Indication	**Colorectal:** For previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency, confirmed to be wild type or mutant RAS positive and wild type or mutant BRAF positive, after prior fluoropyrimidine-based combination chemotherapy (unless contraindicated by DPD deficiency). 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 has been treated with nivolumab and ipilimumab in a company early access scheme. Also, this combination of nivolumab plus ipilimumab is **not funded** after previous treatment with pembrolizumab for MSI-H or dMMR metastatic colorectal cancer. **RENAL CELL CANCER:** For the 1st line treatment of unresectable locally advanced or metastatic renal cell adenocarcinoma (intermediate or poor risk RCC).
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 can be given either every 2 weeks at a dose of 240mg (schedule 1) or if the patient is stable and well every 4 weeks* at a dose of 480mg (schedule 2). *4 week schedule is unlicensed in CRC, Trust policy regarding the use of unlicensed treatments must be followed if using this dosing schedule. Nivolumab monotherapy to continue until progressive disease or unacceptable toxicity or patient choice to discontinue treatment. 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 A formal medical review as to whether treatment with nivolumab in combination with ipilimumab should continue or not will be scheduled to occur at least by the end of the first 6 weeks of treatment and thereafter on a regular basis.
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. • **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. • 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.
- The patient should have no known brain metastases or if the patient has brain metastases, the patient should be symptomatically stable prior to starting nivolumab in combination with ipilimumab.
- **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 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 in combination 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.
- If nivolumab has to be discontinued as a consequence of toxicity, ipilimumab must also be stopped.
- 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 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. • **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 who re-quire concomitant anticoagulant therapy should be monitored closely. • 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 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	SPC accessed online 12.1.2023 KMCC protocol MULTI-022 V2

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

Cycle 1-4 combination therapy.

Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Metoclopramide	20mg	PO		
	NIVOLUMAB	**3mg/kg**	IV	30 mins	Can be given undiluted or diluted in sodium chloride 0.9%. The diluted solution should have a final concentration of 1 to 10mg/ml. The total volume of infusion must not exceed 160 ml. 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.**
	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.	

Cycle 5 onwards: Schedule 1 every 14 days starts 3 weeks after 4th cycle of combination treatment (use MULTI-001 regimen on ARIA)

Day	Drug	Dose	Route	Infusion Duration	Administration Details
Day 1	Metoclopramide	20mg	PO		
	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.	

Cycle 5 onwards: Schedule 2 every 28 days (unlicensed in CRC) starts 6 weeks after 4th cycle of combination treatment (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 0.2 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 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.