PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Pembrolizumab Cervical Cancer Compassionate Access

PROTOCOL REF: MPHAPEMCGY
Version No: 1.0

Approved for use in:

Pembrolizumab as monotherapy is indicated for the treatment of adults with cervical cancer where all of the following criteria are met:

- Locally recurrent disease only (i.e. in the pelvis within an irradiated site)
- PD-L1 positive (>1%)
- Received prior chemotherapy for recurrent/advanced disease
- Not eligible for available clinical trials.

Please NOTE: this is unlicensed use.

Please refer to the 'CCC Unlicensed Medicines Policy' for full details on consenting, prescribing, documentation and supply of unlicensed medicines.

As per trust policy please provide the 'Unlicensed Medicines Information' to patients and carers as appropriate

For the individual patient request: approval must be confirmed by Merck Sharp & Dohme (MSD) prior to prescribing

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.

Dosage:

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

Repeated every 3 weeks **for up to a maximum of 2 years** *(or 35 x 3-weekly cycles)*

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

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

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, the patient should be monitored 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 or baseline
CT scan**	X						Every 12 weeks or if clinically indicated
ECG							As clinically indicated **At baseline for all Renal and Melanoma**
Trop T, pro-BNP and CK							

							(ECG to be reviewed by clinical team)
Full Observations	X	X	X			X	Every cycle
Weight recorded	X	X	X			X	Every cycle
Height recorded	X						

Pregnancy test if applicable

Dose Modifications and Toxicity Management:

- Dosing delay or discontinuation may be required based on individual safety and tolerability.
- 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.

Proceed on day 1 of cycle 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	<3 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.

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. Pembrolizumab 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 27 July 2021).
2. H C Chung et al. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results from the Phase II KEYNOTE-158 Study. Journal of Clinical Oncology. April 3, 2019. Vol 37:(17); 1470 -1478

Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
November 2021	1.0	Jennifer Gibson - Gynae SRG Pharmacist	New protocol