Nivolumab

Indication

Advanced renal cell carcinoma after prior therapy
Palliative treatment for metastatic melanoma
Adjuvant treatment for completely resected melanoma
Squamous Cell Cancer of the Head and Neck (SCCHN) progressing on or after platinum-based therapy
Unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy
Non-small cell lung cancer (NSCLC) after prior chemotherapy
Relapsed or refractory classical Hodgkin's lymphoma
Adjuvant monotherapy for patients with completely resected oesophageal or gastro-oesophageal carcinoma who have residual pathological disease at surgery following prior neoadjuvant chemoradiotherapy
Adjuvant treatment for resected high-risk invasive urothelial cancer
Metastatic or locally advanced and unresectable upper gastrointestinal cancers that exhibit microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) - **NICE interim COVID19 guidance**
2nd line treatment for malignant pleural and peritoneal mesothelioma which has progressed during/after 1st line chemotherapy with pemetrexed- and platinum-based chemotherapy **- NICE interim COVID19 guidance**
Compassionate use for pre-treated metastatic/recurrent squamous cell anal cancer
Compassionate use for pre-treated squamous cell vulval cancer

ICD-10 codes

Dependant on tumour site

Regimen details

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

Cycle frequency

14 days or 28 days as above.
4-weekly regimen permitted for all indications during COVID19 amendment period

Number of cycles

Metastatic melanoma and renal cell carcinoma
Until unacceptable toxicity, disease progression or consultant discretion (sustained complete response).

Other metastatic indications
Until unacceptable toxicity, disease progression or consultant discretion (sustained complete response). Treatment should stop at 2 years.

Adjuvant treatment
Adjuvant treatment should continue for 12 months (13x 4 weekly cycles) or until disease progression, withdrawal

of consent, or unacceptable toxicity.

Switching regimens:
When switching from 2-weekly regimen to 4-weekly regimen, give first 480mg dose two weeks after the last 240mg dose
When switching from 4-weekly regimen to 2-weekly regimen, give first 240mg dose four weeks after the last 480mg dose

Administration

Nivolumab 240mg in 50ml sodium chloride 0.9% over 30 minutes or
Nivolumab 480mg in 100ml sodium chloride 0.9% over 60 minutes
Patients should be monitored every 30 minutes during the infusion (blood pressure, pulse and temperature) and 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

Antiemetics as per local policy, if required.

Extravasation

Neutral (Group 1)

Investigations – pre first cycle

PD-L1 tumour expression if required for some indications, please refer to list above.

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFT inc AST	14 days
LDH (melanoma only)	14 days
Thyroid function	14 days
Glucose	14 days
Calcium	14 days
Cortisol	14 days
Luteinizing hormone	14 days
Follicle stimulating hormone	14 days
Testosterone	14 days

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	48 hours
U+E (including creatinine)	48 hours
LFT inc AST	48 hours
LDH (melanoma only)	48 hours
Thyroid function	Every 6 weeks unless otherwise clinically indicated
Glucose	As clinically indicated
Calcium	As clinically indicated
Cortisol	At consultant discretion

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
Serum Creatinine	≤1.5 X ULN
Bilirubin	Serum total bilirubin ≤1.5 X ULN or direct bilirubin ≤ULN for patient with total bilirubin level >1.5 ULN
ALT/AST	≤2.5 X ULN or ≤5 X ULN with liver metastases
Alkaline Phosphatase	< 5 x ULN

Dose modifications

Do not amend the dose of nivolumab

Consider immunotherapy driven toxicity as a potential reason for all changing laboratory results and discuss with a consultant if any concerns.

- **Haematological toxicity**

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

- **Renal impairment/toxicity**

The safety and efficacy of nivolumab has not been studied in patients with renal impairment. No specific dose adjustments are recommended in mild to moderate renal impairment.
Discuss with consultant if CrCl <30mL/min.

- **Hepatic impairment/toxicity**

The safety and efficacy of nivolumab has not been studied in patients with hepatic impairment. No specific dose adjustments are recommended in mild hepatic impairment. See below for management of hepatitis.

- **Endocrine toxicity**

Dose delays are not routinely required for abnormalities in endocrine function. Please seek advice from patient's treating clinican.

- **Other toxicities**

Patients must be advised to seek specialist advice of they experience side effects as these can worsen rapidly.

Immune reactions may occur during or after completion of treatment.

Treatment of toxicities

Immunotherapy toxicities should be aggressively managed as can cause permanent and life threatening complications.
Refer to UKONS and ESMO guidance for treatment of immune related toxicities.
Available at:
https://www.healthierlsc.co.uk/canceralliance/chemotherapy-protocols/immunotherapy-toxicity-guidelines

- **Toxicity monitoring and dose delays/discontinuation.**

All toxicities should be actively management and monitored. Any dose delays or discontinuation should be supervised by the treating clinician and made on an individual patient basis.

Toxicity	Definition	Action
Colitis	Grade 1	Continue and closely monitor
	Grade 2-3	Withhold until symptoms resolve to ≤ grade 1
	Grade 4	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)	Withhold until symptoms resolve to ≤ grade 1
	Grade 3 (creatinine > 3 x ULN)	Permanently discontinue nivolumab
Endocrine	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
Hepatitis	AST/ALT 3-5 x ULN or Bilirubin > 1.5-3 x ULN	Withhold until resolves to ≤ grade 1
	AST/ALT > 5 x ULN or Bilirubin > 3 x ULN	Permanently discontinue nivolumab
	Liver metastasis and baseline AST/ALT 3-5 x ULN or AST/ALT increases ≥ 50% for ≥ 1 week	Permanently discontinue nivolumab
Infusion-related reactions	Grade 3-4	Permanently discontinue nivolumab

Nivolumab should be permanently discontinued if:
- Grade 4 toxicity (except for endocrinopathies that are controlled with replacement hormones)
- Corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks
- Treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose
- Any event occurs a second time at Grade ≥ 3 severity
- Grade 3 or 4 myocarditis
- Grade 3 or 4 encephalitis
- Grade 3 or 4 Guillain-Barré syndrome

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

- **Serious side effects**

Myelosuppression
Pneumonitis
Colitis
Hepatitis
Nephritis
Endocrinopathies
Pancreatitis

- **Frequently occurring side effects**

Myelosuppression
Reduced appetite
Headache
Dizziness
Dry eyes
Cough
Diarrhoea
Nausea
Rash
Fatigue
Hyperglycaemia
Hypocalcaemia

- **Other side effects**

Arthralgia

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 nivolumab. However, systemic corticosteroids or other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions.

Additional comments

Women of child bearing potential should use effective contraception during treatment and for at least 4 months after the last dose.

References

- http://www.swscn.org.uk/guidance-protocols/cancer-protocols/ accessed 9 Jul 2020
- Summary of Product Characteristics Nivolumab via www.medicines.org.uk

THIS PROTOCOL HAS BEEN DIRECTED BY DR BOARD, DESIGNATED LEAD CLINICIAN FOR MELANOMA

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

Date: September 2022
Review: September 2024
VERSION: 18