Nivolumab

Indication
Recurrent or metastatic squamous cell carcinoma of the head and neck, in patients whose disease has progressed on or after platinum based therapy. Disease must have progressed within 6 months of last dose of chemotherapy.

Performance status 0-1.

(NICE TA490)

ICD-10 codes
Codes prefixed with C00-13.

Regimen details

Day	Drug	Dose	Route
1	Nivolumab	240mg	IV infusion

Cycle frequency
Every 14 days

Number of cycles
Continued until disease progression or unacceptable toxicity to a maximum of 2 years uninterrupted treatment.

Administration
Nivolumab may be administered without dilution or in sodium chloride 0.9% or glucose 5% at a concentration between 1-10mg/mL over 30 minutes. Nivolumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 1.2µm).

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
Loperamide if required.

Extravasation
Nivolumab is neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	7 days
U+E (including creatinine)	7 days
LFT	7 days
Thyroid function	7 days
Calcium	7 days
Glucose	7 days
Cortisol	7 days

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	72 hours
U+E (including creatinine)	72 hours
LFT	72 hours
Calcium	As clinically indicated
Thyroid function*	72 hours
Glucose*	72 hours
Cortisol*	72 hours

* every cycle for the first 24 weeks, 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	≥ 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.

Toxicity

Immune related toxicities may affect any organ system and should be considered for any new symptoms. Grade 1 toxicities should be managed symptomatically with close monitoring. Specific management guidelines for immune-related adverse reactions are described in full in the summary of product characteristics for Nivolumab.

- ### Haematological toxicity

Discuss with the consultant if:
WBC <2.0 x 10^9/L
Neutrophils <1.0 x 10^9/L
Platelets <75 x 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 taper steroids slowly over 1 month, treatment may be recommenced when toxicity settled to grade 1 or less.

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

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:
Management of these reactions require high dose systemic corticosteroid therapy: Admit for intravenous corticosteroids (equivalent to 2-4mg/kg/day methylprednisolone) and discuss with consultant.

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)

<u>Withhold</u> treatment in patients with the following symptoms:
Initiate oral corticosteroids (equivalent to 1mg/kg/day methylprednisolone). Once improved taper steroids slowly over 1 month, treatment may be recommenced when toxicity settled to grade 1 or less.

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)

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

Anticoagulants: increased risk of haemorrhage – avoid or closely monitor.

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

The prescriber must discuss the risks of nivolumab therapy with the patient and provide the Patient Alert Card.

All patients on high dose prolonged corticosteroids should be warned about the risk of steroid induced NIDDM.

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

References

- National Institute for Health and Clinical Excellence TA490. Accessed 6 December 2017 via www.nice.org.uk
- Summary of Product Characteristics Nivolumab (Bristol Myers Squibb) accessed 29 August 2018 via www.medicines.org.uk
- Ferris, R.L et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 2016; 375:1856-1867

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