Systemic Anti Cancer Treatment Protocol

IPILIMUMAB

21 day cycle for a total of 4 doses

PROTOCOL REF: MPHAMMEIPI
(Version No: 1.0)

Approved for use in:

Advanced (unresectable or metastatic) melanoma.

Dosage:

Patients should receive the entire induction regimen (4 doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessments of tumour response should be conducted only after completion of induction therapy

Drug	Dosage	Route	Frequency
Ipilimumab	3mg/kg IV	IV	21 day cycle max. 4 doses

Supportive Treatments:

Domperidone 10mg TDS/PRN

Interactions:

Systemic corticosteroids - The use of systemic corticosteroids at baseline, before starting ipilimumab,should be avoided because of their potential interference with efficacy of Ipilimumab

Anticoagulants- increased risk of GI haemorrhage, monitor closely

Vaccinations should not be administered for 4 weeks before and after Ipilimumab

Extravasation:

Ipilimumab is neutral

Administration:

Day	Drug	Dose	Route	Diluent and rate
1	Ipilimumab	3mg/kg	IV Infusion	90 minutes in a non-pyrogenic line with a 0.2 µm filter (no diluent added)

STORAGE INSTRUCTIONS
Do not shake
Store in a fridge

Flushes

Flush the line with sodium chloride 0.9% or glucose 5% at the end of the infusion.

Main Toxicities:

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Immune-related adverse reactions, which can be severe or life-threatening, may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. While most immune-related adverse reactions occur during the induction period of treatment, onset months after the last dose of Ipilimumab has 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.

Investigations:

Investigation	Baseline	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Follow-up (12weeks)
Imaging	√					√
FBC	√	√	√	√	√	√
U & E, LFTs & LDH	√	√	√	√	√	√
TSH and free T4	√	√	√	√	√	√
Cortisol and FSH	Not routinely required, request if endocrinopathy suspected					

Dose Modifications and Toxicity Management:

There are no dose modifications for ipilimumab and no treatment deferrals, dose omissions permitted only.

Proceed on day 1 if:-

Platelets	Neutrophil count	Cr.Cl	Bilirubin	AST/ALT	Alk. Phos.	TSH and free T4
≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≥30 mL/min	<3 x ULN[a]	<5 x ULN	<5 x ULN	Within range or no change from base line

[a] ULN = upper limit of normal

The dose should be omitted if appropriate. Inform consultant if there has been an increase in liver function test from previous results.

Toxicity management:

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 section 4.4 of the Summary of product characteristics available from:

> YERVOY 5 mg/ml concentrate for solution for infusion, Summary of Product Characteristics Bristol-Myers Squibb Pharmaceutical Limited. Available from: www.medicines.org.uk/emc/medicine. Last updated 16/01/14.

Dose reduction is not recommended. Doses that are omitted due to an adverse reaction must not be replaced. Patient may receive a total of 4 doses or 16 weeks of treatment from first dose, whichever occurs earlier.

Adverse reactions should be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010)

Mild to moderate adverse reactions	Action
Gastrointestinal: Patients with mild to moderate (Grade 1 or 2) diarrhoea (an increase of up to 6 stools per day) or suspected mild to moderate colitis (e.g. abdominal pain or blood in stools) may remain on ipilimumab. For persistent (5-7 days) or recurrent diarrhoea see advice below Moderate diarrhoea or colitis that either is not controlled with medical management or that persists (5-7 days) or recurs	Ipilimumab should be omitted until adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline). Symptomatic treatment (e.g. loperamide, fluid replacement) and close monitoring is advised, discuss with oncologist Ipilimumab should be omitted. Discuss with oncologist, consider corticosteroid therapy
Hepatic: Moderate elevations in transaminase (AST or ALT > 5 to ≤ 8 x ULN) or total bilirubin (> 3 to ≤ 5 x ULN) levels	The scheduled dose of ipilimumab should be omitted, and LFTs must be monitored until resolution. After LFT levels improve (AST and ALT ≤ 5 x ULN and total bilirubin ≤ 3 x ULN), ipilimumab may be resumed

Skin: Moderate to severe (Grade 3) skin rash or widespread/intense pruritus regardless of etiology	The scheduled dose of ipilimumab should be omitted. If initial symptoms improve to mild (Grade 1) or resolve, ipilimumab therapy may be resumed
Endocrine: Severe adverse reactions in the endocrine glands, e.g. thyroid or pituitary gland that are not adequately controlled with hormone replacement therapy or high-dose immunosuppressive therapy	Omit treatment until resolution to Grade 1 of Grade 0. Discontinue if resolution to Grade 1 or Grade 0 or a return to baseline does not occur.
Neurological: Moderate (Grade 2) unexplained motor neuropathy, muscle weakness, or sensory neuropathy (lasting more than 4 days)	Omit until reaction resolves to Grade 1 or Grade 0 (or returns to baseline). Discontinue if resolution to Grade 1 or Grade 0 or a return to baseline does not occur.
Other moderate adverse reactions	Omit until reaction resolves to Grade 1 or Grade 0 (or returns to baseline). Discontinue if resolution to Grade 1 or Grade 0 or a return to baseline does not occur.

Permanent discontinuation:

Permanently discontinue in patients with the following adverse reactions. Management of these adverse reactions may also require systemic high-dose corticosteroid therapy if demonstrated or suspected to be immune-related.

Severe or life-threatening adverse reactions requiring discontinuation of treatment	
Gastrointestinal:	Severe symptoms (abdominal pain, severe diarrhoea or significant change in the number of stools, blood in stool, gastrointestinal haemorrhage, gastrointestinal perforation). Grade 3 or 4 diarrhoea or colitis
Hepatic:	AST or ALT elevations > 8 x ULN or bilirubin > 5 x ULN that are suspected to be related to ipilimumab, treatment must be permanently discontinued. Discuss with oncologist
Skin:	Life threatening skin rash (including Stevens-Johnson syndrome or toxic epidermal necrolysis) or severe widespread pruritus interfering with activities of daily living or requiring medical intervention. Grade 4 rash or Grade 3 pruritus
Neurologic:	New onset or worsening severe motor or sensory neuropathy. Grade 3 or 4 motor or sensory neuropathy
Other organ systems:	Including nephritis, pneumonitis, pancreatitis, non-infectious myocarditis ≥ Grade 3 immune-related events ≥ Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy

Endocrinopathy: Ipilimumab can cause inflammation of the endocrine system organs. The most common clinical presentation includes headaches and fatigue. Other symptoms include visual field defects, behavioural changes, electrolyte disturbances and hypotension. Adrenal crisis can occur.

Patients with severe (Grade 3 or 4) endocrinopathy controlled with hormone replacement therapy may continue with treatment course.

Hepatic impairment:

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Safety has not been studied in patients with hepatic impairment. No specific dose adjustment is necessary in patients with mild hepatic impairment. Administered with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline.

Renal impairment:

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Safety and efficacy has not been studied in patients with renal impairment. No specific dose adjustment is necessary in patients with mild to moderate renal dysfunction. For patients with a GFR below 30ml/min discuss with consultant before commencing treatment.

References:

YERVOY 5 mg/ml concentrate for solution for infusion, Summary of Product Characteristics Bristol-Myers Squibb Pharmaceutical Limited. Available from www.medicines.org.uk/emc/medicine. Last updated 16/01/14.

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.