LONDON CANCER ALLIANCE West and South

Skin Pathway Group – Ipilimumab monotherapy in Melanoma

Indication:

NICE TA319

Ipilimumab is recommended as a possible treatment for adults with advanced (unresectable or metastatic) melanoma that has not been treated before

NICE TA268

Advanced (unresectable or metastatic) melanoma in adults who have received prior therapy
An interval of at least 28 days since treatment with chemotherapy, biochemotherapy, surgery, radiation, or immunotherapy, and recovered from any clinically significant toxicity experienced during treatment is recommended

Avoid treatment with Ipilimumab in patients who have an existing autoimmune disease, or who are receiving immunosuppressive therapy

Ipilimumab re-challenge has not been appraised by NICE and is therefore not commissioned

Regimen details:

Ipilimumab 3mg/kg IV Day 1

Round the dose to the nearest 50mg

Administration:

Ipilimumab as an IV infusion over 90 minutes
Can be given intravenously without dilution, or diluted in Sodium Chloride 0.9% or Glucose 5% to a concentration between 1 – 4 mg/ml.

Flush the line with Sodium Chloride 0.9% or Glucose 5% at the end of the infusion

Version: 1.0 Supersedes: all other versions	Approved by LCA Skin Pathway Chemotherapy Lead: Mark Harries
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl
Prepared by: Ravi Shaunak	Approved by LCA Medicines & Chemotherapy Steering Group Chair:
Second check by: Sanna Eestila	Date prepared: January 2014 Review Date: January 2017

Discontinue Ipilimumab in severe infusion related reaction, and treat appropriately. Ipilimumab may be administered with close monitoring in mild or moderate infusion related reactions. Consider pre-medication with antipyretic (paracetamol) and antihistamine (chlorphenamine)
Full resuscitation facilities and an anaphylaxis kit must be available at all times.

Frequency:

Every 21 days, for 4 doses

- Entire course of 4 doses should be given if 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

Pre-medication: Not routinely required

Anti- emetics: Low emetogenicity
Follow Local Anti-emetic Policy

Supportive medication: Not routinely required

Extravasation: Non-vesicant

Regular investigations:

Prior to the first dose:

FBC	Day 1 (within 14 days)
LFTs	Day 1 (within 14 days)
LDH	Day 1 (within 14 days)
U&Es	Day 1 (within 14 days)
TSH & free T4	Day 1 (within 14 days)

Prior to dose 2, 3, and 4:

FBC	Day 1 (within 72 hours)
LFTs	Day 1 (within 72 hours)
LDH	Day 1 (within 72 hours)
U&Es	Day 1 (within 72 hours)
TSH & free T4	Day 1 (within 72 hours)

Monitor for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy during and before every treatment

Toxicities: Immune related adverse reactions (gastro-intestinal, hepatic, skin, neurological, endocrinology) including most commonly diarrhoea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite, abdominal pain.

DOSE MODIFICATIONS

Haematological Toxicity

Neutrophils (x 10^9/L)		Platelets (x 10^9/L)	Dose
≥ 1.0		≥ 75	100% dose
< 1.0	**or**	< 75	Discuss with the Consultant. Dose delays are not recommended, omit the dose if appropriate

Non-haematological Toxicities

Renal Impairment

The safety and efficacy have not been studied in patients with renal impairment. No specific dose adjustment is recommended in mild to moderate renal function.

CrCl	Ipilimumab dose
≤ 30ml/min	Discuss with the Consultant

Hepatic Impairment

The safety and efficacy have not been studied in patients with hepatic impairment.
Administer with caution if transaminases ≥ 5 x ULN or bilirubin > 3 x ULN at baseline.
Refer to table on modifications for other toxicities below.

Increases in AST and ALT or total bilirubin should be evaluated to exclude causes of hepatic injury, including infections, disease progression or medicinal products. Liver biopsies from patients with immune-related hepatotoxicity have shown evidence of acute infection (neutrophils, lymphocytes, macrophages).

Dose modifications for other toxicities

Management of immune-related adverse reactions may require omission of a dose or permanent discontinuation of Ipilimumab and institution of systemic high-dose corticosteroid or, in some cases, the addition of other immunosuppressive therapy.
Early diagnosis and appropriate management are essential to minimise life threatening complications.

Refer to full Summary of product characteristics (www.medicines.org.uk/emc/) for symptom specific management guidelines in treating immune related toxicities.

Dose reduction is not recommended. Doses that are omitted due to an adverse reaction must not be replaced.

Side Effect	Action
Gastrointestinal: Grade 1 or 2 diarrhoea or colitis Mild to moderate diarrhoea or colitis	1. Treat symptomatically with loperamide and fluid replacement. Assess on daily basis, investigate aetiology 2. If not controlled with medical management above or if persists (5-7days) or recurs then OMIT DOSE until resolved to Grade 1 or Grade 0 (or returns to baseline) 3. If symptoms on-going over 1 week and unresponsive to medical treatment start corticosteroids (consider prednisolone 1mg/kg PO once daily) 4. If symptoms resolve before the next scheduled dose, resume therapy at next scheduled dose 5. If resolution has not occurred before next scheduled dose, continue to omit doses until resolution then resume treatment schedule 6. Discontinue IPILIMUMAB if resolution to Grade 1 or Grade 0 or return to baseline does not occur.
Grade 3 or 4 diarrhoea or colitis Severe symptoms (abdominal pain, severe diarrhoea or significant change in the number of stools, blood in stool, gastrointestinal haemorrhage, gastrointestinal perforation)	1. Permanently discontinue Ipilimumab 2. Refer to SPC for investigations. Management may require initiation of systemic high-dose corticosteroid therapy if demonstrated or suspected to be immune-related. Consider initiating methylprednisolone 2mg/kg/day, tapering slowly once symptoms are controlled. Evaluate for evidence of gastrointestinal perforation or peritonitis.
Hepatic: Moderate elevations in transaminases on treatment AST/ALT > 5 and ≤ 8 ULN And/or Bilirubin > 3 and ≤ 5 ULN Severe elevations in transaminases or bilirubin or symptoms of	1. Omit dose Ipilimumab. Monitor LFTs every 3 days until resolution 2. If LFTs resolve to AST/ALT < 5xULN AND bilirubin < 3 xULN, resume therapy at next scheduled dose. Doses omitted must not be replaced. 3. If resolution has not occurred before next scheduled dose, continue to omit doses until resolution then resume treatment schedule. Doses omitted must not be replaced. 4. Discontinue IPILIMUMAB if resolution does not occur. 1. Permanently discontinue Ipilimumab 2. Refer to SPC for investigations. Management may require

Side Effect	Action
hepatotoxicity AST or ALT > 8 x ULN <u>And/or</u> Total bilirubin > 5 x ULN	initiation of systemic high-dose corticosteroid therapy. Consider initiating methylprednisolone 2mg/kg/day, tapering slowly once elevations are normalised.
Skin: <u>Grade 1 or 2 Skin Reactions</u> E.g. rash, pruritis	1. Continue with Ipilimumab 2. Treat symptomatically with antihistamines and topical steroids 3. If rash persists for 1-2 weeks and does not improve with topical steroids, discuss with consultant and consider oral steroids
<u>Grade 3 Skin Reactions</u> Moderate to severe (Grade 3)[a] skin rash or widespread/intense pruritis regardless of aetiology	1. Omit any scheduled dose of Ipilimumab until the adverse reaction resolved to Grade 1 or Grade 0 (or returns to baseline). 2. Treat symptomatically with antihistamines and topical steroids 3. If rash persists for 1-2 weeks and does not improve with topical steroids, discuss with consultant and consider oral steroids (prednisolone 1mg/kg PO once daily) 4. If symptoms resolve to grade 0-1 before the next scheduled dose, resume therapy at next scheduled dose. Dose omitted must not be replaced. 5. If resolution has not occurred before next scheduled dose, continue to omit doses until resolution then resume treatment schedule. 6. Discontinue IPILIMUMAB if resolution to Grade 1 or Grade 0 or return to baseline does not occur.
<u>Grade 3 Pruritis or Grade 4</u> Life threatening skin rash (including Stevens-Johnson syndrome or toxic epidermal necrolysis) or severe widespread pruritis interfering with activities of daily living or requiring medical intervention	1. Permanently discontinue Ipilimumab 2. Management may require initiation of systemic high-dose corticosteroid therapy. Consider initiating methylprednisolone 2mg/kg/day, tapering slowly once rash or pruritis is controlled.
Neurological: <u>Grade 2 Motor Neuropathy</u> Moderate (Grade 2)[a] unexplained	1. Omit any scheduled dose of Ipilimumab until the adverse reaction resolved to Grade 1 or Grade 0 (or returns to

Side Effect	Action
motor neuropathy, muscle weakness, or sensory neuropathy (lasting more than 4 days)	baseline). 2. If resolution occurs before the next scheduled dose, resume therapy at next scheduled dose. 3. If resolution has not occurred before next scheduled dose, continue to omit doses until resolution then resume treatment schedule. 4. Discontinue IPILIMUMAB if resolution to Grade 1 or Grade 0 or return to baseline does not occur.
<u>Grade 3 or 4 motor or sensory neuropathy</u> New onset or worsening severe motor or sensor neuropathy	1. Permanently discontinue Ipilimumab 2. Management may require initiation of systemic high-dose corticosteroid therapy. Consider initiating methylprednisolone 2mg/kg/day. 3. Consider neurological referral for sensory neuropathy. Be aware of the need for ITU support for motor neuropathy affecting respiratory muscles.
Endocrine: Severe adverse reactions in the endocrine glands, such as hypophysitis and thryoiditis that are not adequately controlled with hormone replacement therapy or high-dose immunosuppressive therapy	1. Refer to SPC for management of • Signs of adrenal insufficiency but patient not in adrenal crisis • Signs of adrenal crisis • Pituitary imaging or lab tests of endocrine function abnormal If pituitary imaging or lab tests are abnormal, consider a short course of dexamethasone 4mg 6-hourly to treat the inflammation of the gland, tapering slowly (over at least one month) once symptoms improved. Long-term hormone replacement therapy may be necessary
Other organ systems: Uveitis, easinophilia, lipase elevation, glomerulonephritis, iritis, haemolytic anaemia, amylase elevations, multi-organ failure, pneumonitis	1. Omit dose until the adverse reaction resolved to Grade 2 or Grade 0 (or returns to baseline). 2. If resolution occurs before the next scheduled dose, resume therapy at next scheduled dose. 3. If resolution has not occurred before next scheduled dose, continue to omit doses until resolution then resume treatment schedule. 4. Discontinue IPILIMUMAB if resolution to Grade 1 or Grade 0 or return to baseline does not occur. Treat Ipilimumab related uveitis, iritis or episcleritis with topical corticosteroid eye-drops.

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Side Effect	Action
Severe Adverse Reactions (e.g. nephritis, pneumonitis, pancreatitis, non-infectious myocarditis) • ≥ Grade 3 immune-related events[c] • ≥ Grade 2 for immune-related eye disorders not responding to topical immunosuppressive therapy	1. Permanently discontinue Ipilimumab 2. Consider immediate high-dose corticosteroid therapy if demonstrated or suspected to be immune-related.

Location of regimen delivery:	Day-case setting Availability of resuscitation equipment must be ensured as a standard precaution
Comments:	Each millilitre of concentrate contains 0.1mmol sodium, which is 2.30mg sodium. To be taken into consideration with controlled sodium diet. Adequate contraception methods should be applied during therapy, and for up 8 weeks after completing the treatment.
Drug interactions:	Baseline systemic corticosteroids, initiated before starting Ipilimumab, should be avoided. Anticoagulants- increased risk of GI haemorrhage, monitor closely. Vaccinations should not be administered for 4 weeks before and after Ipilimumab.
References:	www.medicines.org.uk Micromedex review: Ipilimumab, accessed Sept-11