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.** **Second Phase :** Every 14 days NB An alternative 28 day schedule may be used, see below Continue until progressive disease or unacceptable toxicity. 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	• 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. • Monitor FBC, U&Es, LFTs and LDH at each cycle. • Prior to treatment neuts must be >/=1.5 and PLT>/=100 otherwise d/w consultant. During treatment, if neuts <1.0 and/or PLT <50 d/w consultant. • Thyroid function and 9am cortisol level must be assessed at baseline and then before cycle 2 and cycle 4. • 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. • 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. • 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. • Immunosuppressants should not be used during treatment (unless to treat immune-related adverse reactions). • The use of systemic corticosteroids before starting treatment should be avoided. • Dose escalation or reduction is not appropriate. Dosing delay or discontinuation may be required based on individual safety and tolerability. For guidance on permanent discontinuation or withholding of doses refer to the guidelines for the management of immune-related adverse reactions following immunotherapy available at http://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/sact-pathways-guidelines-for-the-management-of-sact-induced-adverse-reactions-and-nursing/ • Immune- related reactions: ○ 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. ○ 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. • 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. • 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. • 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. • Nivolumab can potentially cause fatigue in some patients and therefore use caution when driving or using machines. • 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).
Post treatment observation (if required)	• 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. • 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.
Reference(s)	SpC accessed 9/5/17, St Luke's Cancer Alliance protocol Ipilimumab & Nivolumab
Comments	Guidelines for the management of immune-related adverse reactions following immunotherapy are available at http://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/sact-pathways-guidelines-for-the-management-of-sact-induced-adverse-reactions-and-nursing/

First phase: every 21 days for 4 cycles

	Drug	Dose	Route	InfusionTime	Administration Details
	Metoclopramide	20mg	po		
	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 Give via in-line low protein binding 0.2 micrometre filter. Flush the line with sodium chloride 0.9% for injection at the end of the infusion **Use separate filters for each infusion.**
	Ipilimumab	3mg/kg	IV	90 minutes	In 100ml 0.9% sodium chloride Give via in-line low protein binding 0.22 micrometre filter. Flush the line with sodium chloride 0.9% for injection at the end of the infusion. **Use separate filters for each infusion.**
TTO	Drug	Dose	Route	Directions	
	Metoclopramide	10mg	po	up to 3 times a day for 3 days, then 10mg up to 3 times a day as required (max. 30mg per day including 20mg pre-chemo dose)	
	Loperamide	2-4mg	po	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified.	

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

Day	Drug	Dose	Route	InfusionTime	Administration Details
	Metoclopramide	20mg	po		
	Nivolumab	**240mg**	IV	30 min	Can be given undiluted or diluted. 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 **Flush the line with sodium chloride 0.9% for injection at the end of the infusion.**
TTO	Drug	Dose	Route	Directions	
	Metoclopramide	10mg	po	up to 3 times a day for 3 days, then 10mg up to 3 times a day as required (max. 30mg per day including 20mg pre-chemo dose)	
	Loperamide	2-4mg	po	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified.	

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	InfusionTime	Administration Details
	Metoclopramide	20mg	po		
	Nivolumab	**480mg**	IV	60 min	Can be given undiluted or diluted. 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 **Flush the line with sodium chloride 0.9% for injection at the end of the infusion**
TTO	Drug	Dose	Route	Directions	
	Metoclopramide	10mg	po	up to 3 times a day for 3 days, then 10mg up to 3 times a day as required (max. 30mg per day including 20mg pre-chemo dose)	
	Loperamide	2-4mg	po	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified.	

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.