Enfortumab Vedotin and Pembrolizumab in urothelial cancer (EV-P)

Indication

- Unresectable, advanced or metastatic urothelial cancer eligible for platinum containing chemotherapy as per EMA licence for EV-P.
- Predominant urothelial pathology
- Treatment naïve in metastatic setting
- In the absence of Eb-P the patient would have been deemed eligible for treatment with platinum containing chemotherapy.
- No previous IO unless these were given in a neo adjuvant and/or adjuvant setting and the most recent dose was given >12 months before recurrence was diagnosed
- WHO PS 0-1 (PS2 considered at consultant discretion - must have a haemoglobin of >10g/dl and a GFR >50ml/min, and PS 2 patients in general have worse outcome in urothelial cancer)
- Adequate bone marrow reserve: WBC > 3.0 x 10^9 /L, neutrophils > 1.5 x 10^9 /L, platelets > 100 x 10^9 /L, Hb > 100 g/dL
- Adequate renal function CrCl ≥ 30ml/min ml/min,
- Adequate hepatic function (bilirubin ≤1.5 x ULN)
- All Blueteq criterias are met
- No active CNS metastases-if the patient does have such metastes these must be clinically stable and the patient must not have leptomeningeal disease
- When a treatment break of more than 12 weeks beyond the expected 3-weekly cycle is needed, a treatment break form to restart treatment must be completed & must be approved before treatment is re-commenced
- Enfortumab vedotin and pembrolizumab must be used in combination unless
- ***The patient experiences unacceptable toxicity that is attributable only to pembrolizumab, then they may continue enfortumab vedotin monotherapy until one of the criteria in below is met***
  - ***The patient experiences unacceptable toxicity that is attributable only to enfortumab vedotin, then they may continue pembrolizumab monotherapy until one of the criteria is met***
  - ***Treatment with enfortumab vedotin will be continued until disease progression, unacceptable toxicity, or withdrawal of patient consent, whichever of these events occurs first.***
  - ***Treatment with pembrolizumab will be continued until disease progression, unacceptable toxicity, withdrawal of patient consent, or a maximum treatment duration of 35 cycles (if given 3-weekly, or its equivalent if 6-weekly dosing is used) whichever of these events occurs first.***

Treatment intent is palliative

Cautions

- Active infection
- Co-existing co-morbidities preventing safe administration of chemotherapy eg pre-existing neuropathy, conditions predisposing to diarrhoea. **Patients with ongoing sensory or motor neuropathy of grade 2 or higher are excluded from treatment as per Blueteq criteria**
- Co-existing conditions preventing safe administration of immunotherapy, e.g. pre-existing autoimmune conditions, previous organ transplantation
- Females of reproductive potential should be advised to have a pregnancy test within 7 days prior to starting treatment with enfortumab vedotin, 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 of enfortumab vedotin

- Severe Hepatic Impairment
- Poor performance status (PS >1)
- Poorly controlled diabetes mellitus (not recommended in patients with HbA1c ≥ 64mmol/mol)
- High BMI (>30)

Publication	*Agents*	*N*	*PFS / OSS*
EV-302 trial	Enfortumab Vedotin + Pembrolizumab	442	12.5 months / 31.5 months
	Cisplatin/carboplatin + gemcitabine	444	6.3 months / 16.1 months

Regimen details

Drug	*Dose*	*Route*	*Diluent*	*Duration*	*Frequency*
Cycle 1-3 – 21 day cycle					
Enfortumab Vedotin	1.25mg/kg (capped at 125mg)	IV	50mls 0.9% sodium chloride	30mins	Day 1 and day 8
Flush IV infusion line with at least 20mL diluent (0.9% NaCl) approximately 5 minutes after administration. Monitor patient for infusion reactions for 30 minutes after completion of enfortumab vedotin before commencing pembrolizumab. Assess for infusion site reactions / extravasation					
Pembrolizumab	200mg	IV	100mls 0.9% sodium chloride	30mins	Day 1
Cycle 4-35 – 21 day cycle					
Enfortumab Vedotin	1.25mg/kg (capped at 125mg)	IV	50mls 0.9% sodium chloride	30mins	Day 1 and day 8
Flush IV infusion line with at least 20mL diluent (0.9% NaCl) approximately 5 minutes after administration. Monitor patient for infusion reactions for 15 minutes after completion of enfortumab vedotin before commencing pembrolizumab. Assess for infusion site reactions / extravasation					
Pembrolizumab	200mg	IV	50mls 0.9% sodium chloride	30mins	Day 1
Cycle 36 onwards – 21 day cycle					
Enfortumab Vedotin	1.25mg/kg (capped at 125mg)	IV	50mls 0.9% sodium chloride	30mins	Day 1 and day 8
Flush IV infusion line with at least 20mL diluent (0.9% NaCl) approximately 5 minutes after administration. Monitor patient for infusion reactions for 15 minutes after completion of enfortumab vedotin. Assess for infusion site reactions / extravasation					
Repeat every 21 days. Maximum duration of treatment for pembrolizumab is 2 years (35 x 3-weekly or equivalent 6-weekly cycles). Pembrolizumab may be given at 3-weekly (200mg) or 6-weekly (400mg) dosing schedule at consultant's discretion. After completion of 2 years of pembrolizumab in combination with enfortumab vedotin, patients who are still benefitting from treatment may continue on enfortumab vedotin monotherapy until disease progression.					

Either drug may be continued as monotherapy if the other is stopped due to intolerable toxicity.

Administration

Patients should be observed for infusion reactions for 60 minutes after the *initiation* of the enfortumab vedotin infusion for the first 3 cycles. If previous infusions were tolerated well, patients need only be monitored for 15 minutes after *completion* of the enfortumab vedotin infusion from cycle 4 onwards

Cycle frequency

21 day cycle

Imaging after 4 cycles and every 4 cycles thereafter.

Review on day 1 and 8 in medical/ANP clinic for cycles 1-3. If signs of peripheral neuropathy at Grade 1 9 asymptomatic, but clinical signs using tendon hammer/tuning fork) then for review on day 15 in medical clinic or with ANP. **NB not remote review**.

Cycle 4 onwards- day 8 review by chemotherapy nurse. Day 1 review in medical/ANP clinic

Number of cycles

Pembrolizumab : Maximum duration of treatment for pembrolizumab is 2 years (35 x 3-weekly or equivalent 6-weekly cycles). Pembrolizumab may be given at 3-weekly (200mg) or 6-weekly (400mg) dosing schedule at consultant's discretion.

Enfortumab vedotin: After completion of 2 years of pembrolizumab in combination with enfortumab vedotin, patients who are still benefitting from treatment may continue on enfortumab vedotin monotherapy until disease progression. Either drug may be continued as monotherapy if the other is stopped due to intolerable toxicity. The schedule for EV after discontinuation of Pembrolizumab, either due to completion of 2 years of IO, or due to toxicity, remains on the day 1 day 8 schedule as per the EV302 trial.

Pre-medication

None required

Emetogenicity

Low emetogenic risk

Additional supportive medication

No pre-medication or TTOs required

Extravasation

Enfortumab Vedotin: Neutral
Pembrolizumab: Neutral

Infusion reactions

Infusion site reactions have occurred after administration of enfortumab vedotin. These reactions generally occurred immediately after administration but sometimes may happen days after completion of the infusion (up to 1 in 10 people). Advise patient to seek advice via the Hotline if they experience any redness, swelling, itching or discomfort at the infusion site

Investigations – pre first cycle

Standard network pre-SACT tests

- Observations BP, Pulse and Temp

- Medical / drug history- confirm the dose of any immunosuppressant therapy (ideally <10mg prednisolone daily or equivalent)
- Allergy status
- Physical assessment
- Height and weight recorded
- WHO performance status recorded
- FBC, U&Es, LFTs, calculate creatinine clearance (CrCL)
- Baseline thyroid function tests (TFTs) and cortisol
- Baseline B12 & folate, iron studies
- Baseline ECG
- Blood glucose level. Refer patients with diabetes to DSN team. Consider providing glucometer
- Baseline staging scans (CT TAP +/- MRI)
- Prescribe chemotherapy for cycle 1
- Ensure Blueteq funding completed

Investigations –pre subsequent cycles

- Weight
- FBC, U&Es, Bone, Liver.(including AST)
- Cortisol, TFTs, blood glucose
- Calculated creatinine clearance
- Graded documentation of toxicities
- Assessment of disease related symptoms
- Record of ECOG / WHO performance status
- Fitness for continuation of treatment assessment

NB mandatory assessment for peripheral neuropathy, NB Grade 1 is asymptomatic and thus assessment with tuning fork and tendon hammer for loss of vibrational sense, or reflexes, together with any other sensory changes (proprioception etc) is mandatory before each cycle day 1 and on day 8 of first 4 cycles of EV.
Patients should also be reviewed by parent clinician on day 8 for cycles 1 to 3 of EV for peripheral neuropathy and other toxicity in view of limited clinician experience with ADC in urothelial cancer.

Standard limits for administration to go ahead

- Weight does not differ by >10% from the value used for dosing
- All toxicities are at grade 1 or below
  NB: Patients with an unresolved grade ≥ 2 non-haematological toxicity, any grade 3/4 toxicity or a hospital admission since the last cycle MUST be discussed with the medical team

Blood results fall within the parameters detailed below
If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Enfortumab Vedotin

Haematological			
Neutrophils		*Plt*	*Action*
≥1.5	***and***	*≥ 100*	*None*
≤1.4	**or**	≤ 99	Defer 1 week. Consider dose reduction by 1 dose level (see dose reduction chart)

Anaemia			
Hb (g/L)			*Action*
≥90			*Proceed with treatment*
80-90	***and***	*asymptomatic*	*Proceed with treatment*
80-90	***and***	symptomatic	Proceed with treatment – arrange blood transfusion
<80			Arrange blood transfusion. Consultant decision to proceed with treatment or defer for one week

Infective: Patients who have had admission with neutropenic sepsis to be reviewed in clinic and considered for dose reduction

Renal impairment	
Serum Creatinine	
<1.5xULN or <1.5xbaseline	Proceed with treatment
>1.5xULN or >1.5xbaseline	Consultant decision. Unlikely to be related to enfortumab vedotin
In trials, no dose adjustments were required for patients with patients with CrCl > 15ml/min	

However if patients have significant fall in CrCl this requires investigation and exclusion of hydronephrosis, progressive disease or treatment related toxicity

Hepatic impairment			
Bilirubin		*AST +/or ALT*	*Action*
≤1.5 x ULN	**and**	≤5 x ULN	Proceed with treatment
≤1.5 x ULN	**and**	>5 x ULN	Defer until liver enzymes return to normal levels. Consider dose reduction by one dose level (see dose reduction chart)
>1.5 x ULN	**or**	>20 x ULN	Discontinue treatment

Toxicity: Hyperglycaemia	
Grade 1 7.8-8.8 mmol/L	*No action required*
Grade 2 >8.8 – 13.9mmol/L	*Refer to DSN team. Close monitoring of glucose level is necessary. Check for urinary ketones. Consider oral antiglycaemic agent.*
Grade 3 >13.9 – 27.8 mmol/L	*Refer to DSN team. Manage with insulin. Assess for symptoms of Diabetes/ketoacidosis. Check for urinary ketones. If positive consider admitting patient. Withhold enfortumab vedotin until reduced to minimum Grade 2. Resume at the same level or consider dose reduction by one dose level*
Grade 4 >27.8 mmol/L	*Refer to DSN team / endocrinology. Manage with insulin. Assess for symptoms of Diabetes/ketoacidosis. Check for urinary ketones. If positive admit patient. Follow Trust policy for management of urgent hyperglycemia (DKA or HHS). Permanently discontinue enfortumab vedotin*

Toxicity: Skin reactions	
Grade 1/2 (mild/moderate)	*Consider appropriate treatment such as emollients, topical corticosteroids, antihistamines*
Grade 2 (moderate) worsening, Grade 2 (moderate) with fever or Grade 3 (severe)	*Withhold enfortumab vedotin until ≤ Grade 1. Resume at the same level or consider dose reduction by one dose level. Consider referral to specialised care*
Suspected SJS or TEN, or bullous lesions onset	*Withhold enfortumab vedotin immediately & refer to specialist care*
Confirmed SJS or TEN, Grade 4 (life-threatening) or recurrent Grade 3 (severe) skin reactions	*Permanently discontinue enfortumab vedotin*

Toxicity: Pneumonitis / ILD

Grade 1	*No action*
Grade 2 (moderate)	*Withhold enfortumab vedotin until ≤ Grade 1. Resume at the same level or consider dose reduction by one dose level*
Grade ≥ 3 (severe / life threatening)	*Permanently discontinue enfortumab vedotin*

Toxicity: Ocular disorders	
Grade 1/2 (mild / moderate)	*Treat symptomatically as appropriate. Consider referral to specialist care*
Grade 2 (worsening) or Grade 3 (severe)	*Withhold enfortumab vedotin until ≤ Grade 1. Resume at the same level or consider dose reduction by one dose level. Refer to specialised care*
Grade 4	*Permanently discontinue enfortumab vedotin. Refer to specialised care*
Toxicity: Peripheral neuropathy	
Grace 1 (mild)	*No action NB this is asymptomatic and thus should be assessed with tendon hammer and tuning fork and consider early dose reduction one level. Patients with asymptomatic Grade 1 PN should be reassessed on each cycle day 1 and 15 .*
Grade 2 (moderate)	*Withhold enfortumab vedotin until ≤ Grade 1 (mild and asymptomatic), then resume treatment at the same dose level (if first occurrence). For a recurrence, withhold until ≤ Grade 1 (mild), then resume treatment reduced by one dose level*
Grade 3 (severe/life threatening)	*Permanently discontinue enfortumab vedotin*

Other Toxicities	
Any grade 3/4 toxicity	*Permanently discontinue enfortumab vedotin*

Dose modifications

Doses are capped at effective 100kg weight

Dose level	**Dose**	**Max dose**
Starting dose	1.25mg/kg	125mg
1st dose reduction	1.0mg/kg	100mg
2nd dose reduction	0.75mg/kg	75mg
3rd dose reduction	0.5mg/kg	50mg

iQemo will cap the initial dose at 125mg. iQemo **will not** apply dose caps to reduced doses **so prescribers must ensure that dose caps are not exceeded when making dose reductions**

Immunotherapy toxicity management due to pembrolizumab

Pembrolizumab

Note: Dose reduction of Pembrolizumab is not required. If significant toxicity then treatment should be withheld as per immunotherapy guidance below. Dosing of Enfortumab vedotin may continue, toxicity dependent as per dose modification schedule, and on Day 1 and 8 schedule as per EV302 trial for the combination treatment. There is no day 15 dose addition if enfortumab vedotin continues as monotherapy due to IO related toxicity.

Non- Haematological Toxicity:

- Serum creatinine – see table below
- AST/ALT – see table below
- Bilirubin – see table below

- Thyroid function abnormal – see table below
- New onset hyponatraemia – need to exclude cortisol deficiency and hyperglycaemia (see table below)
- Any new toxicity on the immunotherapy check list
- Patient's general condition is deteriorating
- Cortisol outside normal limits - when off steroids

Refer to UKONS Acute Oncology Initial Management Guidelines and ESMO Clinical Practice Guidelines

If starting steroids at any point, administer with PPI cover and monitor blood glucose for possible steroid-induced diabetes.

If on ≥50mg prednisolone or equivalent, consider opportunistic infection prophylaxis (eg: Fluconazole 50mg OD, Aciclovir 400mg BD, Co-trimoxazole 960mg OD M, W, F or 480mg OD).

Renal impairment		
Serum Creatinine	**Grade**	
<1.5 x ULN or baseline	1	• Continue treatment. If above baseline, monitor weekly until returns to baseline.
1.5 – 3 x ULN or baseline	2	• Medical review. Exclude other causes (eg: medications). • Defer treatment until recovers to Grade 0-1. • Medical team to re-check creatinine in 48-72 hours. • If worsening and clinically immune related nephritis, start oral steroids. • Perform renal screen – urine dip, M,C&S, if proteinuria do urine protein creatinine ratio or 24 hr urine protein, if haematuria then do glomerular nephritis screen (anti-ANA, -ANCA, -GBM*, complement screen, immunoglobulins, protein electrophoresis). • USS to check for obstructive uropathy.
3 – 6 x ULN or baseline	3	• Medical review. Defer treatment. Admit for monitoring and fluid balance. Medical team to re-check creatinine every 24h. • Determine likely cause of AKI – if clinically immune related nephritis, start IV methylprednisolone 1mg/kg. • Renal screen as above. Consider renal biopsy.
>6 x ULN or baseline	4	• Medical review. Stop treatment. Admit for monitoring and fluid balance. Medical team to re-check creatinine every 24h. • Determine likely cause of AKI – if clinically immune related nephritis, start IV methylprednisolone 1mg/kg. • Renal screen as above. Consider renal biopsy and Renal Replacement Therapy (eg: Continuous Veno-Venous Haemofiltration).

*ANA: Anti-Nuclear Antibody, ANCA: Anti-Neutrophil Cytoplasmic Antibody, GBM: Glomerular Basement Membrane antibody

Hepatic impairment		
AST +/- ALT	**Grade**	
<3 x ULN	1	• Continue treatment. If above baseline, monitor weekly until returns to baseline.
3 – 5 x ULN (or bilirubin >1.5 x ULN)	2	• Medical review. Exclude other causes (eg: medications - check if on any other drugs associated with hepatitis, including paracetamol). • Defer treatment until recovers to Grade 0-1. • Medical team to re-check LFTs, clotting screen & albumin in 48-72 hours. If worsening and attributable to irAE, start oral steroids. • Perform liver screen – viral hepatitis serology, autoantibody screen (anti-ANA/SMA/LKM/SLA/LP*) and iron studies. • Do USS Doppler to exclude portal vein thrombosis.

5– 20 x ULN (or bilirubin >3 x ULN)	3	• Medical review. Defer treatment. Admit for monitoring. Daily LFTs/clotting screen/albumin. • Start oral/IV steroids (1-2mg/kg initially) as per ESMO guidelines. • Liver screen as above.
>20 x ULN	4	• Medical review. Stop treatment. Admit for monitoring. Daily LFTs/clotting screen/albumin. • Start IV steroids as per ESMO guidelines. • Liver screen as above. Consider liver biopsy.

*ANA: Anti-Nuclear Antibody, SMA: Smooth Muscle Antibody, LKM: Liver/Kidney Microsomal, SLA/LP: Soluble Liver Antigen/Liver-Pancreas Antibody.

Immune-related endocrinopathies	
Severity/Grade	**Action**
Asymptomatic hyperthyroidism TSH below normal range with normal or elevated free T4 (TSH might be low due to thyroid axis suppression due to acute or subacute illness)	• Continue immunotherapy treatment. • Check TFTs before each cycle or after four weeks. • TFT monitoring is necessary even if the TFTs return to normal because of the risk of developing hypothyroidism subsequently.
Symptomatic hyperthyroidism TSH below normal range with normal or (usually) elevated free T4	• Defer immunotherapy treatment. • Medical review and discussion with Endocrinology. • Check TSH receptor antibody to exclude autoimmune thyrotoxicosis – Grave's disease. • Start beta-blocker (eg: propanolol 40mg TDS), or diltiazem if contra-indications to beta-blockers. • Avoid carbimazole/PTU, unless TSH receptor antibody positive. • Can restart immunotherapy treatment once asymptomatic. Check TFTs before each cycle or after four weeks. • TFT monitoring is necessary even if the TFTs return to normal because of risk of developing hypothyroidism subsequently. • Refer for Endocrinology O/P review.
Subclinical hypothyroidism TSH above ULN but <10 mU/L, with free T4 within normal range on 2 occasions	• Continue treatment. • Check TFTs before each cycle or after four weeks. • If treatment with levothyroxine is considered check serum cortisol first (ideally 9am level) to exclude cortisol deficiency (see cortisol deficiency guidelines below). • In patients under age of 70y start levothyroxine 50 mcg OD, if symptomatic or if TSH is over 7.0 mU/L on repeated testing (x2). • Patients older than 70y should be treated if TSH is between 7.0 – 9.9 mU/L and patient is symptomatic. Otherwise treatment is not necessary but monitoring is necessary (for TSH ≥ 10 mU/L see below). • Re-check TFTs in six weeks and adjust dose if necessary. • If FT4 low and TSH low/normal, check cortisol (ideally 9am level) to exclude cortisol deficiency.

Overt hypothyroidism TSH ≥ 10 mU/L with free T4 below normal reference range	• Continue treatment, but also arrange medical review. • Check serum cortisol (ideally 9am level), if not done recently (see cortisol deficiency guidelines below). Treatment with levothyroxine should not be commenced unless cortisol deficiency is excluded (due to the risk of adrenal crisis). • Start levothyroxine 50mcg OD. Check weight and exclude significant cardiac history (AF/IHD) - in such cases an initial dose of 25mcg OD might be appropriate. In young/symptomatic patients/with substantially elevated TSH an initial dose of Levothyroxine 75 mcg OD mcg might be appropriate. • If symptoms are improving check TFTs in six weeks and adjust the dose as appropriate (it takes 4-6 weeks to see improvement in TSH). If remains symptomatic check TFTs earlier after three weeks of treatment. • Refer for Endocrinology O/P review
Possible cortisol deficiency 9am serum cortisol 200-450 nmol/L, or random cortisol 100-450 nmol/L With mild or moderate symptoms suggesting adrenal insufficiency: Tiredness/fatigue, weight loss, susceptibility to infection, normal BP with no postural drop)	• Continue treatment. • Warn patient to seek urgent medical review if unwell. May become life threatening in case of intermittent illness. • Check ACTH* and rest of pituitary axis (TFTs, LH, FSH, IGF-1, prolactin, oestradiol in pre-menopausal women, testosterone in men), ideally before starting any steroids. • Refer for early Endocrinology O/P review. If delay in referral anticipated consider starting oral hydrocortisone (10/5/5mg) or prednisolone (3-5mg OD). • Advise about sick-day rules.
Possible cortisol deficiency Low serum cortisol (9am <200 or random <100 nmol/L) Without symptoms suggesting adrenal insufficiency: Tiredness/fatigue, weight loss, susceptibility to infection, normal BP with no postural drop)	• Continue treatment. • Warn patient to seek urgent medical review if unwell. May become life threatening in case of intermittent illness. • Check for current or recent history of glucocorticoid treatment (eg: prednisolone, dexamethasone, hydrocortisone, oral, inhaled or injected) as this might cause the low cortisol level. • Check ACTH* and rest of pituitary axis (TFTs, LH, FSH, IGF-1, prolactin, oestradiol in pre-menopausal women, testosterone in men), ideally before starting any steroids. • Discuss with Endocrinology. If cannot contact Endocrinology or it is out of hours, start treatment with oral hydrocortisone (10/5/5mg) or prednisolone (3-5mg). • Advise about sick-day rules. • Refer for early Endocrinology O/P review.

Likely cortisol deficiency Low serum cortisol (9am <200 or random <100 nmol/L) With mild/moderate symptoms suggesting possible adrenal insufficiency: Tiredness/fatigue, weight loss, susceptibility to infection, normal BP with no postural drop, headache (sign of possible hypophysitis).	• Continue treatment, but also arrange medical review. • Check for current or recent history of glucocorticoid treatment (eg: prednisolone, dexamethasone, hydrocortisone, oral, inhaled or injected) as this might cause the low cortisol level. • Check ACTH, renin, aldosterone* (ideally prior to the initiation of any steroids) to exclude adrenalitis. • Check rest of pituitary axis (TFTs, LH, FSH, IGF-1, prolactin, oestradiol in pre-menopausal women, testosterone in men). • Discuss with Endocrinology. If cannot contact Endocrinology or it is out of hours, start treatment with oral hydrocortisone (10/5/5mg) or prednisolone (3-5mg). • Advise about sick-day rules. • Request MRI pituitary. • Refer for Endocrinology O/P follow-up.
Life threatening acute cortisol deficiency Patients who present unwell with life threatening signs/symptoms compatible with possible acute severe cortisol deficiency with random serum cortisol < 450 nmol/L. Eg: hypotension, postural hypotension, dizziness, tachycardia, fever, abdominal pain, nausea, vomiting, confusion or delirium, coma, hyponatremia, hyperkalaemia, hypoglycaemia. Or severe symptoms of mass effect from pituitary swelling (sign of possible hypophysitis): severe headache, any visual disturbance, cranial nerve palsies).	• Defer treatment. Medical review and admit. • Check for current or recent history of glucocorticoid treatment (eg: prednisolone, dexamethasone, hydrocortisone, oral, inhaled or injected) as this might cause the low cortisol level. • Check ACTH, renin, aldosterone* (ideally prior to the initiation of any steroids) to exclude adrenalitis. • Check rest of pituitary axis (TFTs, LH, FSH, IGF-1, prolactin, oestradiol in pre-menopausal women, testosterone in men). • Discuss with Endocrinology. If cannot contact Endocrinology or it is out of hours, start treatment as below: • If symptoms of pituitary gland swelling (eg: headaches, visual disturbance) present consider initial IV methylprednisolone (1mg/kg). • Otherwise start hydrocortisone 100 mg i.v. or i.m. followed by high dose H/C (im/iv or continuous infusion as per guidance; https://doi.org/10.1530/EC-16-0054 - Society for Endocrinology Guidance on emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients). • If using cortisol infusion for management of acute adrenal insufficiency we recommend this is performed in a carefully monitored environment (e.g. HDU) as patient will become hypocortisolemic if infusion is interrupted. • Rehydrate with intravenous fluids. • Request MRI pituitary (urgently if symptoms of mass effect are present). • Refer for Endocrinology O/P follow-up.
Grade 1 Hyperglycaemia 7.8-8.8 mmol/L	• No action required
Grade 2 Hyperglycaemia >8.8 – 13.9mmol/L	• Refer to DSN team. Close monitoring of glucose level is necessary • Check for urinary ketones. Consider oral antiglycaemic agent • Patient should receive glucometer.

Grade 3 Hyperglycaemia >13.9 – 27.8 mmol/L	• Refer to DSN team. Consider management with insulin. • Assess for symptoms of Diabetes/ketoacidosis. • Check for urinary ketones. If positive admit patient • Withhold treatment until reduced to minimum Grade 2.
Grade 4 Hyperglcaemia >27.8 mmol/L	• Discuss with Diabetes nurse/Endocrinology. Manage with insulin. • Defer treatment (permanently discontinue enfortumab vedotin) • Assess for symptoms of Diabetes/ketoacidosis. • Check for urinary ketones. If positive admit patient. • Follow Trust policy for management of urgent hyperglycemia (DKA or HHS)
*Tubes for collection of blood samples for endocrinopathies:	
Serum cortisol	Serum 0.5 ml
TSH receptor Ab	Serum 0.5 ml
ACTH	Plasma EDTA x 2, sent to lab Immediately
Plasma aldosterone + plasma renin activity	Plasma EDTA x 3, sent to lab immediately

Immune-related colitis	
Severity/Grade	**Action**
Grade 1 diarrhoea or colitis (Increase of <4 liquid stools per day over baseline, feeling well)	• Continue treatment. • Advise oral fluids, low fibre diet, loperamide (use with caution). • Send stool samples for M,C&S, including C. Difficile, viral PCR, ova and parasites. • If grade 1 diarrhoea for >14 days, treat as per grade 2.
Grade 2 diarrhoea or colitis (4-6 liquid stools per day over baseline or blood in stools, abdo pain, nausea or nocturnal episodes).	• Defer treatment and arrange medical review. • Advise oral fluids and low fibre diet. Stop loperamide. • Send stool samples for M,C&S, including C. Difficile, viral PCR, ova and parasites. • Send blood for CMV serology and PCR. • AXR to check for colitis. • If grade 1 diarrhoea for >14 days or grade 2 diarrhoea for >3 days, start oral/IV steroids. • Consider sigmoido/colonoscopy (+/- biopsy to evaluate degree of colitis and to check for CMV infection).
Grade 3 or 4 diarrhoea or colitis (≥7 liquid stools per day over baseline or if episodes with 1hr of eating)	• Defer treatment and arrange medical review. • Admit (may need side room if infection not excluded clinically). • Send stool samples for M,C&S, including C. Difficile, viral PCR, ova and parasites. • Send blood for CMV serology and PCR. • AXR and CT abdo/pelvis to check for colitis. • Start IV methylprednisolone 1mg/kg (as per ESMO guidelines). • Consider NBM/clear fluids only/TPN. • Consider sigmoido/colonoscopy (+/- biopsy to evaluate degree of colitis and to check for CMV infection). • Consider early surgical r/v if bleeding, pain or distension.

Other immune-related toxicities	**Severity/Grade**	**Action**
Immune-related pneumonitis	Grade 1 pneumonitis (radiographic changes only,	• Consider delay of treatment and medical review if any concerns.

	ground glass change, non-specific interstitial pneumonia)	
	Grade 2 pneumonitis (mild/moderate new symptoms of breathlessness, cough, chest pain)	• Defer treatment. Medical review. Exclude other causes (eg: infection). • Consider antibiotics and oral steroids. • Consider further investigations (eg: HRCT chest, sputum culture, nose & throat swabs for virology, serum beta-glucan and galactomannan, lung function tests, bronchoscopy + BAL).
	Grade 3 or 4 pneumonitis (Severe new symptoms, new/worsening hypoxia, life threatening difficulty in breathing, ARDS)	• Stop treatment. • Medical review and admit patient. • Start IV steroids as per ESMO guidelines. • Further investigations as per Grade 2. • Discuss and document level of escalation.
Immune-related skin adverse reactions	Grade 1 rash (covering <10% of Body Surface Area)	• Continue treatment. • Consider topical emollients, mild steroid cream and/or anti-histamines.
	Grade 2 rash (covering 10-30% of BSA)	• Continue treatment. • Advise topical emollients, moderate/strong steroid cream and/or anti-histamines. • Consider dermatology referral.
	Grade 3 rash (rash covering >30% of BSA, or grade 2 with substantial symptoms)	• Defer treatment. • Medical +/- dermatology review. • Topical treatments as for grade 2. • Start oral/IV steroids, as per ESMO guidelines.
	Grade 4 rash (skin sloughing >30% of BSA with associated symptoms, eg: erythema, purpura, epidermal detachment)	• Stop treatment. • Urgent medical & dermatology review. • Topical treatments as above. • Start iv steroids, as per ESMO guidelines. Check for signs of Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis (target lesions, oral mucosal ulceration, ocular symptoms, genito-urinary involvement).
Other immune-related adverse reactions	Mild / asymptomatic / Grade 1-2	• Continue treatment. • Consider medical review if Grade 2.
	Grade 3 (first occurrence)	• Defer treatment. Contact Medical Team.
	Grade 4 or recurrent Grade 3	• Stop treatment. Contact Medical Team. • Likely to need steroid treatment.

Adverse effects - for full details consult product literature/ reference texts

During treatment

Enfortumab vedotin:

Peripheral sensory neuropathy, pruritis, alopecia, skin reactions including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), fatigue, diarrhoea, decreased appetite, nausea, hyperglycaemia, pneumonitis, interstitial lung disease, ocular disorders including dry eye, blurred vision & keratitis, neutropenia, thrombocytopenia, anaemia

Pembrolizumab:

Fatigue, skin rashes, pruritus, diarrhoea/colitis, nausea, endocrinopathies (hyper/hypothyroidism, hypophysitis, adrenal insufficiency, diabetes), hepatitis, hyponatraemia, hypokalaemia, pneumonitis, nephritis, arthralgia, peripheral neuropathy, CNS toxicities and neuropathies, uveitis, mucositis, myositis and myocarditis, Guillain-Barré syndrome, myasthenic syndrome, pancreatitis, sarcoidosis, haemolytic anaemia, pneumonitis, myocarditis, rhabdomyolysis, skin

reactions including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)

Late toxicities
Ongoing peripheral neuropathy. Immunotherapy related toxicities can occur at any time in the future following treatment. This can still occur after treatments have been discontinued.

Hypersensitivity
Treat as per standard chemotherapy related hypersensitivity reaction with anti-histamines, O2, fluids, steroid and adrenaline if required

Treat acute episode as per anaphylaxis policy. Treatment may be resumed when the acute event is resolved.

For grade 1-2 hypersensitivity reactions all future administration should be undertaken at 50% infusion rate with paracetamol 1g IV/PO and chlorphenamine 10mg IV premedication.

For grade 3-4 hypersensitivity reactions permanently discontinue drug.

Significant drug interactions – for full details consult product literature/ reference texts

Levels of unconjugated MMAE (vedotin) may be affected by inducers or inhibitors of CYP3A4 enzymes but this is not predicted to affect the exposure of antibody-drug conjugate (ADC) Patients receiving strong CYP3A4 inhibitors should be monitored more closely for signs of toxicity . Patients on strong CYP3A4 inducers may decrease the exposure of MMAE with moderate effect.

Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions. Corticosteroids can also be used as premedication, when pembrolizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

For a complete list of potential interactions see The Electronic Medicines Compendium or use a reputable interaction checker eg: OncoAssist, UpToDate, Stockley's Interactions Checker or www.drugs.com

Stopping criteria

- Progressive disease – clinically or radiologically (by RECIST criteria where possible)
- Life threatening toxicity attributed to chemotherapy or immunotherapy i.e. CTCAE Grades 3-4 toxicities
- Patient choice
- Significant fall in PS (3 or 4)
- Exacerbation of co-morbid condition
- Poor patient compliance
- Consultant discretion
- Maximum duration of therapy for pembrolizumab is 2 years (35 cycles of 3-weekly 200mg dose or equivalent number of 6-weekly 400mg dose) – patients may continue on enfortumab vedotin monotherapy beyond this point until disease progression

Additional comments

References

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THIS PROTOCOL HAS BEEN DIRECTED BY Prof Alison Birtle, DESIGNATED LEAD CLINICIAN FOR BLADDER CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

Date: November2025
Review: November 2027
VERSION: 1.4

Whilst every effort is made to ensure the accuracy of the information in a given protocol it cannot be guaranteed that the protocol is fully up to date. Cancer treatment can be dynamic in nature. Decisions on SACT must therefore be based on the independent judgement of the clinician with reference to changing information on the medicine (eg, available literature and SmPC) and evolving medical practices.
