Nivolumab

Indication

Treatment of relapsed or refractory classical Hodgkin Lymphoma after autologous stem cell transplant and treatment with Brentuximab Vedotin

(NICE TA462)

Second line salvage option for Hodgkin Lymphoma after brentuximab to replace salvage chemotherapy, and in order to reduce admission time and reduce risk of neutropenia.

(COVID-19 interim commissioning)

ICD-10 codes

Codes prefixed with C81.

Regimen details

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

***Note – unlicensed for this indication but Blueteq criteria allows 4 weekly treatment**

Cycle frequency

Every 14 days 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 4 weekly dosing to 2 weekly dosing then the first 240mg dose should be administered 4 weeks after the last 480mg dose.

Number of cycles

Until unacceptable toxicity, disease progression or stem cell transplant.

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 in-line filter with a pore size of 0.2-1.2µm.

Patients must be monitored (blood pressure, pulse and temperature) every 30 minutes during the infusion for infused-related reactions. For mild to moderate reactions, decrease the infusion rate and closely monitor. Pre-medication 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 should be prescribed to be used if required.
Antiemetics as per local policy, if required.

Extravasation

Nivolumab is neutral (group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC	7 days
U+E (including creatinine)	7 days
LFT	7 days
Thyroid function	7 days
Glucose	7 days
Calcium	7 days
Cortisol	7 days

Other baseline investigations:
Hepatitis B core antibody and hepatitis B surface antigen, Hepatitis C antibody, EBV, CMV, VZV, HIV 1+2

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	72 hours
U+E (including creatinine)	72 hours
LFT	72 hours
Thyroid function	72 hours
Glucose	As clinically indicated
Calcium	As clinically indicated
Cortisol	As clinically indicated

After 3 months, pre-Nivolumab investigations and clinical assessment can be performed every 4 weeks rather than every fortnight for those on the 2-weekly regimen.

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	≥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 consultant if:
Neutrophils <1.0 x 10^9/L
Platelets <75 x 10^9/L

- **Renal impairment**

No dose modifications required in patients with mild or moderate renal impairment. There is not enough data available for recommendation in severe renal impairment. Discuss with consultant if creatinine clearance <30mL/min.

- **Hepatic impairment**

Use with caution in patients with moderate (total bilirubin >1.5 x ULN and any AST) or severe hepatic impairment (total bilirubin >3 x ULN and any AST).

- **Other toxicities**

Patients must be advised to seek specialist advice if they experience side effects as these can worsen rapidly. Immune reactions may occur during or after completion of treatment.

The below toxicities are graded using the National Cancer Institute Common Terminology Criteria for adverse Events (CTCAE) Version 5.0. Full details of NCI- CTCAE grading can be accessed via:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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. Should a second episode of pneumonitis occur then permanently discontinue Nivolumab.

≥ 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.

<u>Permanently discontinue</u> treatment in patients with the following symptoms:

Patients may require high dose systemic corticosteroids if the following symptoms are suspected to be immune related.

Toxicity – severe or life threatening	**Definition (NCI-CTC v5.0 grading)**
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

<u>Withhold treatment</u> in patients with the following symptoms:

Treat with systemic corticosteroids. Upon improvement and after steroid taper, reintroduction of Nivolumab may be considered.

Toxicity	**Definition (NCI-CTC v5.0 grading)**
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)

Do not resume Nivolumab if the patient is still receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy for grade 2 or 3 immune-related adverse reactions.

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

- **Serious side effects**

Pneumonitis
Colitis
Hepatitis
Nephritis
Autoimmune neuropathy
Endocrinopathies
Uveitis
Glomerulonephritis
Interstitial lung disease
Cardiac events

- **Frequently occurring side effects**

Pruritis
Dizziness
Hypertension
Muscle pain
Rash
Nausea
Diarrhoea
Decreased appetite
Hyperglycaemia

- **Other side effects**

Headache
Alopecia

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 effects.

Additional comments

Acute GVHD, including fatal GVHD, has been reported after treatment with nivolumab in patients with previous allogeneic HSCT.

Solid organ transplant rejection has been reported in the post- marketing setting in patients treated with PD-1 inhibitors.

Patient must be given a Nivolumab Patient Alert Card. Link: https://www.medicines.org.uk/emc/product/6888/rmms

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

References:

- NICE. TA462 Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma. Published 26/07/2017. Available at https://www.nice.org.uk/guidance/ta462.
- National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Accessed 1st February 2021. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf
- Summary of product characteristics, Nivolumab. Bristol Myers Squibb. Accessed 1st February 2021 via www.medicines.org.uk
- Ansell S, Armand P et al. Nivolumab in Patients (Pts) with Relapsed or Refractory Classical Hodgkin Lymphoma (R/R cHL): Clinical Outcomes from Extended Follow-up of a Phase 1 Study (CA209- 039). Blood 2015;126 (23):583.

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Date: June 2021
