period not required after 3 consecutive doses with no reaction

Repeat every 28 days until disease progression or unacceptable toxicity

DOSE MODIFICATIONS:

enfortumab vedotin Dose Level	Dose (%)	Dose (mg/kg)	Maximum Dose (mg)
0 (starting dose)	100%	1.25	125
-1	80%	1	100
-2	60%	0.75	75
-3	40%	0.5	50

1. Hematological:

Platelets (x10^9/L)		ANC (x 10^9/L)	Dose
greater than 75	and	greater than or equal to 1.0	100 %
25 to 75	or	0.5 to 0.99	Withhold until platelet count improves to 75 or better and ANC improves to 1.5 or better. Resume with same dose level or consider decrease 1 dose level
less than 25	or	less than 0.5	Withhold until platelet count improves to 75 or better and ANC improves to 1.5 or better. Resume with decrease 1 dose level or discontinue therapy

2. Hyperglycemia:

Random Glucose	Dose
less than or equal to 13.9 mmol/L	100 %
greater than 13.9 mmol/L	Delay

3. Peripheral Neuropathy:

Grade	Toxicity	1st occurrence	Recurrent
1	Asymptomatic; loss of deep tendon reflexes or paresthesia. Clinical or diagnostic observations only; intervention not indicated	Continue treatment at current dose	Continue treatment at current dose
2	Moderate symptoms; limiting instrumental ADL	Delay until less than or equal to grade 1, then resume at same dose level	Delay until less than or equal to grade 1, then resume at next lower dose level
3	Severe symptoms; limiting self care ADL +/- assistive device indicated	Permanently discontinue	Permanently discontinue
4	Life-threatening consequences; urgent intervention indicated	Permanently discontinue	Permanently discontinue

4. Pneumonitis:

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)

For development of grade 2 pneumonitis, withhold enfortumab vedotin until recovery to baseline; dose reduction may be required once treatment resumes. Permanently discontinue enfortumab vedotin for development of Grade 3 or 4 pneumonitis.

PRECAUTIONS:

1. **Infusion-related reactions**: isolated cases of severe infusion reactions have been reported. Discontinue enfortumab vedotin with severe reactions (Grade 3 or 4). Patients with mild or moderate infusion reactions may receive enfortumab vedotin with close monitoring and use of premedication.
2. **Hyperglycemia** and diabetic ketoacidosis (DKA): Fatal events have occurred. Can occur in patients with and without pre-existing diabetes mellitus treated with enfortumab vedotin. Antihyperglycemic treatment may be required. Monitor patient for symptoms suggestive of hyperglycemia, such as frequent urination, increased thirst, blurred vision, fatigue, and headache.
3. **Ocular disorders:** are frequently reported during treatment with enfortumab vedotin. Obtain ophthalmologic evaluation if ocular symptoms occur or do not resolve. Ophthalmic topical steroids may be required.
   Consider dose interruption or dose reduction for symptomatic ocular disorders.
   The majority of events involve the cornea and include keratitis, blurred vision, limbal stem cell deficiency, and events associated with dry eyes. Consider artificial tears for prophylaxis of dry eyes.
4. **Skin reactions:** enfortumab vedotin can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Immediately withhold enfortumab vedotin for suspected SJS or TEN or severe skin reactions. Permanently discontinue treatment in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions.
   Skin reactions are reported in approximately 55% of patients treated with enfortumab vedotin. Grade 3 or 4 reactions are reported in about 13% of patients and have included maculo-papular rash, rash erythematous, rash or drug eruption, symmetrical drug related intertriginous and flexural exanthema (SDRIFE), dermatitis bullous, dermatitis exfoliative, and palmar-plantar erythrodysesthesia. Monitor and consider topical corticosteroids and antihistamines for mild to moderate skin reactions.
5. **Drug interactions:** enfortumab vedotin is an antibody-drug conjugate, consisting of a monoclonal antibody component (AGS-22C3) conjugated to the small molecule microtubule-disrupting agent monomethyl auristatin E (MMAE). Strong inhibitors of P-gp or CYP3A4 may increase the serum concentration of MMAE. No dose adjustment required; closely monitor for adverse effects. Strong inducers of P-gp or CYP3A4 may decrease the level of MMAE. Avoid coadministration if possible. Clinical significance unknown.
6. **Peripheral neuropathy** is reported in approximately 52% of patients, although grade 3 reactions are uncommon. Consider dose interruption or dose reduction if symptoms develop, and permanently discontinue enfortumab vedotin for grade 3 or 4 events. Some patients may not see improvement or complete resolution of their symptoms after enfortumab vedotin is stopped.
7. **Pneumonitis** has occurred in patients being treated with enfortumab vedotin. Fatalities have been reported. Monitor patients for signs and symptoms indicative of pneumonitis such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Dose interruption required for grade 2 pneumonitis. See dose modifications, above.

Call Dr. Jean-Michel Lavoie or tumour group delegate at 250-519-5500 or 1-800-670-3322 with any problems or questions regarding this treatment program.

References:

1. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med 2021;384(12):1125-1135.
2. Mamtani R, Rosenberg JE, Powles T, et al. Quality of life, functioning, and symptoms in patients with previously treated locally advanced or metastatic urothelial carcinoma from EV-301: A randomized phase 3 trial of enfortumab vedotin versus chemotherapy (meeting abstract). J Clin Oncol 2021;39(15 suppl):4539.