Enfortumab vedotin & Pembrolizumab (Urothelial)

Please note this protocol has been produced in a new format that is currently being piloted. Any feedback on this new format should be sent to SSGMeetings@uhbw.nhs.uk

Index

Section	Page
Regimen details	2
Pre-meds/Supportive meds	2
Administration information	2
Investigations	3
Limits to go ahead and dose modifications	4
Side effects and toxicity management	5-8
Additional information	8
Drug interactions	8
References	8

Indication

Untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable.

(NICE TA 1097)

Response Rates

Phase 3 EV-302 trial:

- Enfortumab vedotin (EV) + Pembrolizumab (n=442) vs. gemcitabine + platinum (n=444)
- Median PFS: EV + Pembro = 12.5 months vs gemcitabine + platinum = 6.3 months
- Median OS: EV + Pembro = 31.5 months vs gemcitabine + platinum = 16.1 months

Treatment related mortality

<1%

Regimen details

Day	Drug	Dose	Route
Day 1 & 8	Enfortumab vedotin	1.25mg/kg (max. dose 125mg)	IV infusion
Day 1	Pembrolizumab	200mg*	IV infusion

* Pembrolizumab may also be administered as 400mg 6 weekly, i.e. administered on alternate 21-day enfortumab vedotin cycles

Cycle frequency
21 days

Number of cycles
Enfortumab vedotin: Until disease progression or unacceptable toxicity.
Pembrolizumab: Up to a maximum of 35 x 3 weekly cycles (or equivalent if given 6 weekly).
If either drug is stopped due to toxicity the remaining agent can continue as a single agent within the above parameters, in terms of overall duration.

Pre-medication
If patients experience infusion related reactions the following premedications for enfortumab vedotin may be considered 30-60 minutes prior to each subsequent enfortumab vedotin infusion:

- Paracetamol 1g PO
- Chlorphenamine 10mg IV
- Hydrocortisone 100mg IV

Supportive medication
Antiemetics as per local policy
Artificial tears for prophylaxis of dry eye
Hydrocortisone 1% cream, emollient and chlorphenamine if skin toxicity develops

Emetogenicity
This regimen has low emetic potential – refer to local policy.

Administration
Enfortumab vedotin is administered as an intravenous infusion in 50-100mL sodium chloride 0.9% over 30 minutes. Enfortumab vedotin should be administered via an infusion set with a 0.2-1.2 micron filter. The final concentration of the infusion should be between 0.3 and 4 mg/mL.

Pembrolizumab should be administered **after** enfortumab vedotin when they are both administered on the same day. Pembrolizumab should be administered in 100mL sodium chloride 0.9% over 30 minutes via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 5.0µm). After the infusion the line should be flushed with 30mL sodium chloride 0.9%.

Patients should be monitored every 30 minutes during the infusions (blood pressure, pulse and temperature) and for infusion related reactions. For mild to moderate reactions, decrease the infusion rate and closely monitor. Premedication with paracetamol and chlorphenamine should be used for further doses. For severe infusion related reactions discontinue treatment.

Extravasation
Enfortumab vedotin is irritant
Pembrolizumab is neutral

Mandatory investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFT	14 days
LDH	14 days
Thyroid function	14 days
Glucose	14 days
Calcium	14 days
Cortisol	14 days
HbA1c	14 days

Additional investigations advised pre-first cycle

As per IOCN consensus statement, consider the following as part of a baseline cardiac assessment

- ECG
- Troponin
- NT Pro-BNP
- Echocardiogram in high-risk patients (e.g. known CV disease, previous cardiotoxic therapy)

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	Within 4 days of day 1 and 24 hours of day 8*
U+E (including creatinine)	Within 7 days of day 1 and 24 hours of day 8*
LFT	Within 7 days of day 1 and 24 hours of day 8*
LDH	7 days
Thyroid function	6 weekly
Glucose	Within 7 days of day 1 and 24 hours of day 8*
Calcium	As clinically indicated
Cortisol	At consultant discretion

*the ongoing requirement for day 8 bloods may be reviewed by the treating clinician once patients are established on treatment.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer must be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine clearance (CrCl)	≥ 30mL/min
Bilirubin	< 1.5 x ULN
ALT/AST	< ULN
Blood glucose	≤ 13.9 mmol/L

Dose modifications

Dose level	Dose
Starting dose	1.25mg/kg (max dose 125mg)
First dose reduction	1.0mg/kg (max dose 100mg)
Second dose reduction	0.75mg/kg (max dose 75mg)
Third dose reduction	0.5mg/kg (max dose 50mg)

Haematological toxicity

If neutrophils < 1.0 x 10^9/L or platelets <75 x 10^9/L withhold enfortumab vedotin until recovery. Restart at the same dose or dose reduction as per table below:

Toxicity	Action
Neutrophils 0.5-0.99 x 10^9/L *or* platelets 25-99 x 10^9/L	Consider restarting at same dose or at a one level dose reduction – consultant decision
Neutrophils < 0.5 x 10^9/L *or* platelets <25 x 10^9/L	Restart at one level dose reduction

Renal impairment

Enfortumab vedotin: No dose modification is required for mild, moderate or severe renal impairment (CrCl ≥15mL/min). Enfortumab vedotin has not been studied in end stage renal disease (CrCl < 15mL/min)

Pembrolizumab: No dose modification is required for mild or moderate renal impairment (CrCl ≥30mL/min). Pembrolizumab has not been studied in severe renal impairment but no need for dose adjustment is expected. Discuss with consultant if CrCl <30mL/min. See below for management of nephritis emergent on treatment.

Hepatic impairment

Enfortumab vedotin: No dose modification is required for mild hepatic impairment (bilirubin <1.5 x ULN). There is limited data on the use of enfortumab vedotin in patients with moderate or severe hepatic impairment. Hepatic impairment is expected to increase exposure to MMAE (the cytotoxic part of the conjugate) therefore close monitoring for toxicity is recommended, but no specific dose recommendations are available.

Pembrolizumab: No dose adjustment is needed for patients with mild hepatic impairment. Pembrolizumab has not been studied in moderate or severe hepatic impairment but no need for dose adjustment is expected – discuss with consultant. See below for management of hepatitis emergent on treatment.

Other toxicities

Enfortumab vedotin:

Toxicity	Definition	Action/Dose adjustment
Skin reactions	Grade 1-2	Withhold until grade < 1. Restart at same dose or consider one level dose reduction.
	Grade 2 with fever or grade 3	Withhold until grade < 1. Restart at same dose or consider one level dose reduction.
	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) or bullous lesions	Immediately withhold treatment and refer to dermatology
	Confirmed SJS or TEN; Grade 4 or recurrent grade 3	Permanently discontinue enfortumab vedotin
Hyperglycaemia	Blood glucose >13.9mmol/L	Withhold enfortumab vedotin until blood glucose has improved to ≤13.9 mmol/L. Resume treatment at the same dose level.
Pneumonitis/ Interstitial lung disease	Grade 2	Withhold until grade ≤ 1. Restart at same dose or consider one level dose reduction.
	Grade ≥ 3	Permanently discontinue enfortumab vedotin
Peripheral neuropathy	Grade 2	Withhold until grade ≤ 1 For first occurrence, resume treatment at same dose level. For recurrent toxicity, reduce dose by one level
	Grade ≥ 3	Permanently discontinue enfortumab vedotin

Pembrolizumab:

Patients must be advised to seek specialist advice if they experience side effects as these can worsen rapidly. Immune reactions may occur during or after completion of treatment.

Toxicity	Definition	Action
Colitis	Grade 1	Continue and closely monitor
	Grade 2-3	Withhold until symptoms resolve to ≤ grade 1
	Grade 4 or recurrent grade 3	Permanently discontinue pembrolizumab
Pneumonitis	Grade 1	Continue and closely monitor
	Grade 2	Withhold until symptoms resolve to ≤ grade 1
	Grade 3-4 or recurrent grade 2	Permanently discontinue pembrolizumab
Nephritis	Grade 2 (creatinine 1.5-3 x ULN) or Grade 3 (creatinine > 3 x ULN)	Withhold until symptoms resolve to ≤ grade 1
	Grade 4 (creatinine > 6 x ULN)	Permanently discontinue
Endocrine	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grade 3 or 4 adrenal insufficiency or symptomatic hypophysitis	Withhold until symptoms resolve to ≤ grade 1
	Type 1 diabetes with grade > 3 hyperglycaemia (glucose >13.9 mmol/L) or ketoacidosis	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hyperthyroidism ≥ grade 3	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hypothyroidism	Continue and manage with replacement therapy

Toxicity	Definition	Action
Hepatitis	Grade 2: AST/ALT 3-5 x ULN or Bilirubin > 1.5-3 x ULN	Withhold until resolves to ≤ grade 1
	Grade 3: AST/ALT 5-20 x ULN or Bilirubin 3-10 x ULN	May consider recommencing after corticosteroid taper or discontinue treatment – consultant decision
	Grade 4: AST/ALT > 20 x ULN or Bilirubin > 10 x ULN	Permanently discontinue pembrolizumab
	If liver metastasis and baseline AST/ALT 3-5 x ULN and AST/ALT increases ≥ 50% from baseline for ≥ 1 week	Permanently discontinue pembrolizumab
Skin	Grade 3 rash	Withhold until resolves to ≤ grade 1
	Grade 4 rash or Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis	Permanently discontinue pembrolizumab
Cardiac	Grade 2 myocarditis	Withhold until resolves to ≤ grade 1
	Grade 3 or 4 myocarditis	Permanently discontinue pembrolizumab
Neurological	Grade 2 motor or sensory neuropathy	Withhold until resolves to ≤ grade 1
	Grade 3 or 4 motor or sensory neuropathy	Permanently discontinue pembrolizumab
	Grade 3 or 4 encephalitis	Permanently discontinue pembrolizumab
	Grade 3 or 4 Guillain-Barré syndrome	Permanently discontinue pembrolizumab
Infusion-related reactions	Grade 3-4	Permanently discontinue pembrolizumab
Any other toxicity	Grade 3 (first occurrence)	Withhold until resolves to ≤ grade 1
	Grade 4 or recurrent Grade 3	Permanently discontinue pembrolizumab

Pembrolizumab should be permanently discontinued if:
- Corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks
- Treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose

Side Effects

EV-302 study:

Toxicity		Any grade (%)	Grade 3 or 4 (%)
Haematological	Anaemia	13.9	3.4
	Neutropenia/neutrophil count decreased	12.7	7.3
	Thrombocytopenia/platelet count decreased	4.1	0.5
Non-haematological	Peripheral sensory neuropathy	50.0	3.6
	Pruritis	39.8	1.1
	Alopecia	33.2	0.5
	Maculopapular rash	32.7	7.7
	Fatigue	29.3	3.0
	Diarrhoea	27.5	3.6
	Decreased appetite	26.8	1.1
	Nausea	20.2	1.1
	Dry eye	18.6	0
	Hyperglycaemia	10.9	5.0

Specific drug related side effects:

Pembrolizumab

Common (>10%)	Uncommon (1-10%)	Rare (<1%)
Respiratory tract infections	Infusion related reactions	Aseptic meningitis
Decreased appetite	Hyperthyroidism	Histiocytic necrotising lymphadenitis
Hyperglycaemia	Pneumonia	Eosinophilia
Headache	Hypoglycaemia	Sarcoidosis
Dyspnoea, cough	Dizziness	Adrenal insufficiency, hypopituitarism, hypophysitis,
Nausea, vomiting	Peripheral neuropathy	Diabetes mellitus
Diarrhoea, constipation	Blurred vision, dry eye	Uveitis
Rash, pruritis	Tachycardia, AF	Autoimmune neuropathy, Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis
Arthralgia	Pneumonitis	Toxic epidermal necrolysis, Stevens-Johnson syndrome
Fatigue	Colitis	Myocarditis
Deranged LFTs	Stomatitis	Vasculitis
Deranged electrolytes	Dry skin	Pancreatitis
Increased lipase/amylase	Arthritis	Gastritis
Hypothyroidism	Renal failure, acute kidney injury	Cholangitis sclerosing
	Hypertension	Polymyalgia rheumatica
	Hepatitis	Sjogren's syndrome
		Myositis, rhabdomyolysis
		Nephritis

Enfortumab vedotin

Adverse reactions resulting in dose reduction occurred in 40.7% of patients in the trial and 29.5% of patients discontinued enfortumab vedotin due to adverse reactions, with the most common adverse reaction leading to discontinuation being peripheral sensory neuropathy.

Common (>10%)	Uncommon (1-10%)	Rare (<1%)
Anaemia	Thrombocytopenia	Toxic epidermal necrolysis, Stevens-Johnson syndrome
Hyperglycaemia	Pneumonitis, ILD	Neurotoxicity
Decreased appetite	Infusion related reaction	
Peripheral sensory neuropathy	Peripheral motor neuropathy	
Dysgeusia		
Dry eye		
Diarrhoea		
Nausea, vomiting		
Rash, pruritis		
Alopecia		
Fatigue		

Skin reactions
Skin reactions are common during treatment and patients should be monitored throughout treatment. Median time to onset of severe skin reactions was 1.7 months (range 0.1-17.2 months). Antihistamine and topical corticosteroids can be considered for mild to moderate skin reactions. For suspected toxic epidermal necrolysis or Stevens-Johnson syndrome withhold treatment and urgently refer to dermatology.

Pneumonitis/Interstitial Lung Disease
Patients should be monitored for symptoms such as hypoxia, cough and dyspnoea or signs such as interstitial infiltrates on radiologic exams. Administer corticosteroids for ≥ Grade 2 events e.g. prednisolone 1-2mg/kg/day.

Hyperglycaemia
Hyperglycaemia occurred more frequently in patients with pre-existing hyperglycaemia or a high body mass index (≥30 kg/m^2). Patients with baseline HbA1c ≥8% were excluded from clinical studies. Blood glucose levels should be monitored prior to dosing and periodically throughout the course of treatment as clinically indicated in patients with or at risk for diabetes mellitus or hyperglycaemia.

Ocular disorders
Ocular disorders, predominantly dry eye, have occurred in patients treated with enfortumab vedotin. Patients should be monitored for any ocular symptoms. Consider artificial tears for prophylaxis of dry eye and refer for ophthalmologic evaluation if ocular symptoms do not resolve or worsen.

Additional information
Females of reproductive potential should be advised to use effective contraception during treatment and for at least 6 months after stopping treatment. 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.

Significant drug interactions – for full details consult product literature/ reference texts
Strong CYP3A4 and P-gp inhibitors (e.g. ketoconazole) may increase the area under the concentration-time curve (AUC) of unconjugated MMAE (the cytotoxic component of enfortumab vedotin) to a minor extent
Strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenobarbital, phenytoin, St John's wort) may decrease the exposure of unconjugated MMAE.
Corticosteroids: use of systemic corticosteroids at baseline, before starting pembrolizumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of the agent. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.

References

- National Institute for Health and Clinical Excellence TA 1097 accessed 29th September 2025 via www.nice.org.uk
- Summary of Product Characteristics Pembrolizumab - Keytruda®(MSD) accessed 4th September 2025 via www.medicines.org.uk
- Summary of Product Characteristics Enfortumab vedotin (Astellas Pharma) accessed 4th September 2025 via www.medicines.org.uk
- Powles, T. et al. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. N Engl J Med 2024;390:875-888

Version	Issue date	Review date	Revision	Written/Checked/Authorised
1	Sept 2025	Sept 2028	New protocol	**Written/reviewed:** Dr S Hilman (Consultant Oncologist, UHBW NHS Trust) **Checked:** Kate Gregory (Lead Pharmacist for SACT protocols, SWAG Cancer Alliance) **Authorised:** Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)
1.1	Jan 2026	Sept 2028	Addition of requirement for blood tests prior to D8	**Updated by:** Kate Gregory (Lead Pharmacist for SACT Protocols, SWAG Cancer Alliance)