Nivolumab and Ipilimumab

Indication
Advanced (unresectable or metastatic) melanoma.

(NICE TA400)

ICD-10 codes
Codes prefixed with C43

Regimen details
Cycles 1-4 – Nivolumab and Ipilimumab every 3 weeks

Day	Drug	Dose	Route
1	Nivolumab	1mg/kg	IV infusion
1	Ipilimumab	3mg/kg	IV infusion

Subsequent cycles - Nivolumab monotherapy every 2 or 4 weeks

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

The first monotherapy dose should be given 3 weeks after the last combination dose if 240mg every 2 weeks or 6 weeks after last combination dose if 480mg every 4 weeks.

Cycle frequency
Nivolumab and Ipilimumab – every 21 days
Nivolumab monotherapy – 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
Nivolumab and Ipilimumab - 4 cycles

Nivolumab monotherapy – continued until disease progression or unacceptable toxicity.

Administration
Combination treatment: **nivolumab should be given first**, followed by ipilimumab.

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 60 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).

Ipilimumab may be administered without dilution or in sodium chloride 0.9% or glucose 5% at a concentration between 1-4mg/mL over 90 minutes. Ipilimumab 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.

Monotherapy:
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).

Pre-medication
Nil

Emetogenicity
This regimen has low emetogenic potential

Additional supportive medication
Loperamide if required.

Extravasation
Nivolumab and ipilimumab are 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

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	72 hours
U+E (including creatinine)	72 hours
LFT	72 hours
Thyroid function	72 hours

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:
WBC <2.0 x 10^9/L
Neutrophils <1.0 x 10^9/L
Platelets <75 x 10^9/L

- **Renal impairment**

Nivolumab:
No dose modifications required in mild-moderate renal impairment. Use with caution in severe renal impairment.

Ipilimumab:
The safety and efficacy of ipilimumab have 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**

Nivolumab:
Nivolumab has not been studied in moderate to severe hepatic impairment. Use with caution if bilirubin > 1.5 x ULN – consultant decision.

Ipilimumab:
The safety and efficacy of ipilimumab have not been studied in patients with hepatic impairment. No specific dose adjustments are recommended in mild hepatic impairment. Ipilimumab should be administered with caution in patients with AST/ALT ≥ 5 x ULN or bilirubin > 3 x ULN.
See table below for details of when ipilimumab should be omitted or permanently discontinued:

Elevation in AST/ALT and/or bilirubin	Action
Grade 1	Continue
Grade 2	Withhold until ≤ Grade 1 and after steroid taper (if appropriate)
Grade 3-4	Discontinue

- **Other toxicities**

Severe pneumonitis and interstitial lung disease
Severe pneumonitis or interstitial lung disease, including fatal cases, have been observed with nivolumab in combination with ipilimumab or 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.

≥ 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 and ipilimumab.

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.

Permanently discontinue treatment in patients with the following symptoms:
Management of these reactions may require high dose systemic corticosteroid therapy if suspected to be immune related:

Toxicity – severe or life threatening	**Definition**
Gastrointestinal	Grade 3-4 diarrhoea/colitis (Nivolumab and Ipilimumab) Grade 4 diarrhoea/colitis (Nivolumab monotherapy)
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)

Withhold treatment in patients with the following symptoms:
Treat with corticosteroids.
Upon improvement and after steroid taper treatment may recommence.

Toxicity	**Definition**
Gastrointestinal	Grade 2 diarrhoea/colitis (Nivolumab and Ipilimumab) Grade 3 diarrhoea/colitis (Nivolumab monotherapy)
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
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 ipilimumab and/or nivolumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of the agents. However, systemic corticosteroids or other immunosuppressants can be used after starting ipilimumab and/or nivolumab to treat immune-related adverse reactions.

Additional comments

Ipilimumab is contraindicated in patients with active, life-threatening autoimmune disease, or with organ transplantation graft where further immune activation is potentially imminently life threatening.

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

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

Sodium: Ipilimumab and nivolumab concentrate each contain 0.1mmol (2.30mg) sodium per mL. Care if low sodium diet.

References

- National Institute for Health and Clinical Excellence TA400. Accessed 3 August 2016 via www.nice.org.uk
- Summary of Product Characteristics Ipilimumab (Bristol Myers Squibb) accessed 3 August 2016 via www.medicines.org.uk
- Summary of Product Characteristics Nivolumab (Bristol Myers Squibb) accessed 8 August 2018 via www.medicines.org.uk
- Larkin J, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015 Sep 24;373(13):1270-1

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