Pembrolizumab (Melanoma)

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 in patients who have not been previously treated with ipilimumab.

(NICE TA366)

Adjuvant treatment of completely resected stage 3 melanoma

(NICE TA766)

ICD-10 codes

Codes prefixed with C43

Regimen details

Day	Drug	Dose	Route
1	Pembrolizumab	200mg every 3 weeks or 400mg every 6 weeks	IV infusion

Cycle frequency

21 days or 42 days as above.

Number of cycles

Advanced melanoma - Until unacceptable toxicity, disease progression or consultant discretion (sustained complete response). If stable disease after 2 or more years patients may choose to discontinue Pembrolizumab with the option to restart at disease progression
Adjuvant treatment – up to a maximum of 12 months

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
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	7 days
U+E (including creatinine)	7 days
LFT	7 days
LDH	7 days
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	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine Clearance (CrCl)	≥ 30mL/min
Bilirubin	≤ 1.5 x ULN
ALT/AST	< 3.0 x ULN
Alkaline Phosphatase	< 5 x ULN

Dose modifications

Please consider immunotherapy driven toxicity as a potential reason for all changing laboratory results and discuss with a consultant if any concerns.

- **Haematological toxicity**

Discuss with the consultant if:
Neutrophils <1.0 x 10^9/L
Platelets <75 x 10^9/L

- **Renal impairment/toxicity**

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 <30mL/min.

- **Hepatic impairment/toxicity**

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 of 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	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)	Withhold until symptoms resolve to ≤ grade 1
	Grade 3 (creatinine > 3 x ULN)	Permanently discontinue pembrolizumab
Endocrine	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
Hepatitis	AST/ALT 3-5 x ULN or Bilirubin > 1.5-3 x ULN	Withhold until resolves to ≤ 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 ≥ 50% for ≥ 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 ≤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 ≥ 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

- **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

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 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
- National Institute for Health and Clinical Excellence TA766. Accessed 29 June 2022 via

www.nice.org.uk

- Summary of Product Characteristics Pembrolizumab - Keytruda® (MSD) accessed 9 January 2020 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
- Eggermont, A et al; Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial. Lancet Oncol 2021; 22(5):643-654

Written/reviewed by: Dr T Tillett (Consultant Oncologist, Royal United Hospital, Bath)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Clinical Network), Kate Gregory (Lead Pharmacist for SACT Protocols, SWAG Cancer Alliance)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Clinical Network)

Date: February 2016 v2 January 2020 (updated dosing)
