Systemic Anti Cancer Therapy Protocol

Nivolumab Adjuvant Free of charge (FOC) Scheme in Bladder Cancer

PROTOCOL REF: MPHANIVADUR
(Version No: 1.0)

Approved for use in:

Compassionate use as adjuvant treatment, following radical surgery, of urothelial carcinoma (with primary tumor sites including bladder, ureter, or renal pelvis).

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 or history of clinically severe autoimmune disease.

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

Dosage:

Drug	Dose	Route	Frequency
Nivolumab	**240mg**	IV infusion	2 weekly for 52 weeks

- 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' section.
- Detailed guidelines for the management of immune-related adverse reactions is available on the following link:
  CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Administration:

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

- Routine prophylaxis against infusion related reactions is not required.
- However the patient should be monitored during infusion, and treatment given if necessary (antihistamines, steroids etc).
- Please refer to the CCC Hypersensitivity; Management Prevention Policy

Extravasation risk:

Monoclonal antibody – treat symptomatically, no specific recommendations.
Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'.

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: 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	Prior to cycle 3	Cycle 3	Ongoing
Informed Consent	X					
Clinical Assessment	X				X	As clinically indicated or at the end of treatment
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
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
Lipids and cholesterol	X					At baseline then if clinically indicated
CrCl (Cockcroft and Gault)	X					Every cycle only if baseline CrCL ≤40ml/min or creatinine increases above 1.5 x upper limit of normal
CT scan	X					Every 6 months if clinically indicated
Trop-T, CK, pro -BNp						As clinically indicated **At baseline for all Renal and Melanoma** **(ECG to be reviewed by clinical team)**
ECG						
Full Observations	X	X	X		X	Every cycle
Weight recorded	X	X	X		X	Every cycle
Height recorded	X					

Pregnancy test if applicable

Dose Modifications and Toxicity Management:

Haematological toxicity

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

[a] 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.

8.0 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:

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.

References:

1. https://www.medicines.org.uk/emc/medicine/30476
2. ASCO GU 2021: First Results from the Phase 3 CheckMate 274 Trial of Adjuvant Nivolumab vs Placebo in Patients Who Underwent Radical Surgery for High-Risk Muscle-Invasive Urothelial Carcinoma