

Pembrolizumab (skin)

Indication

Advanced (unresectable or metastatic) melanoma after progression with ipilimumab and for BRAF V600 positive disease after a BRAF or MEK inhibitor.

(NICE TA357)

Advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab.

(NICE TA366)

ICD-10 codes

Codes prefixed with C43

Regimen details

Day	Drug	Dose	Route
1	Pembrolizumab	2mg/kg	IV infusion

Cycle frequency

21 days

Number of cycles

Until unacceptable toxicity, disease progression or consultant discretion (sustained complete response).

Administration

Pembrolizumab should be administered in sodium chloride 0.9% over 30 minutes. Doses \leq 100mg should be diluted in 50mL and doses $>$ 100mg in 100mL.

Pembrolizumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 5.0 μ m).

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
LDH	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
LDH	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	$< 2.5 \times \text{ULN}$
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.

- **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
	Liver metastasis and baseline AST/ALT 3-5 x ULN or AST/ALT increases \geq 50% for \geq 1 week	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

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

- **Serious side effects**

Myelosuppression
 Pneumonitis
 Colitis
 Hepatitis
 Nephritis
 Endocrinopathies
 Pancreatitis

- **Frequently occurring side effects**

Myelosuppression
Reduced appetite
Headache
Dizziness
Dry eyes
Cough
Diarrhoea
Nausea
Rash
Fatigue
Hyperglycaemia
Hypocalcaemia

- **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

References

- National Institute for Health and Clinical Excellence TA357. Accessed 23 December 2015 via www.nice.org.uk
- National Institute for Health and Clinical Excellence TA366. Accessed 23 December 2015 via www.nice.org.uk
- Summary of Product Characteristics Pembrolizumab - Keytruda® (MSD) accessed 23 December 2015 via www.medicines.org.uk
- Ribas, A et al; Pembrolizumab v investigator choice chemotherapy. Lancet 2015; 16 (8): 908 – 918
- Robert, C et al; Pembrolizumab v Ipilimumab in advanced melanoma. NEJM 2015 ; 372 :2521 - 2532

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