Nivolumab monotherapy (melanoma)

Indication
Advanced (unresectable or metastatic) melanoma.

(NICE TA384)

Adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease

(NICE TA684)

ICD-10 codes
Codes prefixed with C43

Regimen details

Day	Drug	Dose	Route
1	Nivolumab	240mg every 2 weeks or 480mg every 4 weeks	IV infusion

Cycle frequency
Every 14 or 28 days (see above)

If patients need to switch from 2 weekly dosing to 4 weekly dosing, the first 480mg dose should be administered 2 weeks after the last 240mg dose. If patients need to switch from the 4 weekly dosing to the 2 weekly dosing, the first 240mg dose should be administered 4 weeks after the last 480mg dose.

Number of cycles
Unresectable/metastatic - Continued until disease progression or unacceptable toxicity. Option to discontinue Nivolumab after 2 or more years if response or stable disease with the option to restart Nivolumab monotherapy on disease progression.
Adjuvant – up to a maximum of 12 months (26 x 2-weekly cycles or 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 30 minutes (240mg dose) or 60 minutes (480mg dose). Nivolumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 1.2µm).

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
Nil

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
LDH	14 days
Thyroid function	14 days
Calcium	14 days
Glucose	14 days
Cortisol	14 days
ECG	Baseline

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	7 days
U+E (including creatinine)	7 days
LFT	7 days
LDH	7 days
Calcium	As clinically indicated
Thyroid function	6 weekly
Glucose	As clinically indicated
Cortisol	At consultant discretion

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	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine Clearance (CrCl)	≥ 30mL/min
Bilirubin	≤ 1.5 x ULN
ALT/AST	< ULN
Alkaline Phosphatase	< 5 x ULN

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

- **Haematological toxicity**

Discuss with the consultant if:
Neutrophils <1.0 x 10^9/L
Platelets <75 x 10^9/L

- **Renal impairment**

No dose modifications required in mild or moderate renal impairment (CrCl>30ml/min). No need for dose modification is expected in severe renal impairment (CrCl<30ml/min) but use with caution – consultant decision. See below for management of nephritis emergent on treatment.

- **Hepatic impairment**

No dose modification is required for mild hepatic impairment. There is limited data on the use of Nivolumab in moderate or severe hepatic impairment but no need for dose modification is expected. Use with caution if bilirubin > 1.5 x ULN – consultant decision. See below for management of hepatitis emergent on treatment.

- **Other toxicities**

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.

Toxicity	Definition	Action
Colitis	Grade 1	Continue and closely monitor
	Grade 2-3	Withhold until symptoms resolve to ≤ grade 1
	Grade 4 or recurrent grade 3	Permanently discontinue nivolumab
Pneumonitis	Grade 1	Continue and closely monitor
	Grade 2	Withhold until symptoms resolve to ≤ grade 1
	Grade 3-4 or recurrent grade 2	Permanently discontinue nivolumab
Nephritis	Grade 2 (creatinine 1.5-3 x ULN) or Grade 3 (creatinine > 3 x ULN)	Withhold until symptoms resolve to ≤ grade 1
	Grade 4 (creatinine > 6 x ULN)	Permanently discontinue
Endocrine	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grade 3 or 4 adrenal insufficiency or symptomatic hypophysitis	Withhold until symptoms resolve to ≤ grade 1
	Type 1 diabetes with grade > 3 hyperglycaemia (glucose > 13.9 mmol/L) or ketoacidosis	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hyperthyroidism ≥ grade 3	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hypothyroidism	Continue and manage with replacement therapy

Toxicity	Definition	Action
Hepatitis	Grade 2: AST/ALT 3-5 x ULN or Bilirubin > 1.5-3 x ULN	Withhold until resolves to ≤ grade 1
	Grade 3: AST/ALT 5-20 x ULN or Bilirubin 3-10 x ULN	May consider recommencing after corticosteroid taper or discontinue treatment – consultant decision
	Grade 4: AST/ALT > 20 x ULN or Bilirubin > 10 x ULN	Permanently discontinue nivolumab
	If liver metastasis and baseline AST/ALT 3-5 x ULN and AST/ALT increases ≥ 50% from baseline for ≥ 1 week	Permanently discontinue nivolumab
Skin	Grade 3 rash	Withhold until resolves to ≤ grade 1
	Grade 4 rash or Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis	Permanently discontinue nivolumab
Cardiac	Grade 2 myocarditis	Withhold until resolves to ≤ grade 1
	Grade 3 or 4 myocarditis	Permanently discontinue nivolumab
Neurological	Grade 2 motor or sensory neuropathy	Withhold until resolves to ≤ grade 1
	Grade 3 or 4 motor or sensory neuropathy	Permanently discontinue nivolumab
	Grade 3 or 4 encephalitis	Permanently discontinue nivolumab
	Grade 3 or 4 Guillain-Barré syndrome	Permanently discontinue nivolumab
Infusion-related reactions	Grade 3-4	Permanently discontinue nivolumab
Any other toxicity	Grade 3 (first occurrence)	Withhold until resolves to ≤ grade 1
	Grade 4 or recurrent Grade 3	Permanently discontinue nivolumab

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 a Nivolumab Patient Alert Card and advised to carry the card at all times.
Contraception: Adequate methods of contraception should be used during therapy and for at least 5 months after last dose.

References

- National Institute for Health and Care Excellence TA384. Accessed 14 December 2023 via www.nice.org.uk
- National Institute for Health and Care Excellence TA684. Accessed 14 December 2023 via www.nice.org.uk
- Summary of Product Characteristics Nivolumab (Bristol Myers Squibb) accessed 14 December 2023 via www.medicines.org.uk
- Robert et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015; 372:320-330
- Ascierto, P.A. et al; Adjuvant Nivolumab versus ipilimumab in resected stage IIIB-C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. Lancet Oncol 2020; 21(11):1465-1477

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