ENFORTUMAB VEDOTIN (Padcev) PEMBROLIZUMAB (Keytruda)

INDICATION (ICD10) C67
Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (ENF1)

1. Enfortumab vedotin with pembrolizumab for previously untreated with systemic therapy, unresectable or metastatic urothelial cancer (i.e cancer of the bladder, renal pelvis, ureter, or urethra) Patients with squamous or sarcomatoid differentiation or mixed cell types are eligible), when treatment with cisplatin or carboplatin based chemotherapy is suitable. Does not have ongoing sensory or motor neuropathy of grade 2 or higher. Does not have active central nervous system metastases – if the patient does have such metastases these must be clinically stable, and the patient must not have leptomeningeal disease. PS 0, 1, or 2 though patients with a PS of 2 must have a haemoglobin of >10g/dl and a GFR >50ml/min. (TA1097)

REGIMEN (SC) (pembrolizumab before chemotherapy)
Cycles 1 to 35
Days 1 and 8 ENFORTUMAB VEDOTIN 1.25mg/kg in #ml sodium chloride IV infusion over 30 minutes

Cycles 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33 and 35 only
Day 1 PEMBROLIZUMAB 790mg subcutaneous* (4.8ml) over 2 minutes

Cycle 36 onwards
Days 1 and 8 ENFORTUMAB VEDOTIN 1.25mg/kg in #ml sodium chloride IV infusion over 30 minutes

*Into the thigh or abdomen, avoiding the 5cm area around the navel

REGIMEN (IV) (pembrolizumab before chemotherapy)
Cycles 1 to 35
Days 1 and 8 ENFORTUMAB VEDOTIN 1.25mg/kg in #ml sodium chloride IV infusion over 30 minutes

Cycles 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33 and 35 only
Day 1 PEMBROLIZUMAB 400mg in 100ml sodium chloride IV infusion over 30 minutes

Cycle 36 onwards
Days 1 and 8 ENFORTUMAB VEDOTIN 1.25mg/kg in #ml sodium chloride IV infusion over 30 minutes

diluent and diluent volume for dose prescribed as per national standardised product specification

CYCLE FREQUENCY AND NUMBER OF CYCLES
Enfortumab vedotin every 21 days until disease progression
Pembrolizumab every 42 days (alternate cycles) cycles 1 to 35 only

ANTI-EMETICS
Low risk

CONCURRENT MEDICATION REQUIRED

Enfortumab vedotin	None required
Pembrolizumab	None required

EXTRAVASATION AND TYPE OF LINE / FILTERS

Enfortumab vedotin – treat as vesicant
Pembrolizumab IV – neutral

Enfortumab vedotin - use in-line filters or syringe filters pore size 0.2-1.2micron.
Pembrolizumab IV - use low protein binding 0.2 to 5micron in-line or add-on filter
Peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs every dose
Neutrophils x 10^9/L ≥1.0
Platelets x 10^9/L ≥75
Creatinine baseline, then every dose
Thyroid function baseline, then every cycle
Random cortisol baseline, then every cycle (or as specified in Trust guideline)
Random glucose every dose
Hba1c baseline
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Enfortumab vedotin	Hyperglycaemia Peripheral neuropathy Pneumonitis / interstitial lung disease Skin reactions
Pembrolizumab	Immune related toxicities

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Enfortumab vedotin	Lots of interactions check carefully
Pembrolizumab	-

DOSE MODIFICATIONS

Starting dose	1.25mg/kg up to 125mg
First dose reduction	1.0mg/kg up to 100mg
Second dose reduction	0.75mg/kg up to 75mg
Third dose reduction	0.5mg/kg up to 50mg

Haematological

Enfortumab vedotin

Platelets 25-75x10^9/L or neutrophils 0.5-0.99x10^9/L	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.
Platelets >25x10^9/L or neutrophils >0.5x10^9/L	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.

Pembrolizumab
None required

Non-haematological

Enfortumab vedotin

Hyperglycaemia

Blood (serum) glucose >13.9mmol/L (>250mg/dL)	• Withhold until elevated blood glucose has improved to ≤13.9mmol/L (≤250mg/dL). • Resume treatment at the same dose level.

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.

Pneumonitis / interstitial lung disease

Grade 2	• Withhold until grade ≤1, then resume at the same dose or consider dose reduction by one dose level.
Grade ≥3	Permanently discontinue.

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.

Pembrolizumab

Immune-related adverse reactions - refer to TV immune-oncology agent immune related adverse event clinical guideline.

If the drug-related toxicity does not resolve to grade 0-1 within 12 weeks after onset of toxicity, discontinuation is recommended.

Hepatic impairment

Enfortumab vedotin

Mild hepatic impairment total bilirubin of 1-1.5× ULN and AST any, or total bilirubin ≤ULN and AST >ULN no dose adjustment is necessary.

Enfortumab vedotin has only been evaluated in a limited number of patients with moderate and severe hepatic impairment.

Hepatic impairment is expected to increase the systemic exposure to MMAE (the cytotoxic drug); therefore, patients should be closely monitored for potential adverse events. Due to the sparsity of the data in patients with moderate and severe hepatic impairment, no specific dose recommendation can be given.

Pembrolizumab

No dose adjustment is needed.

Renal impairment

Enfortumab vedotin

Mild CrCL >60–90mL/min, moderate CrCL 30–60mL/min or severe CrCL 15-<30mL/min renal impairment no dose adjustment is necessary.

Enfortumab vedotin has not been evaluated in patients with end stage renal disease CrCL<15mL/min.

Pembrolizumab

No dose adjustment is needed.

REFERENCE

1. CDF
2. SPC