PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Pembrolizumab Melanoma

PROTOCOL REF: MPHAMMEPUR
(Version No.: 1.5)

Approved for use in:

- **First line treatment of advanced (unresectable or metastatic)** melanoma. Treatment is permitted for patients who have relapsed following COMPLETION of prior adjuvant immunotherapy with nivolumab or pembrolizumab. The opportunity exists to discontinue treatment after 2 or more years in patients' continuing in a stable disease or a response disease state and restarting Pembrolizumab on disease progression as the next SACT**.

****** Should this option be chosen then **BOTH the date of discontinuation of Pembrolizumab and the application to re-start treatment must be registered** on blueteq.

- **Adjuvant treatment of newly diagnosed & completely resected stage 2 melanoma** for a maximum of 12 months. Treatment will commence no more than 3 months after the date of surgery which documented the complete resection of stage 2 melanoma.
- **Adjuvant treatment of newly diagnosed & completely resected stage 3 melanoma** for a maximum of 12 months. Treatment will commence no more than 3 months after the date of surgery which documented the complete resection of stage 3 melanoma.
- Treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow any toxicities to settle.

- The patient has a performance status of either 0 or 1.
- **Blueteq registration is required for all indications. Please refer to the blueteq form for full criteria of use.**

Dosage:

Drug	Dosage	Route	Frequency
Pembrolizumab	400mg	IV infusion	6 weekly
Pembrolizumab	*200mg*	IV infusion	*3 weekly*

Where risk factors for toxicity are present e.g. pre-existing autoimmune disease or previous toxicity, the 3 weekly regime may be used.

Metastatic: Repeated every 3 or 6 weeks until disease progression or unacceptable toxicity. Patients continuing in a stable disease or a response disease state after 2 or more years of planned treatment can choose to discontinue pembrolizumab and then to re-start treatment on disease progression as the next systemic therapy.

Adjuvant: Repeated every 3 or 6 weeks until disease progression or unacceptable toxicity for a **maximum of 12 months**.

Extravasation risk:

Monoclonal antibody – considered to be neutral.
Refer to the CCC policy for the '<u>Prevention and Management of Extravasation Injuries</u>'.

Patient Counselling Points

Women of childbearing potential should use effective contraception throughout treatment and for at least 5 months following the last dose of pembrolizumab.

Contact the triage team for the following:

- New or worsening cough, chest pain or shortness of breath
- Diarrhoea or severe abdominal pain (with or without blood/mucous)
- Jaundice, severe nausea or vomiting, or easy bruising or bleeding
- Persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes
- Monitor for signs of infection / sepsis

Administration:

Day	Drug	Dose	Route	Diluent and rate
1	Pembrolizumab	400mg (6 weekly) *or 200mg (3 weekly)*	IV infusion	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron filter

Where risk factors for toxicity are present e.g. pre-existing autoimmune disease or previous toxicity, the 3 weekly regime may be used.

Routine prophylaxis against infusion related reactions is not required. However, monitor during the infusion and treatment given if necessary (antihistamines, steroids etc.).

Please refer to the CCC Hypersensitivity; Management Prevention Policy

Main Toxicities:

For full details on assessment and management of immune-related toxicities refer to CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Immune-Mediated Pneumonitis Pneumonitis occurred in 3% of melanoma patients (including G3 in 0.2%).	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Immune-Mediated Colitis Colitis occurred in 1% of patients (including G3 in 0.5%).	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Other Immune-Mediated Toxicities: Hypophysitis Nephritis Hyperthyroidism or Hypothyroidism Less frequently: Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia	Monitor LFTs, biochemistry, cortisol and TFTs regularly Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Other non-immune adverse events: Fatigue, anaemia Cough, dyspnoea Nausea, decreased appetite Pruritis, rash Constipation, diarrhoea Arthralgia	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Laboratory abnormalities: Hyponatraemia, hypocalcaemia, hyperglycaemia, hypertriglyceridaemia	Refer to Immuno-Oncology toxicity specific guidance for adverse event management

Investigations and treatment plan:

If suspicion of endocrinopathies: request TSH, T4, T3, ACTH, cortisol, LH, FSH, testosterone (men) and prolactin (women)

	Pre	Cycle 1	Cycle 2	Home treatment if eligible	Prior to cycle 3	Cycle 3	Ongoing
Informed Consent	x						
Clinical Assessment	x				x*		Every 12 weeks thereafter or as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x			x	Every cycle
OTR/ Go-ahead	x		x			x	Every cycle
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Calcium, Magnesium, Phosphate, LFTs (AST, ALT, ALP, GGT and bilirubin), TFTs, cortisol, blood glucose, LDH, CRP	x	x	x			x	Every cycle
TFTs, cortisol, blood glucose, HbA1c	x	x	x			x	Every cycle
Lipid profile (cholesterol).	x						At baseline then if clinically indicated
Fatigue profile as per Meditech order set: B12, folate, Iron profile, vitamin D, Zinc, Testosterone (men only), ESR	x						At baseline then if clinically indicated
Full set of observations (*BP, heart rate, temperature, respiratory rate and O_2 sats*)	x	x	x		x	x	Every cycle
Creatinine Clearance (Cockcroft and Gault)	x						Every cycle only if baseline CrCL <30ml/min or creatinine increases

							above 1.5x upper limit of normal or baseline
CT scan**	x						Every 12 weeks/if clinically indicated

Trop-T, CK, pro-BNP	x						At baseline and thereafter as clinically indicated (ECG to be reviewed by clinical team)
ECG	x						
Weight recorded	x	x	x			x	Every cycle
Height recorded	x						

*Formal medical review (can be virtual) to assess the tolerability of treatment and whether treatment should continue (as per NHS England criteria).

**CT Scan only required every 6 months in adjuvant setting.

Pregnancy test if applicable

Dose Modifications and Toxicity Management:

- Dosing delay or discontinuation may be required based on individual safety and tolerability.
- Guidelines for permanent discontinuation or withholding of doses are contained in dose modifications.
- Detailed guidelines for the management of immune-related adverse reactions are provided in the CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Treatment Threshold

Administer treatment on day 1 if:

Platelets	Neutrophils	Serum Creatinine	Bilirubin	AST/ALT	Alkaline Phosphatase	TSH and Free T4
≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≤ 1.5 x ULN or baseline	<1.5 x ULN	<3 x ULN	<5 x ULN	Within range or no change from baseline

ULN = upper limit of normal

Platelets must be within normal range prior to Cycle 1.

Toxicity management:

Detailed guidelines are provided in the CCC clinical network immunotherapy acute oncology guidelines. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

Toxicity Grade	Action
Grade 1 Mild	Continue treatment increase monitoring and provide symptomatic treatment.
Grade 2 Moderate	Withhold treatment until resolved to ≤ grade 1. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Grade 3 and Grade 4 Severe	Withhold treatment. Treatment will be permanently discontinued for any unresolving grade 3-4, severe or life-threatening adverse reaction at the treating clinician's discretion. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.

References:

NICE TA837, Pembrolizumab for adjuvant treatment of resected stage 2B or 2C melanoma
Published: 26 October 2022.

Keytruda 25mg/mL, Summary of Product Characteristics, Merck Sharp & Dohme (UK) Limited.
Available from www.medicines.org.uk/emc/medicine. Last updated 21st September 2021

NICE TA 357, Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab
Published: 07 October 2015.

NICE TA 366, Pembrolizumab for advanced melanoma not previously treated with ipilimumab
Published: 25 November 2015.

Ribas A et al (2015) Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol* 16: 908-918.

Circulation/Dissemination

Date added into Q-Pulse	21st March 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
	1.0	Wesley Artist Skin SRG Pharmacist	New Regimen Protocol
	1.1	Wesley Artist Skin SRG Pharmacist	Change to flat dosing
	1.3	Wesley Artist Skin SRG Pharmacist	Adjuvant Indication added
	1.4	Hala Ghoz Protocols Pharmacist	Aligned with standard IO protocol
October 2022	1.5	Siow Chin Phua Skin SRG Pharmacist	Adjuvant indication added Updated investigation and treatment plan Updated treatment threshold Removed exclusion criteria