

Protocol Contains CHECKPOINT INHIBITOR IMMUNOTHERAPY	
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: Combination treatment: repeat every 21 days for the first 4 cycles. Second Phase: Nivolumab monotherapy can be given either: Every 14 days at a dose of 240mg IV (schedule 1). Or every 28 days at a dose of 480mg IV (schedule 2) or 1200mg SC (schedule 3). 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	• 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. • Monitoring parameters for First phase only, for Second Phase see KMCC SACT protocol MULTI-001. • Monitor FBC, U&Es, LFTs and LDH at each cycle. • Pre-treatment cardiac assessment: ○ ECG baseline and as clinically indicated. ○ Check BNP, and Troponin T prior to treatment. • Random blood glucose on day 1 each cycle. • Prior to treatment neuts must be ≥ 1.5 and $PLT \geq 100$ otherwise d/w consultant. • During treatment, if neuts < 1.0 and/or $PLT < 50$ d/w consultant. • Thyroid function must be assessed at baseline and then before cycle 2 and cycle 4. • 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. • 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 $ALT/AST \geq 5 \times ULN$ or bilirubin $\geq 3 \times ULN$ at baseline. • Recommended for use in patient with a performance status of 0-1, if patients have brain metastases this should be stable or asymptomatic. Use with caution in patients with 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 Modification: ○ Dose escalation or reduction is not appropriate. Dosing delay or discontinuation may be required based on individual safety and tolerability.

Protocol No	SKI-009	Kent and Medway SACT Protocol Disclaimer: No responsibility will be accepted for the accuracy of this information when used elsewhere.	
Version	V5	Written by	M. Archer
Supersedes version	V4	Checked by	C. Waters D. Midda
Date	21.09.2026	Authorising consultant (usually NOG Chair)	S. Qureshi

	○ 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. ● Nivolumab Sub cutaneous administration: ○ If SC Injection is being prepared on the ward, Trust SOP should be followed. ○ Remove from fridge and allow to reach room temperature before administration. ○ The solution for injection should NOT be diluted or mixed with other medicinal products. ○ A syringe, a transfer needle, and a hypodermic injection needle (23G-25G) are needed to withdraw the medicinal product from the vial and inject it subcutaneously. ○ Administer the full contents of the syringe. ○ Inject into the subcutaneous tissue of the abdomen or thigh only, over 3 to 5 minutes. ○ Do not inject at other sites of the body. ○ Injection site should be alternated between left and right thigh/abdomen for successive injections. ○ New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or where there are scars or moles. ○ During the treatment other medicinal products for subcutaneous administration should preferably be injected at different sites. ● Infusion / injection related reactions: In the event of severe infusion / injection 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. ● 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. ○ 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/ ● 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. ● 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. ● 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. ● 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.
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	• Driving: Nivolumab and ipilimumab can potentially cause fatigue in some patients and therefore use caution when driving or using machines. • 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. • The patient should be provided with the appropriate OPDIVO® Patient Alert card and a copy of the Yervoy® patient brochure and alert card with each prescription (to be carried until at least 5 months after completion of treatment). • 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.
References	KMCC protocol SKI-009 V4 SPC accessed online 07.10.2025 CDF list V1.374 accessed online 07.10.2025

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

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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 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	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 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	
Day 1	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously.	

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Phase 2: Schedule 1 IV administration- starts 3 weeks after the last dose of the combination of nivolumab and ipilimumab: Repeated 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. 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 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) Do not take for more than 5 days continuously.	

Alternative schedule for Phase 2: Schedule 2 IV administration – 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. 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 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) Do not take for more than 5 days continuously.	

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

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Alternative schedule for Phase 2: Schedule 3 SC administration –**starts 6 weeks after the last dose of the combination of nivolumab and ipilimumab. Repeated every 28 days**

Day	Drug	Dose	Route	Injection Time	Administration Details
1	Metoclopramide	20mg	PO		
	NIVOLUMAB	1200mg	SC	3 to 5 mins	Inject into the subcutaneous tissue of the left or right thigh or abdomen. Do not inject at other sites of the body. Injection sites should be rotated for successive injections.
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) Do not take for more than 5 days continuously.	

Nivolumab may be given SC at a dose of 600mg every 2 weeks if clinically necessary. If patients need to be switched from the SC 1200mg every 4 weeks schedule to the SC 600mg every 2 weeks schedule, the first SC 600mg dose should be administered four weeks after the last SC 1200mg dose.

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