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| **Indication** | Advanced (unresectable or metastatic) melanoma in adult patients as per criteria in commissioning circular |
| **Treatment Intent** | Palliative |
| **Frequency and number of cycles** | **First Phase**: Every 21 days **for the first 4 cycles.**<br>**Second Phase:** Every 14 days NB an alternative 28-day schedule may be used, see below<br><br>Continue until progressive disease or unacceptable toxicity.<br><br>NB: Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed. |
| **Monitoring Parameters pre-treatment** | • **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion.<br>• Monitoring parameters for **First phase only,** for Second Phase see KMCC SACT protocol MULTI-001.<br>• Monitor FBC, U&Es, LFTs and LDH at each cycle.<br>• Prior to treatment neuts must be >/=1.5 and PLT>/=100 otherwise d/w consultant.<br>• During treatment, if neuts <1.0 and/or PLT <50 d/w consultant.<br>• Thyroid function must be assessed at baseline and then before cycle 2 and cycle 4.<br>• Cortisol monitoring should be undertaken in line with ESMO immunotherapy toxicity guidance available on KMCC website (see link below). Cortisol level should not be taken within 24 hours of the last steroid dose.<br>• **Renal impairment:** No specific dose adjustment of either agent is necessary in patients with mild to moderate renal impairment. Severe renal impairment d/w consultant.<br>• **Hepatic impairment**. No dose adjustment of either drug in mild hepatic impairment. Use with caution in patients with moderate or severe hepatic impairment. No data for use of ipilimumab when ALT/AST >/=5 x ULN or bilirubin >/= 3 x ULN at baseline.<br>• Use with caution in patients with a baseline performance score >/= 2, active brain metastases, autoimmune disease, patients with ocular/uveal melanoma and patients who have had a Grade 4 adverse reaction that was related to anti-CTLA-4 therapy.<br>• Immunosuppressants should not be used during treatment (unless to treat immune-related adverse reactions).<br>• The use of systemic corticosteroids before starting treatment should be avoided.<br>• **Dose Modification:**<br>  ○ Dose escalation or reduction is not appropriate. Dosing delay or discontinuation may be required based on individual safety and tolerability.<br>  ○ If either agent is withheld, the other agent should also be withheld. 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.<br>• **Infusion-related reactions:** In the event of severe infusion-related reactions, discontinue Ipilimumab or nivolumab and administer appropriate treatment. In the event of a mild or moderate reaction, treatment may be continued with close monitoring. Pre-medication with paracetamol and chlorphenamine should be considered for subsequent treatment. |

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| | • **Immune- related reactions:**<br>  ○ Most common reactions are pneumonitis, colitis, nephritis, hepatitis, hyperthyroidism, hypothyroidism, hypophysitis, diabetes, diabetic ketoacidosis, immune-related rash, hypopituitarism, confusion, peripheral neuropathy, blurred vision, eye pain, hypotension, flushing, arthralgia, myalgia.<br>  ○ If corticosteroids are used to treat an immune related reaction they should be tapered over at least 1 month. Treatment should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.<br>  ○ For guidance on managing immune-related adverse reactions, refer to SPC and guidelines available on KMCC website: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/<br>• **Cardiac adverse events** and pulmonary embolism have also been reported with combination therapy. Nivolumab in combination with ipilimumab should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions.<br>• **Gastrointestinal disorder:** These post-marketing reports have included fatalities. Patients on ipilimumab who present with diarrhoea/other colitis symptoms, and those who do not respond to steroids for immune-related colitis, should be investigated to exclude other causes, including infections such as CMV.<br>• **Haemophagocytic lymphohistiocytosis (HLH**) has been observed with nivolumab in combination with ipilimumab. If HLH is confirmed, administration of nivolumab in combination with ipilimumab should be discontinued and treatment for HLH initiated.<br>• **Common drug interactions (for comprehensive list refer to BNF/SPC):** The use of anticoagulants is known to increase the risk of gastrointestinal haemorrhage. Since gastrointestinal haemorrhage is an adverse reaction with ipilimumab, patients on anticoagulation therapy should be closely monitored.<br>• **Driving:** Nivolumab and ipilimumab can potentially cause fatigue in some patients and therefore use caution when driving or using machines.<br>• Each ml of ipilimumab and nivolumab contains 0.1mmol (or 2.3mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet.<br>• The patient should be provided with the OPDIVO® Patient Alert card and a copy of the Yervoy® patient brochure and alert card with each prescription (to be carried until 1 year after completion of treatment).<br>• Patients must 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.<br>• Patients should be monitored (for at least up to 5 months after the last dose) for immune related adverse reactions as these can occur any time during or after stopping treatment with combination therapy. |
| **References** | KMCC protocol SKI-009 v3 SPC accessed online 12.10.2023 |

NB For funding information, refer to CDF and NICE Drugs Funding List

**First phase: every 21 days for 4 cycles**

| Day | Drug | Dose | Route | Infusion Duration | Administration |
|---|---|---|---|---|---|
| 1 | Metoclopramide | 20mg | PO | | stat |
| | **NIVOLUMAB** | **1mg/kg** | IV | 30 min | Can be given undiluted or diluted in sodium chloride 0.9%. The diluted solution should have a final concentration of 1 to 10mg/ml<br><br>Give via in-line low protein binding 0.2 micrometre filter.<br><br>Flush the line with sodium chloride 0.9% for injection at the end of the infusion<br><br>**Use separate filters for each infusion.** |
| | **IPILIMUMAB** | 3mg/kg | IV | 30 min | Administer undiluted or diluted with 0.9% sodium chloride to a concentration of 1-4mg/ml usually diluted in 100ml 0.9% sodium chloride<br>Give via in-line low protein binding 0.22 micrometre filter.<br><br>Flush the line with sodium chloride 0.9% for injection at the end of the infusion.<br><br>**Use separate filters for each infusion.** |
| TTO | Drug | Dose | Route | Directions | |
| Day 1 | Metoclopramide | 10mg | PO | 10mg up to 3 times a day as required. (max. 30mg per day including 20mg pre-chemo dose)<br>Do not take for more than 5 days continuously. | |

**Phase 2 starts 3 weeks after 4th cycle of combination treatment: every 14 days (continue until PD or unacceptable toxicity)**

| Day | Drug | Dose | Route | Infusion Duration | Administration |
|---|---|---|---|---|---|
| 1 | Metoclopramide | 20mg | PO | | stat |
| | **NIVOLUMAB** | **240mg** | IV | 30 min | Can be given undiluted or diluted.<br>If diluted, give in 100ml Sodium Chloride 0.9% via in-line low- protein binding 0.2 micrometre filter. The diluted solution should have a final concentration ranging from 1 to 10mg/mL<br>**Flush the line with sodium chloride 0.9% for injection at the end of the infusion.** |
| TTO | Drug | Dose | Route | Directions | |
| Day 1 | Metoclopramide | 10mg | PO | 10mg up to 3 times a day as required. (max. 30mg per day including 20mg pre-chemo dose)<br>Do not take for more than 5 days continuously. | |

**Alternative schedule for Phase 2 – starts 6 weeks after the last dose of the combination of nivolumab and ipilimumab. Repeated every 28 days**

| Day | Drug | Dose | Route | Infusion Duration | Administration |
|---|---|---|---|---|---|
| 1 | Metoclopramide | 20mg | PO | | stat |
| | **NIVOLUMAB** | **480mg** | IV | 30min | Can be given undiluted or diluted.<br>If diluted, give in100ml Sodium Chloride 0.9% via in-line low- protein binding 0.2 micrometre filter. The diluted solution should have a final concentration ranging from 1 to 10mg/mL<br>**Flush the line with sodium chloride 0.9% for injection at the end of the infusion** |
| TTO | Drug | Dose | Route | Directions | |
| Day 1 | Metoclopramide | 10mg | PO | 10mg up to 3 times a day as required. (max. 30mg per day including 20mg pre-chemo dose)<br>Do not take for more than 5 days continuously. | |

NB: If patients need to be switched from the 240 mg every 2 weeks schedule to the 480 mg every 4 weeks schedule, the first 480 mg dose should be administered two weeks after the last 240 mg dose. Conversely, if patients need to be switched from the 480 mg every 4 weeks schedule to the 240 mg every 2 weeks schedule, the first 240 mg dose should be administered four weeks after the last 480 mg dose.