SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti-Cancer Therapy Protocol

Ipilimumab with Nivolumab Combination treatment in Malignant Pleural Mesothelioma Compassionate Access Scheme

PROTOCOL REF: MPHAINCAS
(Version No.: 1.0)

Approved for use in:

First line treatment of unresectable malignant mesothelioma of pleural origin.

No known brain metastases or symptomatically stable brain metastases prior to start of treatment.

PS 0 – 1

Individual patient registration and drug ordering to be submitted to BMS Individual Patient Supply Request (IPSR) Team (IPSR.UKI@bms.com).

Dosage:

Combination

Drug	Dosage	Route	Frequency	Duration of Treatment
Nivolumab	360mg	IV Infusion	Days 1 and 22 6 weekly	Until disease progression, unacceptable toxicity, or **up to 2 years* in patients without disease progression whichever is sooner**
Ipilimumab	1mg/kg	IV Infusion	Day 1 only 6 weekly	

OR

Monotherapy

ONLY if ipilimumab has to be discontinued as a consequence of toxicity, nivolumab can be continued as monotherapy.

Drug	Dosage	Route	Frequency	Duration of Treatment
Nivolumab*	**360mg**	IV Infusion	Days 1 3 weekly	Until disease progression, unacceptable toxicity, or **up to 2 years* in patients without disease progression whichever is sooner**

*** Maximum of 35 cycles of nivolumab and 17 cycles of ipilimumab inclusive of both combination and monotherapy.**

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

History of clinically severe autoimmune disease

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	Ipilimumab Nivolumab	eGFR < 30ml/min/1.73)- limited data use with caution

Hepatic	Ipilimumab	Administered with caution in patients with: Transaminase levels (ALT and/or AST) ≥ 5 x ULN or bilirubin levels > 3 x ULN

	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

Counselling points:

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

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	Sodium chloride 0.9%	250mL	IV	Flush
1	**Nivolumab**	**360mg**	**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
Switch to a new administration infusion set and ensure a 30 minute infusion break occurs between Nivolumab and Ipilimumab.				
1	**Ipilimumab**	**1mg/kg**	**IV**	No diluent added. Infused over 30 minutes in a non-pyrogenic line with a 0.2 to 1.2 micron filter

22	Sodium chloride 0.9%	250mL	IV	Flush
22	**Nivolumab**	**360mg**	**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

Repeated every 6 weeks

Monotherapy

Day	Drug	Dose	Route	Diluent and rate
1	Sodium chloride 0.9%	250mL	IV	Flush
1	**Nivolumab**	**360mg**	**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

Repeated every 3 weeks

Total duration of treatment 2 years (combination and monotherapy) provided no disease progression

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 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

The most common adverse reactions (incidence ≥ 20%) in patients receiving the combination of nivolumab plus ipilimumab as per the clinical trial were fatigue, musculoskeletal pain, rash, diarrhoea, dyspnoea, nausea, decreased appetite, cough, and pruritus.

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		x		Then every 12 weeks or as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x	x	Every cycle Combination: Days 1 and 22 Monotherapy: Day 1 ONLY
OTR/ Go-ahead	x		x	x	Every cycle
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs, TFTs, cortisol, blood glucose, LDH, CRP	x	x	x	x	Every cycle Combination: Days 1 and 22 Monotherapy: Day 1 ONLY
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 Combination: Days 1 and 22 Monotherapy: Day 1 ONLY
Creatinine Clearance (Cockcroft and Gault)	x	x	x	x	Every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal or baseline Combination: Days 1 and 22 Monotherapy: Day 1 ONLY
CT scan	x				Every 12 weeks or as clinically indicated
Trop-T, CK, pro-BNP	x				**At baseline and thereafter as clinically indicated** (ECG to be reviewed by clinical team)
ECG	x				

Weight recorded	x	x	x	x	Every cycle Combination: Days 1 and 22 Monotherapy: Day 1 ONLY
Height recorded	x				

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**.**

If nivolumab has to be discontinued as a consequence of toxicity, ipilimumab must also be stopped.

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

Treatment Threshold (combination and monotherapy)

Administer treatment on day 1 and 22 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. EAMS Information for HCP MHRA [Nivolumab and Ipilimumab, Version 2, 24/12/2020]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/957061/Nivolumab_Treatment_protocol_Information_for_healthcare_practitioners.pdf
2. Opdivo 10mg/mL, Summary of Product Characteristics, Bristol-Myers Squibb Pharmaceutical Limited. Available from www.medicines.org.uk/emc/medicine. Last updated 23rd March 2021
3. Scherpereel A, Antonia S, Bautista Y, et al. First-line nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) for the treatment of unresectable malignant pleural mesothelioma (MPM (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. *The Lancet.* Volume 397, Issue 10272, pp. 375-386
4. 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

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Version History

		Author name and designation	Summary of main changes
		Hala Ghoz Lead Protocols Pharmacist	New regimen protocol V1.0
