Protocol Contains CHECKPOINT INHIBITOR IMMUNOTHERAPY	
Indication	For the treatment of previously untreated, unresectable or metastatic urothelial cancer, which in the absence of enfortumab vedotin & pembrolizumab would have been deemed eligible for treatment with cisplatin or carboplatin. NB the patient has not received prior treatment with any of the following for urothelial cancer: anti-PD-1, anti-PD-L1, anti-PD-L2 and anti-CD137 treatments, unless these were given in a neo adjuvant and/or adjuvant setting and the most recent dose was given more than 12 months before recurrence was diagnosed.
Treatment Intent	Palliative
Frequency and number of cycles	Enfortumab vedotin with pembrolizumab every 21 days to a maximum of 35 cycles followed by enfortumab vedotin monotherapy. Continue pembrolizumab until progressive disease or unacceptable toxicity or patient choice to discontinue treatment or to a maximum of 35 cycles (if given 3 weekly or its equivalent if given 6 weekly), whichever is sooner. Enfortumab vedotin monotherapy can continue until loss of clinical benefit or excessive toxicity or withdrawal of patient consent.

Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion.
	• **Pre-treatment cardiac assessment:**
	  ○ ECG baseline and as clinically indicated.
	  ○ Check BNP, and Troponin T prior to treatment.
	• **Thyroid function** must be assessed at baseline then every 6-8 weeks or as clinically indicated whilst receiving pembrolizumab.
	• **Cortisol monitoring** should be undertaken in line with ESMO immunotherapy toxicity guidance available on KMCC website (see link below). Cortisol level should not be taken within 24 hours of the last steroid dose.
	• **Monitor blood glucose** prior to treatment and throughout enfortumab vedotin therapy. More frequent monitoring may be required in patients with or at risk for diabetes mellitus or hyperglycaemia. If blood glucose is elevated >13.9 mmol/L (>250 mg/dL), enfortumab vedotin should be withheld until blood glucose is </=13.9 mmol/L (≤250 mg/dL) and treat as appropriate.
	• Confirm the patient has no symptomatically active brain metastases or leptomeningeal metastases.
	• **Cycle 1 to 35**
	• **Day 1** - Monitor FBC, U&Es, LFTs, LDH, Ca++ and glucose at each cycle. Patients with a PS of 2 must have a haemoglobin of >10g/dl and a GFR >50ml/min.
	• If PLT <75 or neuts <1.0 delay treatment.
	• **Day 8** – FBC, U&Es LFTS and glucose.
	• If PLT <75 or neuts <1.0 delay treatment.
	• **Cycle 36 onwards**
	• Monitor FBC, U&Es, LFTs and glucose at each cycle.
	• **Hepatic impairment:**
	  ○ **Enfortumab vedotin:** No dose adjustment in mild impairment (total bilirubin 1 to 1.5 × ULN and any AST, or total bilirubin </= ULN and AST > ULN). Limited data in moderate to severe hepatic

impairment, patients should be monitored closely for adverse events. Hepatic impairment is expected to increase the systemic exposure to MMAE (the cytotoxic drug); therefore, patients should be closely monitored for potential adverse events.
    - **Pembrolizumab:** No dose adjustment is needed for patients with mild or moderate hepatic impairment. Pembrolizumab has not been studied in patients with severe hepatic impairment.
- **Renal impairment:**
    - **Enfortumab vedotin:** No dose adjustment required. Use with caution in end stage renal disease, CrCl <15ml/min due to no available data.
    - **Pembrolizumab:** No specific dose adjustment is necessary in patients with mild to moderate renal impairment. Severe renal impairment (CrCl<30ml/min) d/w consultant.
- **Management of adverse reactions:**
    - **Enfortumab vedotin: see table 1**
    - **Peripheral neuropathy:** Patients must not have ongoing sensory or motor neuropathy of grade 2 or higher prior to initiation of treatment. Patients should be monitored for symptoms of new or worsening peripheral neuropathy treatment delay, dose reduction or discontinuation of enfortumab vedotin may be required (see Table 1). Enfortumab vedotin should be permanently discontinued for Grade >/=3 peripheral neuropathy.
    - **Skin reactions:** Fever or flu-like symptoms may be the first sign of a severe skin reaction, and patients should be observed, if this occurs. Severe cutaneous adverse reactions, including SJS and TEN, with fatal outcome have also occurred in patients treated with enfortumab vedotin, predominantly during the first cycle of treatment.
    - **Interstitial lung disease/pneumonitis:** Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspneoa). See table 1 below for dose modification and guidance in patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis.
    - **Ocular disorders:** Patients should be monitored for ocular disorders. Consider artificial tears for prophylaxis of dry eye and referral for ophthalmologic evaluation if ocular symptoms do not resolve or worsen.
    - **Extravasation:** Skin and soft tissue injury following enfortumab vedotin administration has been observed when extravasation occurred, monitor for possible infusion site extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.
    - **Pembrolizumab:**
    - Immune-related adverse reactions may appear during or after treatment with pembrolizumab. The most common immune-related reactions are: pneumonitis, colitis, nephritis, hepatitis, symptomatic hypophysitis, hyperthyroidism, hypothyroidism and type 1 diabetes. The following additional, immune related adverse reactions have been reported in patients receiving pembrolizumab: uveitis, arthritis, myositis, pancreatitis, severe skin reactions, myasthenic syndrome, encephalitis, Guillian-Barre syndrome, optic neuritis, rhabdomyolysis, sarcoidosis, myocarditis, haemolytic anaemia and partial seizures arising in a patient with inflammatory foci in brain parenchyma. See guidelines for management of immune-related adverse reactions following immunotherapy: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/ available on KMCC website and the SPC.
    - Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported. For signs or symptoms of SJS or TEN, pembrolizumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, pembrolizumab should be permanently discontinued.
    - **Dose Modification:** If toxicity can be related to either enfortumab vedotin or pembrolizumab, treatment can continue with either enfortumab vedotin monotherapy (until loss of clinical benefit or excessive toxicity or withdrawal of patient consent) or pembrolizumab monotherapy (until progressive disease or unacceptable toxicity or patient choice to discontinue treatment or to a maximum of 35 cycles (if given 3 weekly or its equivalent if given 6 weekly).

	○ **Enfortumab vedotin:** When a dose reduction of enfortumab vedotin is required, the first dose reduction should be 1mg/kg (up to 100mg), second dose reduction 0.75mg/kg (up to 75mg) and the third and final dose reduction 0.5mg/kg (up to 50mg). ○ **Pembrolizumab:** dose reductions are not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. • **Infusion-related reactions:** If the infusion related reaction can be attributed to a particular agent, treat as follows: ○ **Pembrolizumab and Enfortumab vedotin:** Severe infusion-related reactions have been reported in patients receiving pembrolizumab and enfortumab vedotin. For severe infusion reactions (grade 3-4), infusion should be stopped and pembrolizumab and/or enfortumab vedotin permanently discontinued. ○ Patients with mild or moderate infusion reaction may continue to receive pembrolizumab and/or enfortumab vedotin with close monitoring; premedication with antipyretic and antihistamine may be considered. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** ○ **Enfortumab vedotin:** Caution is advised in case of concomitant treatment with strong CYP3A4 inhibitors (e.g. clarithromycin, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, telaprevir, telithromycin, voriconazole) and strong CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, St. John's wort). ○ **Pembrolizumab:** The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided. Systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions. ○ Vaccines should only be given where the benefit outweighs the risk and after discussion between consultant and patient. • **Missed dose:** If a planned dose is missed, it should be administered as soon as possible. The schedule of administration must be adjusted to maintain the appropriate interval between doses. • **Pregnancy and contraception:** Females of reproductive potential should be advised to have a pregnancy test within 7 days prior to starting treatment with enfortumab vedotin, use effective contraception during treatment and for at least 6 months after stopping enfortumab vedotin treatment. Females of reproductive potential should use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose of pembrolizumab. • Men being treated with enfortumab vedotin are advised not to father a child during treatment and for at least 4 months following the last dose of treatment. • **Driving/ using machinery:** • Pembrolizumab: Pembrolizumab may have a minor influence on the ability to drive and use machines. Fatigue has been reported following administration of pembrolizumab. • **Patient information documents:** Each patient should be given a copy of the Keytruda® and Padcev® patient alert card at each cycle. • Patients must be advised to contact the oncology team or the 24-hour hot-line immediately if they experience any side effect, as some side effects worsen rapidly. Prompt management of side effects can ensure that the patient continues with treatment.
References	CDF list accessed online 03.09.2025 SPC accessed online 03.09.2025 https://www.padcev.com/Content/hcp/pdf/PADCEV-Dosing-and-Administration-Guide.pdf

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1 Dose interruption, reduction and discontinuation of enfortumab vedotin

Adverse reaction	Severity*	Dose modification*
Skin reactions	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) or bullous lesions	Immediately withhold and refer to specialised care.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3	Permanently discontinue.
	Grade 2 worsening Grade 2 with fever Grade 3	• Withhold until Grade ≤1. • Referral to specialised care should be considered. • Resume at the same dose level or consider dose reduction by one dose level.
Hyperglycaemia	Blood glucose >13.9 mmol/L (>250 mg/dL)	• Withhold until elevated blood glucose has improved to ≤13.9 mmol/L (≤250 mg/dL). • Resume treatment at the same dose level.
Pneumonitis/ interstitial lung disease (ILD)	Grade 2	• Withhold until Grade ≤1, then resume at the same dose or consider dose reduction by one dose level.
	Grade ≥3	Permanently discontinue.
Peripheral neuropathy	Grade 2	• Withhold until Grade ≤1. • For first occurrence, resume treatment at the same dose level. • For a recurrence, withhold until Grade ≤1, then resume treatment reduced by one dose level.
	Grade ≥3	Permanently discontinue.

*Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) where Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe and Grade 4 is life-threatening.

Cycles 1 to 35 (pembrolizumab should be stopped after 35 cycles) – combination therapy repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Metoclopramide	20mg	PO		Stat
	ENFORTUMAB VEDOTIN	**1.25mg/kg Max Dose 125mg**	IV	30min	In 50ml sodium chloride 0.9% via in-line low-protein binding 0.22 microns filter. Final dilution should be 0.3mg/ml – 4mg/ml **Flush the line with sodium chloride 0.9% for injection at the end of the infusion**
	Administer pembrolizumab 30 minutes after completion of enfortumab vedotin infusion				
	PEMBROLIZUMAB	**200mg**	IV	30min	In 100ml Sodium Chloride 0.9% via in-line low-protein binding 0.22 microns filter. **Flush the line with sodium chloride 0.9% for injection at the end of the infusion**
Day 8	Metoclopramide	20mg	PO		Stat
	ENFORTUMAB VEDOTIN	**1.25mg/kg Max Dose 125mg**	IV	30min	In 50ml sodium chloride 0.9% via in-line low-protein binding 0.22 microns filter. Final dilution should be 0.3mg/ml – 4mg/ml **Flush the line with sodium chloride 0.9% for injection at the end of the infusion**
TTO	Drug	Dose	Route	Directions	
Day 1	Metoclopramide	10mg	PO	Up to TDS PRN (max. 30mg per day including 20mg pre-med dose). Do not take for more than 5 days continuously. Dispense only if required.	
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. **Do not take for longer than 3 days without contacting the oncology team.** Dispense 30 capsules on cycle 1 then only if required	
	Hypromellose	0.3%	topical	One drop into each eye QDS. Dispense on cycle 1 then only if required.	

NB if required an alternative dosing schedule of pembrolizumab can be given at a dose of 400mg every 6 weeks

Cycle 36 onwards – monotherapy repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1 and 8	Metoclopramide	20mg	PO		Stat
	ENFORTUMAB VEDOTIN	**1.25mg/kg Max Dose 125mg**	IV	30min	In 50ml sodium chloride 0.9% via in-line low-protein binding 0.22 microns filter. Final dilution should be 0.3mg/ml – 4mg/ml **Flush the line with sodium chloride 0.9% for injection at the end of the infusion**
TTO	Drug	Dose	Route	Directions	
Day 1	Metoclopramide	10mg	PO	Up to TDS PRN (max. 30mg per day including 20mg pre-med dose). Do not take for more than 5 days continuously. Dispense only if required.	
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense only if required.	
	Hypromellose	0.3%	topical	One drop into each eye QDS. Dispense only if required.	