BC Cancer Protocol Summary for the First-Line Treatment of Locally Advanced or Metastatic Urothelial Carcinoma using Enfortumab Vedotin and Pembrolizumab

Protocol Code	*GUAVEVPEM*
Tumour Group	*Genitourinary*
Contact Physicians	*GU Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Unresectable locally advanced or metastatic urothelial cancer, and
- No prior systemic therapy in the advanced setting

Notes:

- The use of enfortumab vedotin and pembrolizumab in this protocol precludes the use of enfortumab vedotin or pembrolizumab as any subsequent line of therapy.
- Patients who started on, but have not completed, first-line chemotherapy prior to September 1, 2025, may switch to GUAVEVPEM, provided all other eligibility criteria are met and not progressing.
- Patients who completed first-line chemotherapy and are initiating or have initiated maintenance avelumab (GUBAVE), may not switch to GUAVEVPEM.
- At time of subsequent disease progression, pembrolizumab retreatment (with or without enfortumab vedotin) may be allowed for an additional 1 year of therapy (17 cycles) through BC Cancer Compassionate Access Program (CAP) approval (retreatment is not funded if progression occurs on enfortumab vedotin monotherapy after completion of 2 years of combination treatment).

Patients should have:

- Good performance status
- Adequate hematologic, renal and hepatic function
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of pembrolizumab

EXCLUSIONS:

Patients must not have:

- Relapsed on or within 6 months of completing adjuvant immunotherapy
- Relapsed on or within 12 months of completing adjuvant chemotherapy following cystectomy or completing neoadjuvant chemotherapy
- 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

CAUTIONS:
- Active autoimmune disease
- Patients with long term immunosuppressive therapy or systemic corticosteroids (requiring more than 10 mg predniSONE/day or equivalent)

TESTS:
- Baseline: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, sodium, TSH, potassium, phosphate, random glucose, uric acid, lipase, hemoglobin A1C (HbA1c), LDH
- Baseline if clinically indicated: BNP, troponin, creatine kinase, ECG, echocardiogram, ophthalmologic consult
- Prior to Day 1 of each cycle: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, sodium, potassium, phosphate, random glucose, TSH, LDH
- Prior to Day 8 of each cycle: CBC & Diff, random glucose
- If clinically indicated: uric acid, lipase, HbA1c, chest x-ray, morning serum cortisol, lipase, serum or urine HCG (required for woman of child bearing potential if pregnancy suspected), free T3 and free T4, serum ACTH levels, testosterone, estradiol, FSH, LH, ECG, C-reactive protein, creatine kinase, troponin, ophthalmologic consult
- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (Optional).

PREMEDICATIONS:
- Antiemetic protocol for low emetogenic chemotherapy protocols (see protocol SCNAUSEA).
- If prior infusion reaction to enfortumab vedotin or pembrolizumab: 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 and 8 (maximum 125 mg)	IV in 50 mL NS over 30 minutes Observe for 60 minutes post infusion*
pembrolizumab	2 mg/kg on Day 1 (maximum 200 mg)	IV in 50 mL NS over 30 minutes using a 0.2 micron in-line filter

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

- Repeat every 3 weeks.
- enfortumab vedotin treatment: until disease progression or unacceptable toxicity.
- pembrolizumab treatment: until disease progression, unacceptable toxicity or a maximum of 35 cycles or 2 years of treatment.
- Retreatment may be allowed (refer to Eligibility section above).

Note: if unacceptable toxicity occurs with either drug, treatment may continue as monotherapy.

DOSE MODIFICATIONS:

enfortumab vedotin:

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

pembrolizumab:

No specific dose modifications for pembrolizumab. Toxicity managed by treatment delay and other measures (see SCIMMUNE protocol for management of immune-mediated adverse reactions to checkpoint inhibitors immunotherapy).

1. Hematological:

Platelets (x10^9/L)		ANC (x 10^9/L)	enfortumab vedotin Dose
Greater than or equal to 75	and	Greater than or equal to 1.0	100 %
25 to 74	or	0.5 to 0.99	Withhold until platelet count improves to greater than 75 and ANC improves to 1.0 or greater. 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 greater than 75 and ANC improves to 1.0 or greater. Resume with decrease 1 dose level or discontinue therapy

2. Hyperglycemia:

Random glucose	enfortumab vedotin Management	pembrolizumab Management
Less than or equal to 13.9 mmol/L	Continue treatment at current dose	Continue treatment at current dose
Greater than 13.9 mmol/L	Delay	Delay

3. Peripheral Neuropathy:

Grade	Toxicity	enfortumab vedotin Management		pembrolizumab Management
		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	see SCIMMUNE protocol
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	Toxicity	enfortumab vedotin Management	pembrolizumab Management
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Continue treatment at current dose	see SCIMMUNE protocol
2	Symptomatic; medical intervention indicated; limiting instrumental ADL	Hold until recovery to baseline, then resume same dose or reduce dose	
3	Severe symptoms; limiting self care ADL; oxygen indicated	Permanently discontinue	
4	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Permanently discontinue	

PRECAUTIONS:

1. **Serious Immune-mediated Reactions**: these can be severe to fatal and usually occur during the pembrolizumab treatment course. They may include enterocolitis, intestinal perforation or hemorrhage, hepatitis, dermatitis, neuropathy, endocrinopathy, as well as toxicities in other organ systems. Early diagnosis and appropriate management are essential to minimize life-threatening complications (see **SCIMMUNE** protocol for management of immune-mediated adverse reactions to checkpoint inhibitors immunotherapy).
2. **Infusion-related Reactions**: isolated cases of severe infusion reactions with both enfortumab vedotin and pembrolizumab have been reported. Discontinue enfortumab vedotin and/or pembrolizumab with severe reactions (Grade 3 or 4) and administer appropriate medical therapy. Patients with mild or moderate infusion reactions may receive enfortumab vedotin and pembrolizumab with close monitoring, reduced rates of administration and use of premedication.

3. **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. Dose interruption may be required. See Dose Modifications, above.
4. **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.
5. **Skin Reactions:** enfortumab vedotin and pembrolizumab can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Immediately withhold treatment 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 (see SCIMMUNE protocol for pembrolizumab management). 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.
6. **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 is unknown.
7. **Peripheral neuropathy** is reported in approximately 52% of patients treated with enfortumab vedotin, 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. See Dose Modifications, above.
8. **Pneumonitis** has occurred in patients being treated with enfortumab vedotin and pembrolizumab. 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 and SCIMMUNE protocol for pembrolizumab management.

Contact the GU Systemic Therapy physician at your regional cancer centre or GU Systemic Therapy Chair with any problems or questions regarding this treatment program.

REFERENCES:

1. Powles T, Valderrama BP, Gupta S, et al; EV-302 Trial Investigators. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. N Engl J Med. 2024 Mar 7;390(10):875-888.
2. Enfortumab vedotin (Padcev) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies Dec 2024; 4(12): 1-21.