

Nivolumab monotherapy (Urothelial)

Indication

Adjuvant treatment of muscle-invasive urothelial cancer that is at high risk of recurrence after radical resection if PD-L1 expression $\geq 1\%$ and adjuvant treatment with platinum-based chemotherapy is unsuitable in patients that meet the following criteria:

- M0 disease prior to surgery and R0 resection has taken place
- Less than 4 months between surgery and start date for adjuvant nivolumab therapy.
- Radiological restaging has taken place after surgery and patient remains disease-free within 1 month of expected start date for adjuvant nivolumab therapy.
- High risk disease defined as:
 - If prior neoadjuvant therapy, pathological stage of the resected tumour must be ypT2-ypT4a or any ypN+ stage
 - If *no* prior neoadjuvant therapy, pathological stage of the resected tumour must be pT3-pT4a or any pN+ stage

(NICE TA817)

ICD-10 codes

Codes prefixed with C65-67

Regimen details

Day	Drug	Dose	Route
1	Nivolumab	480mg	IV infusion

Cycle frequency

28 days. NB. Blueteq criteria specifically state for 4 weekly treatment.

Number of cycles

Until disease progression or unacceptable toxicity up to a maximum of 1 year (i.e. 13 x 4 weekly cycles).

Administration

Nivolumab may be administered without dilution as a 10mg/mL solution or in sodium chloride 0.9% or glucose 5% at a concentration between 1-10mg/mL over 60 minutes. Nivolumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 1.2 μ m).

Patients should be monitored (blood pressure, pulse and temperature) every 30 minutes during the infusion for infusion related reactions. For mild to moderate reactions, decrease the infusion rate and closely monitor. Premedication with paracetamol and chlorphenamine should be used for further doses. For severe infusion related reactions discontinue treatment.

Pre-medication

Nil

Emetogenicity

This regimen has low emetogenic potential

Additional supportive medication

Loperamide if required.

Extravasation

Nivolumab is neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFT	14 days
Thyroid function	14 days
Calcium	14 days
Glucose	14 days
Cortisol	14 days

Investigations – pre subsequent cycles

Investigation	Validity period (or as per local policy)
FBC	7 days
U+E (including creatinine)	7 days
LFT	7 days
Calcium	As clinically indicated
Thyroid function	Every other cycle
Glucose	Prior to each cycle for the first 4 cycles then every other cycle
Cortisol	Prior to each cycle for the first 4 cycles then every other cycle

Patients should be monitored for up to 5 months after last dose for adverse reactions.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophil count	$\geq 1.0 \times 10^9/L$
White cell count	$\geq 2.0 \times 10^9/L$
Platelets	$\geq 75 \times 10^9/L$
Creatinine Clearance (CrCl)	$\geq 30\text{mL}/\text{min}$
Bilirubin	$\leq 1.5 \times \text{ULN}$
ALT/AST	$< \text{ULN}$
Alkaline Phosphatase	$< 5 \times \text{ULN}$

Dose modifications

Dose reductions are not recommended. Doses should be delayed until an adverse reaction resolves to \leq grade 1.

- **Haematological toxicity**

Discuss with the consultant if:

WBC $< 2.0 \times 10^9/L$

Neutrophils $< 1.0 \times 10^9/L$

Platelets $< 75 \times 10^9/L$

- **Renal impairment**

No dose modifications required in mild-moderate renal impairment. Use with caution in severe renal impairment.

- **Hepatic impairment**

Nivolumab has not been studied in moderate to severe hepatic impairment. Use with caution if bilirubin > 1.5 x ULN – consultant decision.

- **Other toxicities**

Severe pneumonitis and interstitial lung disease

Severe pneumonitis or interstitial lung disease, including fatal cases, have been observed with nivolumab monotherapy. Patients should be monitored for signs and symptoms of pneumonitis including radiographic changes, dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.

Grade 2 pneumonitis: withhold treatment, initiate corticosteroids (equivalent to 1mg/kg/day methylprednisolone). Once improved and corticosteroids tapered, treatment may be recommenced.

≥ Grade 3 pneumonitis: permanently discontinue treatment and initiate corticosteroids (equivalent to 2-4mg/kg/day methylprednisolone). If doses > 2mg/kg/day methylprednisolone are required consider alternative immunosuppressive agents, discuss with the consultant.

Immune-related adverse reactions

Immune-related adverse reactions can be severe or life-threatening and may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. While most immune-related adverse reactions reported occurred during the induction period, onset months after the last dose have also been reported. Unless an alternate aetiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and treatment-related. Early diagnosis and appropriate management are essential to minimise life-threatening complications.

Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions. Specific management guidelines for immune-related adverse reactions are described in full in the summary of product characteristics for nivolumab.

Management of immune-related adverse reactions may require a dose delay or permanent discontinuation of treatment and initiation of systemic high-dose corticosteroid or, in some cases, the addition of other immunosuppressive therapy. Dose reduction is not recommended.

Withhold treatment in patients with the following symptoms:

Treat with corticosteroids.

Upon improvement and after steroid taper treatment may recommence.

Toxicity	Definition
Gastrointestinal	Grade 2-3 diarrhoea/colitis
Hepatic	Grade 2 elevation in AST/ALT and or bilirubin
Nephritis/renal dysfunction	Grade 2-3 elevation in serum creatinine
Skin	Grade 3 rash
Endocrine	Symptomatic grade 2-3 hypothyroidism Symptomatic grade 2-3 hyperthyroidism Symptomatic grade 2-3 hypophysitis Grade 2 adrenal insufficiency Grade 3 diabetes
Neurological	Grade 2 motor or sensory neuropathy
Pneumonitis	Grade 2 pneumonitis
Other	Grade 3 (first occurrence)

Permanently discontinue treatment in patients with the following symptoms:

Management of these reactions may require high dose systemic corticosteroid therapy if suspected to be immune related:

Toxicity – severe or life threatening	Definition
Gastrointestinal	Grade 4 diarrhoea/colitis
Hepatic	Grade 3-4 elevation in AST/ALT and or bilirubin
Nephritis/renal dysfunction	Grade 4 elevation in serum creatinine
Skin	Grade 4 rash Grade 3 pruritus
Endocrine	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3-4 adrenal insufficiency Grade 4 diabetes
Neurological	Grade 3 or 4 motor or sensory neuropathy
Pneumonitis	Grade 3 or 4 pneumonitis
Other	Grade 4 Recurrent grade 3 Persistent grade 2-3 despite treatment modification; inability to reduce corticosteroid dose to 10mg prednisolone/day (or equivalent)

Adverse effects - for full details consult product literature/ reference texts

• **Serious side effects**

Immune reactions may occur during or after completion of treatment.

Colitis

Hepatitis

Peripheral neuropathy

Hypopituitarism

Hypothyroidism

Uveitis

Glomerulonephritis

Cardiac events

Thromboembolism

Interstitial lung disease

• **Frequently occurring side effects**

Pruritus

Rash

Nausea and vomiting

Diarrhoea

Fatigue

Decreased appetite

Hyperglycaemia

Abdominal pain

Anorexia

• **Other side effects**

Tumour pain

Headache
Raised transaminases

Significant drug interactions – for full details consult product literature/ reference texts

Corticosteroids: use of systemic corticosteroids at baseline, before starting nivolumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of the agent. However, systemic corticosteroids or other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions.

Additional comments

Patients should be issued with the Patient Alert Card and advised to carry the card at all times.

Contraception: Adequate methods of contraception should be used during therapy and for 8 weeks after last dose.

References

- National Institute for Clinical Excellence (TA817) accessed 5th October 2022 via www.nice.org.uk
- Summary of Product Characteristics Nivolumab (Bristol Myers Squibb) accessed 5th October 2022 via www.medicines.org.uk
- Bajorin, D. et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. N Engl J Med 2021; 384:2102-2114

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