Systemic Anti Cancer Treatment Protocol

Nivolumab
Pleural or Peritoneal Mesothelioma
(Unlicensed Use)

PROTOCOL REF: MPHANIVPPLU
(Version No: 1.0)

Approved for use as an interim measure during COVID-19 pandemic.

Approved for use in:

Nivolumab as monotherapy is approved 2nd line for the treatment of malignant pleural or peritoneal mesothelioma when the following conditions are met:

- ECOG performance status of 0 or 1
- The patient would otherwise been eligible for 2nd line cytotoxic chemotherapy.
- The patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody.
- The patient has no symptomatically active brain metatstases or leptmeningeal metastases.
- It should be fully discussed with the patient as to the risks/benefits of giving this regimen including the discussion as to likely clinical benefit and toxicities of this treatment option compared with any cytotoxic chemotherapy regimen.

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

Blueteq registration required

Dosage:

Drug	Dosage	Route	Frequency
Nivolumab	240mg	IV infusion	2 weekly

OR

Drug	Dosage	Route	Frequency
Nivolumab	480 mg	IV infusion	4 weekly*

- Patients who have no comorbidities may be started on a dose of 480mg every 4 weeks. A starting dose of 240mg every 2 weeks should be considered in all other patients. The dose can be increased if the patient tolerates the two weekly dosing schedule.
- Treatment will be continued until disease progression or unacceptable toxicity
- 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 is provided in the CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Extravasation risk:

None

Administration:

2-weekly schedule:

Day	Drug	Dose	Route	Diluent and rate
1	Nivolumab	240mg	IV infusion	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron filter

4-weekly schedule:

Day	Drug	Dose	Route	Diluent and rate
1	Nivolumab	480mg	IV infusion	100mL sodium chloride 0.9%. Infused over 60 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.

Nivolumab	
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 G2 or greater.
Immune-Mediated Colitis Colitis occurred in 1% of patients (including G3 in 0.5%).	Monitor patients for signs and symptoms and administer corticosteroids for G2 or greater.
Other Immune-Mediated Toxicities: Hepatitis Hypophysitis Nephritis Hyperthyroidism or Hypothyroidism Less frequently:	Monitor LFTs, biochemistry and TFTs As above, consider corticosteroids for G2 or greater

Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia	
Other non-immune adverse events: Fatigue, anaemia Cough, dyspnoea Nausea, decreased appetite Pruritis, rash Constipation, diarrhoea Arthralgia	Symptomatic management for G1/G2 Monitor diarrhoea – as this may be the first sign of colitis
Laboratory abnormalities: Hyponatraemia, hypocalcaemia, hyperglycaemia, hypertriglyceridaemia	Monitor at each cycle

Investigations and treatment plan:

2 weekly or 4-weekly schedule

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 thereafter or as clinically indicated
SACT Assessment (to include PS and toxicities)	X	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
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
CrCl (Cockcroft and Gault)	X				Every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal
CT scan	X				Every 6 months or if clinically indicated
Trop-T, CK, pro-BNP	X*				As clinically indicated ***At baseline for all Renal and Melanoma** (ECG to be reviewed by clinical team)
ECG	X*				
Full set of observations	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	Every cycle
Height recorded	X				

Dose Modifications and Toxicity Management:

Haematological toxicity

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

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

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

The dose should be omitted if appropriate. Inform consultant if there has been an increase in liver function test from previous results.

Toxicity management:

Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

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 Nivolumab until resolved to <grade 1. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Grade 3 and Grade 4 Severe	Withhold Nivolumab. Refer to Immuno-Oncology toxicity specific guidance for adverse event management. Nivolumab will be permanently discontinued for any unresolving grade 3-4, severe or life-threatening adverse reaction at the treating clinician's discretion.

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

References:

- https://www.medicines.org.uk/emc/medicine/30476
- https://www.nice.org.uk/guidance/ng161/resources/interim-treatment-change-options-during-the-covid19-pandemic-endorsed-by-nhs-england-pdf-8715724381
- Immune related adverse event guidelines available via: https://www.clatterbridgecc.nhs.uk/professionals/guidance-1