Systemic Anti Cancer Therapy Protocol

Pembrolizumab
Metastatic Colorectal Cancer

PROTOCOL REF: MPHAPEMCGA
(Version No: 1.0)

Approved for use in:

Pembrolizumab as monotherapy is indicated as FIRST line treatment of patients with metastatic colorectal cancer exhibiting high microsatellite instability (MSI-H) or DNA mismatch repair deficiency (dMMR) when the following conditions are met:

- No previous systemic therapy for metastatic colorectal cancer other than with neoadjuvant intent (prior adjuvant chemotherapy for colorectal cancer therapy is allowed)
- ECOG performance status of 0 or 1
- The patient does not have symptomatic brain metastases or leptomeningeal metastases.

*********BLUETEQ registration required *********

Exclusions

History of pneumonitis, organ transplantation, HIV infection, active hepatitis B or C infection,

Active infection requiring systemic treatment, Less than 4 weeks from major surgery' or history of clinically severe autoimmune disease.

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

Dosage:

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

For a maximum treatment duration of 2 years of uninterrupted treatment (or 35 x 3-weekly cycles of pembrolizumab or its equivalent if 6-weekly pembrolizumab monotherapy dosing is used).

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

Extravasation risk:

Monoclonal antibody – treat symptomatically, no specific recommendations.
Refer to the CCC policy for the '**Prevention and Management of Extravasation Injuries'**.

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

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 related toxicities	
Immune-Mediated Pneumonitis Pneumonitis occurred in 3% of melanoma patients (including G3 in 0.2%).	Monitor patients for signs and symptoms and evaluate with radiographic imaging. Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Immune-Mediated Colitis	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Other Immune-Mediated Toxicities: Hepatitis Hypophysitis Nephritis Hyperthyroidism or Hypothyroidism Less frequently: Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia, Guillain-Barré syndrome	Monitor LFTs, biochemistry, cortisol, 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 **Please note when dosing schedule is 6 weekly, a mid-cycle blood check is required. The treating nurse should book the patient onto the on treatment review list. They will need bloods but as SACT assessment can be done by phone.**
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs **(BIL, AST and ALT)**, TFTs, cortisol, blood glucose, LDH, CRP	X	X	X			X	Every cycle
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
Lipids and cholesterol	X						At baseline then if clinically indicated
CrCl (Cockcroft and Gault)	X						Every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal
CT scan**	X						Every 12 weeks or if clinically indicated
ECG							As clinically indicated **At baseline for all Renal and Melanoma (ECG to be reviewed by clinical team)**
Trop T, pro-BNP and CK							

Full Observations	X	X	X			X	Every cycle
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).
Pregnancy test if applicable

Dose Modifications and Toxicity Management:

Haematological toxicity

- Dosing delay or discontinuation may be required based on individual safety and tolerability.
- Detailed guidelines for the management of immune-related adverse reactions are provided in the CCC clinical network immunotherapy acute oncology guidelines.

Proceed on day 1 if:-

Platelets	Neutrophils	Creatinine Clearance	Bilirubin	AST/ALT	Alkaline Phosphatase	TSH and Free T4
≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≥30 mL/min	<3 x ULN*	<5 x ULN	<5 x ULN	Within range or no change from base line

* ULN = upper limit of normal

The dose should be omitted if appropriate. Inform consultant if there has been an increase in liver function test from previous results.

8.0 Toxicity management:

Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

Non-haematological toxicity

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	No action. Provide symptomatic treatment
Grade 2 Moderate	Withhold Pembrolizumab until resolved to < grade 1. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Grade 3 and Grade 4 Severe	Withhold Pembrolizumab. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.Nivolumab will be permanently discontinued for any unresolving grade 3-4, severe or life-threatening adverse reaction at the treating clinician's discretion.

References:

1. Keytruda® SMPC Merck Sharp and Dohme Accessed via https://www.medicines.org.uk/emc/product/2498/smpc (last updated 12 May 2021).
2. T Andre et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *New England Journal of Medicine*, December 3,2020; Vol. 383 no.23