PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Ipilimumab with Nivolumab Combination treatment in Advanced Melanoma

PROTOCOL REF: MPHAMMEINI
(Version No.: 2.2)

Approved for use in:

First line treatment for advanced (unresectable or metastatic) melanoma irrespective of BRAF status. Second or subsequent line after the following permitted prior therapies:

- Adjuvant therapy with adjuvant nivolumab or pembrolizumab OR
- Immune checkpoint inhibitors when given as part of a clinical trial either as monotherapy or in combination with ipilimumab AND/OR
- BRAF/MEK inhibitor targeted therapies when given for adjuvant indication OR
- BRAF/MEK inhibitor targeted therapies when given for advanced disease indication.

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 nivolumab on disease progression as the next SACT**.

ECOG performance status (PS) 0 – 1.

Separate blueteq registration is required at the start of combination treatment and on continuing maintenance nivolumab

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

Exclusions

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

Active infection requiring systemic treatment

Less than 4 weeks from major surgery

History of clinically severe autoimmune disease

Dosage:

Drug	Dosage	Route	Frequency
Nivolumab	**1mg/kg** (while having combination treatment with ipilimumab)	IV	1mg/kg 3 weekly in combination with ipilimumab.
	480mg (monotherapy following completion of ipilimumab treatment)		Followed by monotherapy 480mg 4 weekly, continued until disease progression or unacceptable toxicity
Ipilimumab	**3mg/kg**	IV	3 weekly for a maximum of 4 doses in combination with nivolumab

Extravasation risk:

Both agents are monoclonal antibodies – considered to be neutral.

Refer to the CCC policy for the '[Prevention and Management of Extravasation Injuries]'.

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

Renal	Nivolumab	eGFR < 30ml/min/1.73- limited data use with caution
	Ipilimumab	CrCl ≥ 10ml/min proceed with treatment CrCl < 10ml/min- use with caution.

Hepatic	Nivolumab	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
	Ipilimumab	

Patient Counselling Points

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

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:

Combination

Day	Drug	Dose	Route	Diluent and rate
1	**Nivolumab**	**1mg/kg**	**IV**	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron to 1.2 micron filter
1	Sodium chloride 0.9%	100mL	IV	Flush
Switch to a new administration infusion set and ensure a 30 minute infusion break occurs between Nivolumab and Ipilimumab.				
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.

Treatment then continues with nivolumab monotherapy starting at least 6 weeks after last Nivolumab/Ipilimumab combination dose given.

Monotherapy

Day	Drug	Dose	Route	Diluent and rate
1	**Nivolumab**	**480mg**	**IV**	100mL sodium chloride 0.9%. Infused over 60 minutes in a non-pyrogenic line with a 0.2 micron to 1.2 micron filter.

Repeated every 28 days until unacceptable toxicity or disease progression. Patients continuing in a stable disease or a response disease state after 2 or more years of planned treatment can choose to discontinue nivolumab and then to re-start treatment on disease progression as the next systemic therapy.

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	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, hear rate, temperature, respiratory rate and O_2 sats*)	x	x	x	x	Every cycle
Creatinine Clearance (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 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.

When nivolumab is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the combination treatment or nivolumab monotherapy could be resumed based on the evaluation of the individual patient. **There is no evidence supporting the use of single agent Ipilimumab.**

For full details on assessment and management of immune-related toxicities refer to 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 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:

Larkin J et al (2015) Combined nivolumab and ipilimumab or monotherapy in untreated melanoma *NEJM*

NICE TA 400. Nivolumab in combination with ipilimumab for treating advanced melanoma
Published: 27 July 2016.

Opdivo 10mg/mL, Summary of Product Characteristics, Bristol-Myers Squibb Pharmaceutical Limited, Available from https://www.medicines.org.uk/emc last updated 6/10/21.

YERVOY 5 mg/ml concentrate for solution for infusion, Summary of Product Characteristics Bristol-Myers Squibb Pharmaceutical Limited. Available from https://www.medicines.org.uk/emc Last updated 6/10/21.

Circulation/Dissemination

Date added into Q-Pulse	20th January 2022
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
November 2021	2.2	**Hala Ghoz** **Protocols Pharmacist**	**Aligned with standard IO protocol** **Version 2.2**