Protocol Contains CHECKPOINT INHIBITOR IMMUNOTHERAPY	
Indication	For the treatment of previously untreated metastatic or locally advanced and inoperable colorectal cancer with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), confirmed to be wild type or mutant RAS and wild type or mutant BRAF. NB patients may have received neoadjuvant systemic therapy for non-metastatic disease and/or adjuvant chemotherapy after surgery. NB the patient cannot have received prior treatment with an anti-PD-1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless the patient was enrolled in the NEOPRISM-CRC clinical trial and did not have clear evidence of radiologically-assessed progressive disease at the end of neoadjuvant pembrolizumab therapy. Also, this combination of nivolumab plus ipilimumab is **not funded** after previous treatment with pembrolizumab for MSI-H or dMMR metastatic colorectal cancer.
Treatment Intent	Palliative
Frequency and number of cycles	**First phase:** Combination treatment. Repeat every 21 days for a maximum of 4 cycles. **Second Phase:** Nivolumab monotherapy every 4 weeks at a dose of 480mg IV (schedule 1) or 1200mg SC (schedule 2). To continue until progressive disease or unacceptable toxicity or patient choice to discontinue treatment or on completion of 2 calendar years of treatment, whichever occurs first.

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>/=100 otherwise d/w consultant. During treatment, if neuts <1.0 and/or PLT <75 d/w consultant.
	• Thyroid function must be assessed at baseline then every 6-8 weeks or as clinically indicated.
	• 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.
	• **Hepatic impairment:** No dose adjustment of either agent in mild hepatic impairment. Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions on these populations.
	Nivolumab must be administered with caution in patients with moderate (total bilirubin > 1.5 × to 3 × the upper limit of normal [ULN] and any AST) or severe (total bilirubin > 3 × ULN and any AST) hepatic impairment.
	Ipilimumab must be administered with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline.

- **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.
- Patients with known brain metastases should be symptomatically stable prior to starting nivolumab in combination with ipilimumab.
- **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 should be considered for subsequent treatment.
- **Immune- related reactions:**
  - Most common reactions are pneumonitis, colitis, hepatitis, nephritis hyperthyroidism, hypothyroidism, hypophysitis, diabetes, diabetic ketoacidosis, immune-related rash, hypopituitarism, confusion, peripheral neuropathy, blurred vision, eye pain, hypotension, flushing, arthralgia, and myalgia.
  - Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported. For signs or symptoms of SJS or TEN, nivolumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, nivolumab should be permanently discontinued.
  - 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/
- **Management of adverse reactions and dose adjustments:**
  - **Dose Modification:** 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 SPC.
  - 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 and/or with ipilimumab should be permanently discontinued for Grade 4 or recurrent Grade 3 adverse reactions or persistent Grade 2 or 3 adverse reactions despite management, unless otherwise stated in SPC. Treatment must also be permanently

	discontinued if corticosteroid dosing cannot be reduced to < 10mg prednisolone or equivalent per day. o If nivolumab has to be discontinued as a consequence of toxicity, ipilimumab must also be stopped. o If ipilimumab has to be discontinued as a consequence of toxicity, nivolumab can be continued as monotherapy (in which case consult the nivolumab SmPC for guidelines on the management of immune-related adverse reactions). • **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. • Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. • **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. • **Gastrointestinal disorder**: These post-marketing reports have included fatalities. Patients 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. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** o The use of anticoagulants is known to increase the risk of gastrointestinal haemorrhage. Since gastrointestinal haemorrhage is an adverse reaction with ipilimumab, patients who re-quire concomitant anticoagulant therapy should be monitored closely. o The use of systemic corticosteroids and other immunosuppressants at baseline, before starting treatment, should be avoided, however, systemic corticosteroids and other immunosuppressants can be used after starting treatment to treat immune-related adverse reactions. • Each ml of nivolumab contains 0.1mmol (or 2.5mg) sodium and each ml of ipilimumab contains 0.1mmol (or 2.3mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet. • **Driving:** Nivolumab and ipilimumab can potentially cause fatigue in some patients and therefore use caution when driving or using machines. • Patients treated with nivolumab in combination with ipilimumab must be given the appropriate patient alert card (to be carried until at least 5 months after the last dose of treatment) and be informed about the risks of nivolumab and ipilimumab which may occur during or after discontinuation of treatment.
References	CDF list V1.379 accessed online 08.12.2025 KMCC protocol COL-046 V1 10.06.2025 Colorectal NOG agree to only offer 4 weekly nivolumab monotherapy.

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

Phase 1: Cycle 1-4 combination therapy.

Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Metoclopramide	20mg	PO		
	NIVOLUMAB	**240mg**	IV	30 mins	Can be given undiluted or diluted in sodium chloride 0.9%. If diluted, give in 100ml Sodium Chloride 0.9% via in-line low- protein binding 0.22 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. **Use separate filters for each infusion.**
	IPILIMUMAB	**1mg/kg**	IV	30 mins	Administer undiluted or diluted with 0.9% sodium chloride to a concentration of 1-4mg/ml (usually diluted in 50ml) 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.	

Phase 2 Cycle 5 onwards: Schedule 1 IV administration- Repeat every 28 days - starts 3 weeks after the last dose of the combination of nivolumab and ipilimumab. (use MULTI-001 regimen on ARIA)

Day	Drug	Dose	Route	Infusion Time	Administration Details
Day 1	Metoclopramide	20mg	PO		
	NIVOLUMAB	**480mg**	IV	30 min	Can be given undiluted or diluted. If diluted, give in100ml Sodium Chloride 0.9% via in-line low- protein binding 0.22 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.	

Phase 2 Cycle 5 onwards Schedule 2 SC administration: Repeat every 28 days starts 3 weeks after the last dose of the combination of nivolumab and ipilimumab (use MULTI-001 regimen on ARIA)

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	
	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: 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.

If 600mg sub-cutaneous schedule (every 14 days) is given on cycle 5 see SPC for dosing interval between cycle 4 and 5.