Systemic Anti Cancer Therapy Protocol

Nivolumab
Adjuvant Treatment
Melanoma and Gastro-oesophageal Cancer

PROTOCOL REF: MPHANIADSK
(Version No.1.2)

Approved for use in:

Melanoma

Nivolumab monotherapy, as first line adjuvant treatment of newly diagnosed and completely resected stage III or completely resected stage IV malignant melanoma.

Gastro-oesophageal Cancer

- Adjuvant treatment for completely resected oesophageal or gastro-oesophageal junction cancer in adults who have residual pathological disease after prior neo-adjuvant platinum-containing chemo-radiotherapy which satisfies the following criteria:
- Histologically confirmed:
    - Squamous cell or adenocarcinoma of the oesophagus
      OR
    - Adenocarcinoma of the gastro-oesophageal junction
  - Treatment to start less than 16 weeks from surgical resection of the tumour.
  - Radiologically confirmed M0 disease within 4 weeks of starting treatment.
  - ECOG PS 0 or 1

***** Blueteq registration is required for BOTH indications *****

Dosage:

Drug	Dosage	Route	Frequency
Nivolumab	480mg	IV infusion	4 weekly for a maximum of 12 months (or a maximum of 13 cycles when given 4-weekly)
Nivolumab	*240mg*	IV infusion	*2 weekly for a maximum of 12 months (or a maximum of 26 cycles when given 2-weekly)*

Where risk factors for toxicity are present e.g. pre-existing autoimmune disease or previous toxicity, the 2 weekly regime may be used.

- Dosing delay or discontinuation may be required based on individual safety and tolerability.
- Guidelines for permanent discontinuation or withholding of doses are contained in the 'Dose Modifications' Section.
- For full details on assessment and management of immune-related toxicities refer to CCC Immuno-Oncology toxicity specific guidance for adverse event management.

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:

Nivolumab is a monoclonal antibody- 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

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

Patient 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:

Day	Drug	Dose	Route	Diluent and rate
1	Nivolumab	480mg (4 weekly) *or 240mg (2 weekly)*	IV infusion	100mL sodium chloride 0.9%. Infused over 60 minutes (for 480mg) *or 30 minutes (for 240mg)* in a non-pyrogenic line with a 0.2 micron filter

For a maximum of 12 months (maximum of 13 cycles when given 4 weekly or a maximum of 26 cycles when given 2-weekly)

Where risk factors for toxicity are present e.g. pre-existing autoimmune disease or previous toxicity, the 2 weekly regime may be used

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:

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: Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia	Monitor LFTs, biochemistry and TFTs As above, consider corticosteroids for G2 or greater
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:

If suspicion of endocrinopathies: request TSH, T4, T3, ACTH, cortisol, LH, FSH, testosterone (men) and prolactin (women)

	Pre	Cycle 1	Cycle 2	Home treatment if eligible	Prior to cycle 3	Cycle 3	Ongoing
Informed Consent	x						
Clinical Assessment	x				x*		Every 12 weeks thereafter 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					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	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/if 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						

*Formal medical review (can be virtual) to assess the tolerability of treatment and whether treatment should continue (as per NHS England criteria).
**CT Scan only required every 6 months in adjuvant setting.
Pregnancy test if applicable

Dose Modifications and Toxicity Management:

Haematological 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 are provided in the CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Proceed 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[a]	<5 x ULN	<5 x ULN	Within range or no change from base line

[a] ULN = upper limit of normal

Platelets must be within normal range prior to Cycle 1.

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	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:

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

NICE TA 684 Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease. Published: 17 March 2021

NICE: TA 746 Nivolumab for adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer.
Published date: November 2021

NHS England - Cancer Drugs Fund Application Form – Nivolumab as adjuvant monotherapy for patients with completely resected oesophageal or gastro-oesophageal carcinoma who have residual pathological disease at surgery following prior neoadjuvant chemoradiotherapy (ID1676) - NIV17_ver1.0 (available at https://www.blueteq-secure.co.uk/trust/default , accessed November 2021)

Circulation/Dissemination

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

Version History

		Author name and designation	Summary of main changes
		Wesley Artist **Skin SRG Pharmacist**	New Regimen Protocol V1.0
		Wesley Artist **Skin SRG Pharmacist**	**4 weekly dosing added** **V1.1**
		Hala Ghoz **Lead Pharmacist for protocols**	**Aligned with standard IO protocol template** **UGI adjuvant indication added** **V1.2**