IPILIMUMAB & NIVOLUMAB for melanoma

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

**Blueteq registration is required before treatment may start**

<table>
<thead>
<tr>
<th>Drugs/Dosage:</th>
<th>Nivolumab 1mg/kg IV</th>
<th>Day 1 every 3 weeks for 4 cycles (then continue with nivolumab monotherapy)</th>
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<tbody>
<tr>
<td></td>
<td>Ipiilimumab 3mg/kg IV</td>
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**Administration:**
- Nivolumab should be given first, in 100ml 0.9% sodium chloride over 30 minutes
- Ipiilimumab in 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, they may continue to receive treatment, but with close monitoring for all future doses.
- Premedication with paracetamol and chlorphenamine should also 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:**
- Ipiilimumab 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)

*After the 4th cycle is administered, continue with nivolumab monotherapy 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: made clear for melanoma only; alert card wording updated; nivolumab over 30 minutes; volume for ipl removed

Approved by Consultant: Dr T Crook

Version: 4

Approved by Lead Chemotherapy Nurse: E Masters

Supersedes: Version 3

Date: 7.5.19

Prepared by: S Taylor

Checked by: H Kimber
Comments: Patients must be given an Immunotherapy 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. Prompt management of side effects can ensure that the patient continues with treatment.

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

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 $\geq 75 \times 10^9$/l and Neutrophils $\geq 1.0 \times 10^9$/l
and
AST/ALT $\leq 3 \times$ ULN
and
Serum creatinine $\leq 1.5 \times$ 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 $\leq 1$ and the corticosteroid dose has been reduced to $\leq 10$ mg prednisone or equivalent per day.

If dosing is resumed after a delay, either the combination treatment or nivolumab monotherapy could be resumed, based on the evaluation of the individual patient.

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 $\geq 5 \times$ ULN or bilirubin $> 3 \times$ 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 $> 1.5 \times$ ULN and any AST.

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