LONDON CANCER ALLIANCE West and South

Skin Pathway Group – Pembrolizumab monotherapy in Melanoma

Indication:

NICE TA366 Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in adults who have not been treated with ipilimumab before.

NICE TA357 For treating advanced (unresectable or metastatic) melanoma in adults who have progressed with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor.

Regimen details: Pembrolizumab 2mg/kg IV Day 1

Round the dose to the nearest 50mg

Administration: Pembrolizumab as an IV infusion over 30 minutes
Given intravenously in 100ml Sodium Chloride 0.9% or Glucose 5% to a concentration between 1 – 10 mg/ml.

Discontinue pembrolizumab in Grade 3-4 infusion related reactions, and treat appropriately. Pembrolizumab may be administered with close monitoring in mild or moderate infusion related reactions.
Full resuscitation facilities and an anaphylaxis kit must be available at all times.

Frequency: Every 21 days, until progression or unacceptable toxicity

Pre-medication: Consider pre-medication with antipyretic (paracetamol) and antihistamine (chlorphenamine) for infusion related reactions.

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

Version: 2.0 Supersedes: all other versions	Approved by LCA Skin Pathway Chemotherapy Lead: Mark Harries 22/12/15
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla and Rebecca Johl 21/01/2016
Prepared by: Melanie Dalby	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jatinder Harchowal 21/01/2016
Second check by: Lisa Yuen	Date prepared: November2015 Review Date: November 2017

Supportive medication: Not routinely required, however patients should be counselled to report side effects (e.g. diarrhoea) early to allow for prompt intervention.

Extravasation: Non-vesicant

Regular investigations:

Prior to the first dose:

FBC	Day 1 (within 14 days)
LFTs	Day 1 (within 14 days)
U&E and glucose	Day 1 (within 14 days)
HIV and Hepatitis serology	

Prior to Day 1 (all cycles):

FBC	Day 1 (within 72 hours)
LFTs	Day 1 (within 72 hours)
U&E and glucose	Day 1 (within 72 hours)

Patients should have regular assessment of endocrine function

Toxicities: Immune related adverse reactions (gastro-intestinal, hepatic, lung, skin, neurological, endocrinology, nephrological) 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		≥ 50	100% dose
≤ 0.5	**or**	≤ 25	Discuss with the Consultant. Dose delays are not recommended, consider discontinuation

Non-haematological Toxicities

Renal Impairment No specific dose adjustment is recommended in mild to moderate renal function. Pembrolizumab has not been studied in patients with severe renal impairment.

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CrCl	Pembrolizumab dose
≤ 30ml/min	Discuss with Consultant

Hepatic Impairment

No specific dose adjustment is recommended in mild hepatic impairment.
Pembrolizumab has not been studied in patients with moderate or severe hepatic impairment.

Dose modifications for other toxicities

Most immune-related adverse reactions occurring during treatment with pembrolizumab are reversible and can be managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab.
For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.

Side Effect	Action
Gastrointestinal: <u>Grade 1 or 2 diarrhoea or colitis</u> Mild to moderate diarrhoea or colitis	1. Monitor for signs and symptoms of colitis 2. Withhold for grade 2 3. Corticosteriods should be administered for grade ≥ 2 events (prednisolone 1-2mg/kg or equivalent with a taper)
<u>Grade 3 or 4 diarrhoea or colitis</u> Severe symptoms (abdominal pain, severe diarrhoea or significant change in the number of stools, blood in stool, gastrointestinal haemorrhage, gastrointestinal perforation)	1. Withhold pembrolizumab for grade 3 colitis and permanently discontinued for grade 4 2. Corticosteriods as above 3. The potential risk of gastrointestinal perforation should be taken into consideration
Hepatic:	1. Monitor for changes in liver function and symptoms of hepatitis

Side Effect	Action
Hepatitis	2. Corticosteroids should be administered (initial dose of 0.5-1 mg/kg/day [for Grade 2 events] and 1-2 mg/kg/day (for Grade ≥ 3 events) prednisolone or equivalent followed by a taper) 3. Withold pembrolizumab if AST/ALT > 3-5 x ULN or bilirubin > 1.5-3 x ULN with hepatitis 4. Discontinue pembrolizumab if AST/ALT > 5 x ULN or bilirubin > 3 x ULN with hepatitis
Lung: Pneumonitis	1. Monitor for signs and symptoms 2. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded 3. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisolone or equivalent followed by a taper) 4. Pembrolizumab should be withheld for Grade 2 pneumonitis, and permanently discontinued for Grade 3, Grade 4 or recurrent Grade 2 pneumonitis
Renal: Nephritis	1. Monitor for changes in renal function, and exclude other causes of renal dysfunction. 2. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisolone or equivalent followed by a taper) and, based on severity of creatinine elevations, pembrolizumab should be withheld for Grade 2 with creatinine > 1.5-3 x ULN, and permanently discontinued for Grade 3 or Grade 4 nephritis with creatinine > 3 x ULN.
Endocrine: Severe adverse reactions in the endocrine glands, such as hypophysitis, T1DM, diabetic ketoacidosis, hypo and hyperthyroidism that are not adequately controlled with hormone replacement therapy or high-dose immunosuppressive therapy	1. Withold treatment in patients with: a. symptomatic hypophysitis b. type 1 diabetes associated with hyperglycaemia (glucose > 13.9 mmol/L) or associated with ketoacidosis c. Grade ≥ 3 hyperthyroidism 2. Continuation of pembrolizumab may be considered if endocrinopathies improve to grade 2 or lower and is controlled with hormone replacement or after corticosteriod tapering. 3. Hypothyroidism may be managed with replacement therapy without treatment interruption.
Other organ systems:	1. Based on the severity of the adverse reaction,

Side Effect	Action
uveitis, arthritis, myositis, pancreatitis, severe skin reactions, myasthenic syndrome, optic neuritis, rhabdomyolysis, haemolytic anaemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma	pembrolizumab should be withheld and corticosteroids administered. 2. Pembrolizumab may be restarted within 12 weeks after the last dose if the adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisolone or equivalent per day. 3. Pembrolizumab must be permanently discontinued for any Grade 3 immune related adverse reaction that recurs and for any Grade 4 immune related adverse reaction toxicity or if prednisolone cannot be reduced within 12 weeks.

Location of regimen delivery:	Day-case setting Availability of resuscitation equipment must be ensured as a standard precaution Adequate contraception methods should be applied during therapy, and for at least 4 months after the last dose.
Comments:	All patients must be provided with the Patient Alert Card with each prescription as per the marketing authorisation. All prescribers must be familiar with the Physician Information and Management Guidelines for pembrolizumab.
Drug interactions:	The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided wherever possible because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.
References:	www.medicines.org.uk, accessed Oct 2015 NICE TA357 NICE TA366 Robert. C, et al. Pembrolizumab versus Ipilimumab in advanced melanoma. (2015) N Engl J Med 2015; 372:2521-2532

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