IPILIMUMAB & NIVOLUMAB
combination immunotherapy x 4 cycles

For the treatment of advanced (unresectable or metastatic) melanoma in immunotherapy-naïve patients (NICE 2016)

Blueteq registration is required before treatment may start

Drugs/Dosage:	Nivolumab	1mg/kg IV	Day 1 every 3 weeks for 4 cycles
	plus		*(then continue with nivolumab monotherapy)*
	Ipilimumab	3mg/kg IV	

Administration:

Nivolumab should be given first, in 100ml 0.9% sodium chloride over 60 minutes
then
Ipilimumab in a minimum of 90ml sodium chloride 0.9% and infused over 90 minutes
Administer both agents via a 0.2 – 1.2 micron in-line filter.
A new filter should be used for the ipilimumab.

Infusion-related reactions:

If a patient experiences a mild or moderate infusion-related reaction to either agent, decrease the rate of infusion and monitor closely. Give any further doses with close monitoring. Premedication with paracetamol and chlorphenamine should be considered for further doses.

In case of a severe infusion reaction to either agent, the infusion must be discontinued and appropriate medical therapy administered.

Frequency:

Ipilimumab and nivolumab combination immunotherapy every 3 weeks for 4 cycles only.
Review for toxicities before each cycle.
In addition, it is very important that the patient is educated to immediately report any key signs or symptoms to the treating oncology team (see Comments)

3 weeks *after the 4th cycle is administered, continue with nivolumab monotherapy every 2 weeks, according to the Alliance Nivolumab protocol, for as long as clinical benefit is observed or until no longer tolerated.*

Main Toxicities:

The most common immune-related reactions are: diarrhoea, rash, pruritis, abdominal pain, abnormal hepatic function, hypothyroidism, hypopituitarism, confusion, peripheral neuropathy, blurred vision, eye pain, hypotension, flushing, arthralgia, myalgia

Anti- emetics:

mildly emetogenic

Extravasation:

non-vesicants

Regular Investigations:

FBC	before each dose
U&Es & LFTs	before each dose, and as indicated
Random blood glucose	before each dose
LDH	before each dose
Thyroid function*	every 3 weeks
Random cortisol	every 3 weeks

**to avoid treatment delays, use previous results for prescribing purposes, if previous result was within normal limits and no current concerns*

Reason for Update: details for toxicity management removed; blood test cut-offs added	Approved by Consultant: Dr M Ajaz
Version: 3	Approved by Lead Chemotherapy Nurse: S Wills-Percy
Supersedes: Version 2	Date: 12.10.17
Prepared by: S Taylor	Checked by: C Tucker

Comments:

Patients must be given a Nivolumab (Opdivo™) patient alert card and an Ipilimumab (Yervoy™) patient alert card, and be advised to contact the oncology team or the 24 hour hot-line immediately they experience any side effect, as some side effects worsen rapidly.

Patients may be given a supply of loperamide, along with counselling to contact the oncology team in the event of any diarrhoea.

Prompt management of side effects can ensure that the patient continues with treatment.

Dose Delays and Toxicity Management:

Any diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash or endocrinopathy must be considered immunotherapy-related and managed appropriately to minimise life-threatening complications.

For detailed guidelines for the management of immune-related adverse events, please refer to the Alliance "Guidelines for Management of Immunotherapy-Related Adverse Events" document.

With regards to blood tests, proceed with next cycle of immunotherapy if:
Platelets ≥ 75 x 10^9/l and Neutrophils ≥ 1.0 x 10^9/l
and
AST/ALT ≤ 3 x ULN
and
Serum creatinine ≤ 1.5 x baseline
and
TSH / free T_4 within range, or no change from baseline

Immunotherapy may be restarted within 12 weeks after the last dose, only if an adverse reaction remains at Grade ≤ 1 and the corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

Renal Impairment:

No ipilimumab or nivolumab dose adjustment is required in patients with mild or moderate renal impairment. Data from patients with severe renal impairment (CrCl < 30ml/min) are too limited to draw conclusions.

Hepatic Impairment:

If ALT/AST ≥ 5 x ULN or bilirubin > 3 x ULN at baseline, use ipilimumab only with caution, as there is no data on this population.
No nivolumab dose adjustment is required in mild hepatic impairment. Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions. Nivolumab must be administered with caution in patients with moderate or severe hepatic impairment, i.e. bilirubin > 1.5 x ULN and any AST.

Reference:

Larkin, J et al; NEJM 2015; 373: 23 - 34