Ipilimumab

Indication
Advanced (unresectable or metastatic) melanoma in patients who have received prior therapy.

(NICE TA268)

Previously untreated advanced (unresectable or metastatic) melanoma.

(NICE TA319)

ICD-10 codes
Codes prefixed with C43

Regimen details

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

Cycle frequency
21 days

Number of cycles
4 cycles
Patients should receive all 4 cycles as long as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessments of tumour response should be carried out after treatment completed.

Administration
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 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
Loperamide if required. Patient should be advised to contact the oncology department if any diarrhoea.

Extravasation

Neutral (Group 1)

Investigations – pre first cycle

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

Investigations – pre subsequent cycles

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

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
Haemoglobin*	>10 g/dL
Creatinine Clearance (CrCl)*	≥ 30mL/min
Bilirubin	≤3 x ULN (baseline)
ALT/AST*	<5 x ULN (baseline)
Alkaline Phosphatase	<5 x ULN

***For all subsequent cycles: If ALT/AST increases > 20% from baseline or if CrCl, platelets or haemoglobin decreases > 20% from baseline discuss with consultant before go ahead.** Please remember that changing blood results can suggest a treatment toxicity and in this case the drug should be held and steroid initiation considered.

Dose modifications

Dose reductions are not recommended, doses should be delayed until an adverse reaction resolves to ≤ grade 1. If resolution occurs within 12 weeks, treatment may be recommenced.

- **Haematological toxicity**

Discuss with the consultant if platelets and/ or haemoglobin < 20% reduction from baseline or if:
WBC <2.0 x 10^9/L
Neutrophils <1.0 x 10^9/L
Platelets <75 x 10^9/L
Haemoglobin < 10g/dL

- **Renal impairment**

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 or if creatinine clearance < 20% from baseline.

- **Hepatic impairment**

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.

LFTs should be monitored prior to each dose of ipilimumab. If ALT/AST increases by > 20% from baseline, discuss with consultant.

See below for details of when ipilimumab should be omitted or permanently discontinued.

- **Other toxicities**

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 of ipilimumab 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 ipilimumab-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.

Management of immune-related adverse reactions may require a dose delay or permanent discontinuation of ipilimumab and institution of systemic high-dose corticosteroid or, in some cases, the addition of other immunosuppressive therapy. Dose reduction is not recommended.

Permanently discontinue ipilimumab 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 or 4 diarrhoea or colitis Severe abdominal pain Blood in stool GI haemorrhage GI perforation
Hepatic	Grade 3-4 elevations in ALT/AST and/or bilirubin
Skin	Grade 4 rash (Life threatening skin rash (including Stevens-Johnson syndrome or toxic epidermal necrolysis) Grade 3 pruritus
Neurological	Grade 3 or 4 motor or sensory neuropathy
Other	≥ Grade 3 immune related events ≥ Grade 2 immune related eye events not responding to topical immunosuppressive therapy

Withhold scheduled dose of ipilimumab in patients with the following symptoms:

Toxicity	Action
Gastrointestinal – moderate diarrhoea or colitis not controlled with medical management, that persists (5-7 days) or recurs	1. Withhold dose until an adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline). 2. If resolution occurs resume therapy*. 3. If resolution has not occurred, continue to withhold doses until resolution then resume treatment*. 4. Discontinue Ipilimumab if resolution to Grade 1 or Grade 0 or return to baseline does not occur.
Hepatic – grade 2 elevations in ALT/AST and/or bilirubin	
Skin – moderate to severe (Grade 3) skin rash or widespread grade 2 pruritus	
Endocrine – severe endocrine reactions not controlled by hormone replacement or high dose immunosuppressive therapy	
Neurological – moderate (Grade 2) unexplained motor neuropathy, muscle weakness or sensory neuropathy	
Other moderate adverse reactions	

* Until administration of all 4 doses from the first dose, whichever occurs earlier.

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

Immune reactions may occur during or after completion of treatment.

- **Serious side effects**

Colitis
Hepatitis
Peripheral neuropathy
Hypopituitarism
Hypothyroidism
Uvetis
Glomerulonephritis

- **Frequently occurring side effects**

Pruritus
Rash
Nausea and vomiting
Diarrhoea
Fatigue
Decreased appetite
Abdominal pain

- **Other side effects**

Tumour pain
Headache

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, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of ipilimumab. However, systemic corticosteroids or other immunosuppressants can be used after starting ipilimumab to treat immune-related adverse reactions.

Additional comments

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

Sodium: Each mL of the concentrate contains 0.1mmol (2.30mg) sodium. Care if low sodium diet.

References

- National Institute for Health and Clinical Excellence TA268. Accessed 12 September 2019via www.nice.org.uk
- National Institute for Health and Clinical Excellence TA319. Accessed 12 September 2019 via www.nice.org.uk
- Summary of Product Characteristics Ipilimumab - Yervoy® (Bristol Myers Squibb) accessed 12 September 2019 via www.medicines.org.uk
- Hodi FS, O'Day SJ, McDermott DF et al Improved survival with ipilimumab in patients with metastatic melanoma. New England Journal of Medicine, 2010 Aug 19;363(8):711-23. Epub 2010 Jun 5
- Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med.2011;364:2517- 2526

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