Nivolumab-Relatlimab (Opdualag®) (Melanoma)

Indication
Untreated advanced (unresectable or metastatic) melanoma

(NICE TA950)

ICD-10 codes
Codes prefixed with C43

Regimen details

Day	Drug	Dose	Route
1	Nivolumab-Relatlimab (Opdualag®)	480mg/160mg	IV infusion

Cycle frequency
28 days

Number of cycles
Until disease progression or unacceptable toxicity up to a maximum of 2 years

Administration
Nivolumab-relatlimab (Opdualag®) is administered as an IV infusion over 30 minutes. Nivolumab-relatlimab (Opdualag®) may be administered without dilution or may be diluted with 100mL sodium chloride 0.9% or glucose 5% (final concentration should be 3-12mg/mL of Nivolumab and 1-4mg/mL of relatlimab and total volume should not exceed 160mL). Nivolumab-relatlimab (Opdualag®) 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 emetic potential – refer to local policy

Additional supportive medication
Nil

Extravasation
Nivolumab-relatlimab (Opdualag®) 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	4 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). Data from patients with severe renal impairment are too limited to provide recommendations. See below for management of nephritis emergent on treatment.

- **Hepatic impairment**

No dose modifications required in mild or moderate hepatic impairment. Data from patients with severe hepatic impairment are too limited to provide recommendations. 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-relatlimab (Opdualag®).

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 treatment
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 treatment
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
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until resolves to ≤ grade 1
	Grade 4 rash or confirmed SJS/TEN	Permanently discontinue treatment

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 treatment
	If liver metastasis and baseline AST/ALT 3-5 x ULN and AST/ALT increases ≥ 50% from baseline for ≥ 1 week	Permanently discontinue treatment
Cardiac	Grade 2 myocarditis	Withhold until resolves to ≤ grade 1
	Grade 3 or 4 myocarditis	Permanently discontinue treatment
Neurological	Grade 2 motor or sensory neuropathy	Withhold until resolves to ≤ grade 1
	Grade 3 or 4 motor or sensory neuropathy	Permanently discontinue treatment
	Grade 3 or 4 encephalitis	Permanently discontinue treatment
	Grade 3 or 4 Guillain-Barré syndrome	Permanently discontinue treatment
Infusion-related reactions	Grade 3-4	Permanently discontinue treatment
Any other toxicity	Grade 3 (first occurrence)	Withhold until resolves to ≤ grade 1
	Grade 4 or recurrent Grade 3 Persistent grade 2 or 3 despite treatment modification Inability to reduce corticosteroid dose to 10mg prednisolone or equivalent per day	Permanently discontinue treatment

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

- **Serious side effects**

Adrenal insufficiency
Colitis
Myocarditis
Pneumonitis
Endocrinopathies
Hepatitis
Uveitis
Nephritis
Guillain-Barre syndrome
Pancreatitis

- **Frequently occurring side effects**

Fatigue
Musculoskeletal pain
Rash, pruritis
Arthralgia
Diarrhoea, constipation

Headache
Nausea, vomiting
Cough
Decreased appetite
Dizziness
Dysgeusia
Abdominal pain
Electrolyte disturbance

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

Corticosteroids and other immunosupressants: The use of systemic corticosteroids and other immunosupressants at baseline, before starting nivolumab-relatlimab (Opdualag®) should be avoided because of their potential interference with pharmacodynamic activity. However, systemic corticosteroids and other immunosupressants can be used after starting nivolumab-relatlimab to treat immune-related adverse reactions.

Additional comments

The patient should be provided with a treatment alert card and advised to carry it with them at all times.

References

- National Institute for Health and Care Excellence TA950. Accessed 07 February 2024 via www.nice.org.uk
- Summary of Product Characteristics Opdualag (Bristol Myers Squibb) accessed 07 February 2024 via www.medicines.org.uk
- Tawbi H. A. et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N Engl J Med 2022; 386:24-34.

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