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)

Adjuvant treatment of completely resected stage 2B or 2C melanoma
(NICE TA837)

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

* For adjuvant treatment NHSE recommend that pembrolizumab is administered 6 weekly.

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 or a maximum of 9 cycles if given 6 weekly.

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
Nil

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	14 days
ECG	Baseline

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	< ULN
Alkaline Phosphatase	< 5 x ULN

Dose modifications

Dose reductions are not recommended. Doses should be delayed until an adverse reaction resolves to ≤ grade 1.

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**

No dose adjustment is needed in mild to moderate renal impairment (CrCl > 30ml/min). Pembrolizumab has not been studied in severe renal impairment but no need for dose adjustment is expected. Discuss with consultant if CrCl <30mL/min. See below for management of nephritis emergent on treatment.

- **Hepatic impairment**

No dose adjustment is needed for patients with mild hepatic impairment. Pembrolizumab has not been studied in moderate or severe hepatic impairment but no need for dose adjustment is expected – discuss with consultant. See below for management of hepatitis emergent on treatment.

- **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 ≤ grade 1
	Grade 4 or recurrent grade 3	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) or Grade 3 (creatinine > 3 x ULN)	Withhold until symptoms resolve to ≤ grade 1
	Grade 4 (creatinine > 6 x ULN)	Permanently discontinue
Endocrine	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grade 3 or 4 adrenal insufficiency or 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

Toxicity	Definition	Action
Hepatitis	Grade 2: AST/ALT 3-5 x ULN or Bilirubin > 1.5-3 x ULN	Withhold until resolves to ≤ grade 1
	Grade 3: AST/ALT 5-20 x ULN or Bilirubin 3-10 x ULN	May consider recommencing after corticosteroid taper or discontinue treatment – consultant decision
	Grade 4: AST/ALT > 20 x ULN or Bilirubin > 10 x ULN	Permanently discontinue pembrolizumab
	If liver metastasis and baseline AST/ALT 3-5 x ULN and AST/ALT increases ≥ 50% from baseline for ≥ 1 week	Permanently discontinue pembrolizumab
Skin	Grade 3 rash	Withhold until resolves to ≤ grade 1
	Grade 4 rash or Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis	Permanently discontinue pembrolizumab
Cardiac	Grade 2 myocarditis	Withhold until resolves to ≤ grade 1
	Grade 3 or 4 myocarditis	Permanently discontinue pembrolizumab
Neurological	Grade 2 motor or sensory neuropathy	Withhold until resolves to ≤ grade 1
	Grade 3 or 4 motor or sensory neuropathy	Permanently discontinue pembrolizumab
	Grade 3 or 4 encephalitis	Permanently discontinue pembrolizumab
	Grade 3 or 4 Guillain-Barré syndrome	Permanently discontinue pembrolizumab
Infusion-related reactions	Grade 3-4	Permanently discontinue pembrolizumab
Any other toxicity	Grade 3 (first occurrence)	Withhold until resolves to ≤ grade 1
	Grade 4 or recurrent Grade 3	Permanently discontinue pembrolizumab

Pembrolizumab should be permanently discontinued if:
• 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

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

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Date: December 2023