Ipilimumab and Nivolumab (Mesothelioma)

Indication

Metastatic or unresectable malignant pleural mesothelioma as first line systemic anti-cancer therapy for people with performance status 0 or 1

(NICE TA818)

ICD-10 codes

C45

Regimen details

Day	Drug	Dose	Route
1	Ipilimumab	1mg/kg every 6 weeks	IV infusion
1	Nivolumab	360mg every 3 weeks	IV infusion

Cycle frequency

Ipilimumab: 42 days
Nivolumab: 21 days

Number of cycles

Continue until disease progression or excessive toxicity or completion of 2 years of treatment (a maximum of 35 cycles of nivolumab and a maximum of 17 cycles of ipilimumab), whichever is the sooner.
NB: If Ipilimumab is discontinued because of drug toxicity, nivolumab can be continued as monotherapy. If Nivolumab is stopped, then ipilimumab must also be discontinued.

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 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).

Ipilimumab may be administered without dilution or in sodium chloride 0.9% or glucose 5% at a concentration between 1-4mg/mL over 30 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 infusions 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

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+Es (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	7 days
U+E (including creatinine)	7 days
LFT	7 days
Thyroid function	Every other cycle
Calcium	7 days
Glucose	7 days
Cortisol	7 days

Patients should be monitored 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
White blood cell count	> 2.0 x 10^9/L
Neutrophil count	≥ 1.0 x10^9/L
Platelets	≥ 75 x10^9/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 consultant if:
WBC <2.0 x10^9/L
Neutrophils <1.0 x10^9/L
Platelets <75.0 x10^9/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.

If creatinine increases to >1.5 x ULN (or >1.5 x baseline if baseline abnormal) whilst on treatment, consider nephritis – see immune-related adverse reactions section below

- **Hepatic impairment**

Nivolumab:
Nivolumab has not been studied in moderate to severe hepatic impairment. Use with caution if baseline 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 at baseline.

If ALT increases to >3 x ULN (or >3 x baseline, if baseline abnormal) or bilirubin increases to >1.5 x ULN (or >1.5 x baseline, if baseline abnormal) whilst on treatment, consider hepatitis – see immune related adverse reactions section below.

- **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 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.

<u>Permanently discontinue</u> 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
Hepatic	Grade 3-4 elevation in AST/ALT and/or bilirubin
Skin	Grade 4 rash, Steven-Johnson syndrome, toxic epidermal necrolysis Grade 3 pruritis
Neurological	Grade 3 or 4 motor or sensory neuropathy
Other (eg. Nephritis, pneumonitis, pancreatitis, non-infectious myocarditis, diabetes)	Any grade 4 Any recurrent grade 3 Persistent grade 2 – 3 despite treatment modification; inability to reduce corticosteroid dose to 10mg prednisolone/day (or equivalent)

<u>Withhold treatment</u> 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
Hepatic	Grade 2 elevation in AST/ALT and/or bilirubin
Endocrine	Severe adverse reactions in the endocrine glands, such as hypophysitis and thyroiditis that are not adequately controlled with hormone replacement therapy or high-dose immunosuppressive therapy Grade 3 diabetes
Neurological	Grade 2 motor or sensory neuropathy, muscle weakness
Pneumonitis	Grade 2 pneumonitis
Other moderate adverse reactions	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.
Infusion related reactions
Colitis
Hepatitis
Peripheral neuropathy
Hypopituitarism
Hypothyroidism
Uveitis
Renal failure
Cardiac events
Thromboembolism
Interstitial lung disease
Pneumonia
Upper respiratory tract infection

- **Frequently occurring side effects**

Pruritus
Rash
Nausea and vomiting
Diarrhoea
Fatigue
Decreased appetite
Abdominal pain
Hypertension
Arthralgia

- **Other side effects**

Tumour pain
Headache
Dizziness
Blurred vision
Raised transaminases

Significant drug interactions – for full details consult product literature/ reference texts
Anticoagulants: increased risk of GI haemorrhage with ipilimumab – monitor closely.

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 patients who are receiving immunosuppressive treatment following organ transplantation graft where immune activation is potentially imminently life threatening.

The prescriber must discuss the risks of ipilimumab/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 TA818. Accessed 26 August 2022 via www.nice.org.uk
- Summary of Product Characteristics Ipilimumab (Bristol Myers Squibb) accessed 26 August 2022 via www.medicines.org.uk
- Summary of Product Characteristics Nivolumab (Bristol Myers Squibb) accessed 26 August 2022 via www.medicines.org.uk
- Baas P, Scherpereel A, Nowak AK, Fujimoto N, Peters S, Tsao AS, Mansfield AS, Popat S, Jahan T, Antonia S, Oulkhouir Y. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. The Lancet. 2021 Jan 30;397(10272):375-86.

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