PROTOCOL

Systemic Anti Cancer Therapy Protocol

Ipilimumab
Advanced Melanoma

PROTOCOL REF: MPHAMMEIPI
(Version No.: 1.1)

Approved for use in:

First line treatment of advanced (unresectable or metastatic) melanoma in adults.

Dosage:

Drug	Dosage	Route	Frequency
Ipilimumab	3mg/kg	IV	3 weekly for a maximum of 4 doses

Patients should receive the entire induction regimen (4 doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessments of tumour response should be conducted only after completion of induction therapy.

Extravasation risk:

Ipilimumab is a monoclonal antibody- neutral
Refer to the CCC policy for the '[Prevention and Management of Extravasation Injuries]'.

Patient Counselling Points

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

Contact the triage team for the following:

- New or worsening cough, chest pain or shortness of breath
- Diarrhoea or severe abdominal pain

- 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

Dosing in renal and hepatic impairment (Prior to start of treatment ONLY/Baseline):

Renal	Ipilimumab	CrCl ≥ 10ml/min proceed with treatment CrCl < 10ml/min- use with caution.

Hepatic	Ipilimumab	Administered with caution in patients with: Moderate (total bilirubin > 1.5 -3 × ULN and any AST) or Severe (total bilirubin > 3 × ULN and any AST*) hepatic impairment. * Within normal limits or high

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Ipilimumab**	**3mg/kg**	**IV**	No diluent added. Infused over 90 minutes in a non-pyrogenic line with a 0.2 to 1.2 micron filter
1	Sodium chloride 0.9%	100mL	IV	Flush

Repeated every 21 days for 4 cycles only.

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%).	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 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: 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	Cycle 3	Ongoing
Informed Consent	x				
Clinical Assessment	x				Every 12 weeks 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, Magnesium, LFTs (AST, ALT and bilirubin), TFTs, cortisol, blood glucose, LDH, CRP	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	Every cycle
Creatinine Clearance	x				Every cycle only if baseline CrCL <40ml/min or creatinine

(Cockcroft and Gault)					increases above 1.5x upper limit of normal or baseline
CT scan	x				Every 12 weeks or as clinically indicated
Trop-T, CK, pro-BNP	x				**At baseline for all Renal and Melanoma 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				

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	<3 x ULN	<5 x ULN	<5 x ULN	Within range or no change from base line

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:

1. Hodi FS, O'Day SJ, McDermott DF et al Improved survival with ipilimumab in patients with metastatic melanoma. New England Journal of Medicine, 2010 Aug 19;363(8):711-23.

2. NICE TA 319. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma Published: 23 July 2014.

3. YERVOY 5 mg/ml concentrate for solution for infusion, Summary of Product Characteristics Bristol-Myers Squibb Pharmaceutical Limited. Available from www.medicines.org.uk/emc/medicine. Last updated 15th January 2021.

Circulation/Dissemination

Date added into Q-Pulse	20th January 2022
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Version History

		Author name and designation	Summary of main changes
		Wesley Artist- Melanoma SRG Pharmacist	Version 1.0
		Hala Ghoz- Lead Pharmacist for protocols	**Version 1.1** **Protocol updated in line with standard IO protocol format**