Systemic Anti Cancer Treatment Protocol

Ipilimumab with Nivolumab
Combination treatment

PROCTOCOL REF: MPHAMMEINI
(Version No: 2.0)

Approved for use in:

First line treatment for advanced (unresectable or metastatic) melanoma

PS 0 - 1

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 nivoloumab

Extravasation risk:

Both considered to be neutral.

Patient Counselling Points

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

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 30 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

Main Toxicities:

Please refer to Acute Oncology I-O Management Guidance for specific advice

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 and administer corticosteroids for toxicities of grade 2 or above.
Immune-Mediated Colitis	Monitor patients for signs and symptoms and administer corticosteroids for grade 2 or greater.
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, TFTs and blood glucose, consider corticosteroids for grade 2 or greater.

Other non-immune adverse events: Fatigue, anaemia Cough, dyspnoea Nausea, decreased appetite Pruritis, rash Constipation, diarrhoea Arthralgia	Symptomatic management for grade 1 with close monitoring
Laboratory abnormalities: Hyponatraemia, hypocalcaemia, hyperglycaemia, hypertriglyceridaemia	Monitor at each cycle and rule out immune-medicated reaction

Investigations:

Investigation	Baseline	Each cycle	Every 12 weeks	Follow-up
Informed Consent	X			
Medical review (Immune-mediated toxicities assessment)	X		X	X
Nursing review (Immune-mediated toxicities assessment)		X		
Weight	X	X	X	X
Chest X-Ray	As indicated	As indicated	As indicated	As indicated
Imaging	X		X	X
FBC	X	X	X	X
U & E, LFTs	X	X	X	X
Toxicities documented	X	X	X	X
Blood pressure measurement	X	X	X	X
CT scan	X	As indicated	As indicated	As indicated
ECG	X	As indicated	As indicated	As indicated
PS recorded	X	X	X	X

LDH, TFT's and random cortisol and blood glucose	X	X	X	X
Testosterone	X	X	X	X
Prolactin	X	X	X	X

Dose Modifications and Toxicity Management:

Dose reductions for toxicity management are not recommended.

Detailed guidelines for the management of immune-related adverse reactions are provided in the network immunotherapy acute oncology guidelines.

Haematological toxicity

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

Toxicity management:

Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions. Refer to the network immunotherapy acute oncology guidelines.

Toxicity Grade	Action
Grade 1 Mild	Continue treatment increase monitoring and provide symptomatic treatment.
Grade 2 Moderate	Withhold treatment until resolved to <grade 1. For immune – mediated reactions consider systemic corticosteroids in addition to appropriate symptomatic treatment; refer to network guidelines for immune therapy toxicity management for detailed clinical information.
Grade 3 and Grade 4 Severe	**Withhold treatment for any grade 3 reaction, review if clinically appropriate to restart treatment only if reaction resolves to <grade 1. Discontiune treatment for any grade 4 reaction.** **For immune related reactions systemic corticosteroids (Intravenous methylprednisolone 2 mg/kg or equivalent per day) are indicated in addition to appropriate symptomatic treatment. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks – refer to network guidelines for immune therapy toxicity management for detailed clinical information.**

Dosing in hepatic impairment:

Nivolumab
No dose adjustment is required in patients with mild hepatic impairment. Data from patients with moderate or severe hepatic impairment are data are too limited to make any specific dose recommendations. Manufacturers of nivolumab advise caution in patients with moderate (total bilirubin > 1.5 × to 3 × the upper limit of normal [ULN] and any AST) or severe (total bilirubin > 3 × ULN and any AST) hepatic impairment.

Ipilimumab
Safety has not been studied in patients with hepatic impairment. No specific dose adjustment is necessary in patients with mild hepatic impairment. Administer with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline.

Dosing in renal impairment:

Nivolumab
Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to make any specific dose recommendation.

Ipilimumab
Safety and efficacy has not been studied in patients with renal impairment. No specific dose adjustment is necessary in patients with mild to moderate renal dysfunction. For patients with a GFR below 30ml/min discuss with consultant before commencing treatment.

References:

Larkin J et al

Combined nivolumab and ipilimumab or monotherapy in untreated melanoma

NEJM 2015

Opdivo 10mg/mL, Summary of Product Characteristics, Bristol-Myers Squibb Pharmaceutical Limited, 19/06/2015. Available from www.medicines.org.uk/emc/medicine. Last updated 21/12/2015

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 16/01/14.