

Pembrolizumab

Indication

Treatment of metastatic or locally advanced urothelial carcinoma in untreated patients where treatment with cisplatin-containing regimens is not suitable or in patients who have previously had platinum-containing chemotherapy (funding via CDF).

(NICE TA519 and TA522)

ICD-10 codes

Codes prefixed with C67.

Regimen details

Day	Drug	Dose	Route
1	Pembrolizumab	200mg	IV infusion

Cycle frequency

21 days

Number of cycles

Until unacceptable toxicity, disease progression or to a maximum of 2 years.

Administration

Pembrolizumab should be administered in 100mL sodium chloride 0.9% over 30 minutes.

Pembrolizumab should be administered 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 infusion (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.

Pre-medication

Nil

Emetogenicity

This regimen has low emetogenic potential

Additional supportive medication

Loperamide should be supplied to be used if required.
Antiemetics as per local policy, if required.

Extravasation

Neutral (Group 1)

Investigations – pre first cycle

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

Investigations – pre subsequent cycles

Investigation	Validity period (or as per local policy)
FBC	96 hours
U+E (including creatinine)	96 hours
LFT	96 hours
Thyroid function	6 weekly
Glucose	As clinically indicated
Calcium	As clinically indicated
Cortisol	At consultant discretion

Standard limits for administration to go ahead

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

Investigation	Limit
Neutrophil count	$\geq 1.0 \times 10^9/L$
Platelets	$\geq 75 \times 10^9/L$
Creatinine Clearance (CrCl)	$\geq 30\text{mL}/\text{min}$
Bilirubin	$\leq 1.5 \times \text{ULN}$
ALT/AST	$< 3 \times \text{ULN}$
Alkaline Phosphatase	$< 5 \times \text{ULN}$

Dose modifications

- **Haematological toxicity**

Discuss with the consultant if:

Neutrophils $< 1.0 \times 10^9/L$

Platelets $< 75 \times 10^9/L$

- **Renal impairment**

The safety and efficacy of pembrolizumab has not been studied in patients with renal impairment. No specific dose adjustments are recommended in mild to moderate renal impairment.

Discuss with consultant if CrCl $< 30\text{mL}/\text{min}$.

- **Hepatic impairment**

The safety and efficacy of pembrolizumab has not been studied in patients with hepatic impairment. No specific dose adjustments are recommended in mild hepatic impairment. See below for management of hepatitis.

- **Other toxicities**

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 \leq grade 1
	Grade 4	Permanently discontinue pembrolizumab
Pneumonitis	Grade 1	Continue and closely monitor
	Grade 2	Withhold until symptoms resolve to \leq grade 1
	Grade 3-4 or recurrent grade 2	Permanently discontinue pembrolizumab
Nephritis	Grade 2 (creatinine 1.5-3 x ULN)	Withhold until symptoms resolve to \leq grade 1
	Grade 3 (creatinine > 3 x ULN)	Permanently discontinue pembrolizumab
Endocrine	Symptomatic hypophysitis	Withhold until symptoms resolve to \leq grade 1
	Type 1 diabetes with grade > 3 hyperglycaemia (glucose > 13.9 mmol/L) or ketoacidosis	Withhold until \leq grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hyperthyroidism \geq grade 3	Withhold until \leq grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hypothyroidism	Continue and manage with replacement therapy
Hepatitis	AST/ALT 3-5 x ULN or Bilirubin > 1.5-3 x ULN	Withhold until resolves to \leq grade 1
	AST/ALT > 5 x ULN or Bilirubin > 3 x ULN	Permanently discontinue pembrolizumab
	If liver metastasis with baseline AST/ALT 3-5 x ULN: - If AST/ALT increases \geq 50% for \geq 1 week	Permanently discontinue pembrolizumab
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis	Withhold until resolves to \leq grade 1
	Grade 4 or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis	Permanently discontinue pembrolizumab
Infusion-related reactions	Grade 3-4	Permanently discontinue pembrolizumab

Pembrolizumab should be permanently discontinued if:

- Grade 4 toxicity (except for endocrinopathies that are controlled with replacement hormones)
- Corticosteroid dosing cannot be reduced to \leq 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
- Any event occurs a second time at Grade \geq 3 severity
- Grade 3 or 4 myocarditis
- Grade 3 or 4 encephalitis
- Grade 3 or 4 Guillain-Barré syndrome

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

• **Serious side effects**

Myelosuppression
 Pneumonitis
 Colitis
 Hepatitis
 Nephritis
 Endocrinopathies
 Pancreatitis
 Myocarditis
 Encephalitis

- **Frequently occurring side effects**

Myelosuppression
Reduced appetite
Headache
Dizziness
Dry eyes
Cough
Diarrhoea
Nausea
Rash, pruritis
Fatigue
Hyperglycaemia
Hypocalcaemia
Hyperthyroidism, hypothyroidism

- **Other side effects**

Arthralgia

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

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 pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.

Additional comments

Women of child bearing potential should use effective contraception during treatment and for at least 4 months after the last dose.

References

- National Institute for Health and Clinical Excellence TA519
- accessed 13 June 2018 via www.nice.org.uk
- National Institute for Health and Clinical Excellence TA522 accessed 13 June 2018 via www.nice.org.uk
- Summary of Product Characteristics Pembrolizumab - Keytruda® (MSD) accessed 13 June 2018 via www.medicines.org.uk
- Balar A.V et al; First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet. 2017 18 (11) p1483-1492
- Bellmunt J, et al; Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017; 376:p1015-1026

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