Pembrolizumab

Indication

- Metastatic or unresectable stage 3 and stage 4 melanoma
- Adjuvant treatment of adults with stage 2b, 2c and 3 melanoma who have undergone complete resection
- 1st line treatment of metastatic non-small cell lung cancer (NSCLC) in patients whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations
- Locally advanced or metastatic PD-L1 positive (≥ 1% PD-L1 expression) NSCLC in patients who have had at least one previous chemotherapy
- Relapsed or refractory classical Hodgkin lymphoma (cHL) in patients who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV
- Relapsed or refractory classical Hodgkin lymphoma (cHL) in patients who are currently ineligible for stem cell transplantation and who have not received brentuximab vedotin
- 1st line treatment of PD-L1 positive metastatic or unresectable recurrent squamous cell carcinoma of the head and neck
- 1st line treatment of patients with metastatic colorectal cancer exhibiting microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR)
- Adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions
- Tumours with high microsatellite instability (MSI) or mismatch repair (MMR) deficiency in adults with:
    - advanced or recurrent endometrial cancer that has progressed during or after a platinum-based therapy, who cannot have curative surgery or radiotherapy
    - unresectable or metastatic gastric, small intestine or biliary cancer that has progressed during or after 1 therapy
    - colorectal cancer after fluoropyrimidine combination therapy, only if they cannot have nivolumab with ipilimumab

ICD-10 codes

Dependant on tumour site.

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

Melanoma (metastatic) and Renal Cell Carcinoma

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

Melanoma (adjuvant)

Adjuvant treatment should continue for 12 months (18 cycles of 200mg or 9 cycles of 400mg) or until disease progression, withdrawal of consent, or unacceptable toxicity.

Other indications

Until unacceptable toxicity, disease progression or consultant discretion (sustained complete response). Treatment should stop at 2 years.

Renal Cell Carcinoma (adjuvant)

Adjuvant treatment should continue for 17 cycles of 200mg or 9 cycles of 400mg

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

Antiemetics as per local policy, if required.

Extravasation

Neutral (Group 1)

Investigations – pre first cycle

PD-L1 tumour expression if required for some indications, please refer to list above.

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFT inc AST	14 days
LDH (melanoma only)	14 days
Thyroid function	14 days
Glucose	14 days
Calcium	14 days
Cortisol	Baseline
Follicle stimulating hormone	Baseline
Luteinizing hormone	Baseline
Testosterone	Baseline

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	48 hours
U+E (including creatinine)	48 hours
LFT inc AST	48 hours
LDH (melanoma only)	48 hours
Thyroid function	Every 6 weeks unless otherwise clinically indicated
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	Serum total bilirubin ≤1.5 X ULN or direct bilirubin ≤ULN for patient with total bilirubin level >1.5 ULN
ALT/AST	≤2.5 X ULN or ≤5 X ULN with liver metastases
Alkaline Phosphatase	< 5 x ULN

Dose modifications

Do not amend the dose of pembrolizumab

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.

- **Endocrine toxicity**

Dose delays are not routinely required for abnormalities in endocrine function. Please seek advice from patient's treating clinican.

- **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.

Treatment of toxicities

Immunotherapy toxicities should be aggressively managed as can cause permanent and life threatening complications.
Refer to UKONS and ESMO guidance for treatment of immune related toxicities.
Available at:
https://www.healthierlsc.co.uk/canceralliance/chemotherapy-protocols/immunotherapy-toxicity-guidelines

- **Toxicity monitoring and dose delays/discontinuation.**

All toxicities should be actively management and monitored. Any dose delays or discontinuation should be supervised by the treating clinician and made on an individual patient basis.

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

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THIS PROTOCOL HAS BEEN DIRECTED BY DR BOARD, DESIGNATED LEAD CLINICIAN FOR MELANOMA

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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