Protocol Contains CHECKPOINT INHIBITOR IMMUNOTHERAPY	
Indication	**RENAL CELL CANCER** For the 1st line treatment of unresectable locally advanced or metastatic RCC (intermediate or poor risk RCC) for the **SECOND PHASE** of treatment only for patients started on protocol MULTI-022*. For advanced or metastatic RCC after only 1 or 2 previous lines of antiangiogenic therapy for advanced or metastatic disease*. **UROTHELIAL** For adjuvant treatment in patients with high risk muscle invasive urothelial cancer with tumour cell PD-L1 expression of >/=1% and in whom adjuvant treatment with platinum-based chemotherapy is unsuitable. Treatment must commence within 4 months of surgery and the patient must be confirmed to be disease-free within 1 month of treatment*. **UPPER GI** For unresectable advanced, recurrent or metastatic squamous cell or adenosquamous oesophageal carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy*. As adjuvant treatment of completely resected oesophageal (squamous or adenocarcinoma) carcinoma or adenocarcinoma of the gastro-oesophageal junction (GOJ) who have residual pathological disease at surgery following prior neoadjuvant platinum based chemoradiotherapy. The Blueteq application should be made within 16 weeks of surgical resection*. **CRC** 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 positive and wild type or mutant BRAF positive for the SECOND PHASE of treatment only for patients started on protocol **COL-046.** NB SC administration is not licensed, use IV only. For previously treated metastatic colorectal cancer (CRC) with high microsatellite instability or mismatch repair deficiency, after prior fluoropyrimidine-based combination chemotherapy (unless contraindicated by DPD deficiency) for the **SECOND PHASE** of treatment only for patients started on protocol MULTI-022*. **HEAD AND NECK** For recurrent or metastatic squamous cell carcinoma of the head and neck after platinum-based chemotherapy. The patients' disease must have progressed or recurred during or within six months of the last dose of previously received platinum-based chemotherapy*. **MELANOMA** For the adjuvant treatment of newly diagnosed and completely resected stage III or IV melanoma*. For either treatment-naïve advanced (unresectable or metastatic) melanoma or following BRAF/MEK-targeted therapy or ipilimumab monotherapy or both BRAF/MEK-targeted treatment and ipilimumab monotherapy*.

	Advanced (unresectable or metastatic) melanoma for the **SECOND PHASE** of treatment following ipilimumab with nivolumab (SKI-009) *. **LUNG** For locally advanced or metastatic squamous cell* or PD-L1 positive non-squamous cell stage IIIB, IIIC or IV NSCLC in patients who have progressed after receiving at least two cycles of platinum-based doublet chemotherapy for stage IIIB or IIIC or IV or recurrent NSCLC after previous potentially curative local management or has progressed within 6 months of completing platinum-based adjuvant or neoadjuvant therapy or chemoradiation and if appropriate that the patient has had all appropriate targeted treatments if the patient has a tumour which is positive for an actionable genomic change in relation to EGFR or ALK or ROS1 or MET exon 14 or KRAS G12C or RET or BRAF V600 status. N.B. Non-squamous patients must have a PD-L1 tumour proportion score >/= 1%. SC administration is not licensed, use IV only for non-squamous NSCLC. **HODGKINS DISEASE** For relapsed or refractory classical Hodgkin Lymphoma after high-dose conditioning chemotherapy followed by autologous stem cell transplant (ASCT) and prior treatment with brentuximab vedotin. NB SC administration is not licensed use IV only. NB Nivolumab was available as an interim treatment option during the COVID-19 pandemic, from 1st April 2023 some options have been retained until the agreed exit strategy for those indications is complete i.e. a decision from NICE which supersedes the COVID-friendly interim option or completion of assessment of a Clinical Policy application by the NHS England Specialised Services Clinical Panel. The options will be removed from this list when the final commissioning position is known or sooner if there is no longer a clinical need to retain these options. See national CDF list section c https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/ ***see frequency and number of cycles box for information on route of administration and cycle length.
Treatment Intent	Palliative treatment for RCC, CRC, Melanoma, NSCLC, **unresectable** Oesophageal, and Head and Neck. Adjuvant treatment for urothelial, melanoma and **adjuvant** oesophageal (squamous or adenocarcinoma) carcinoma or adenocarcinoma of the GOJ. Disease modification / palliative treatment for Hodgkins disease.

Frequency and number of cycles	**Schedule 1:** Every 14 days IV **Schedule 2:** Every 28 days IV **Schedule 3:** every 28 days SC **NB** 4 weekly IV schedule is licensed for **adjuvant** urothelial, RCC, **adjuvant** oesophageal (squamous or adenocarcinoma) carcinoma or adenocarcinoma of the GOJ, **previously untreated** CRC (MSI-H or dMMR) and Melanoma only. It can be prescribed unlicensed for all other indications, therefore Trust policy regarding the use of unlicensed treatments must be followed if using this dosing schedule. *SC nivolumab is licensed for use in the indications shown above. Patients can be switched between nivolumab SC and IV therapy if the clinical need arises. For RCC, head and neck, **previously treated** CRC and **unresectable** oesophageal continue until progressive disease or unacceptable toxicity. For NSCLC, **previously untreated** CRC (MSI-H or dMMR) and Hodgkin Lymphoma indication a maximum treatment duration of 2 years of uninterrupted treatment or 52 administrations (where administered every 2 weeks) or 26 administrations (where administered every 4 weeks) with nivolumab, whichever is later. Advanced melanoma, continue until disease progression, unacceptable toxicity or patient choice. Patients can have the option of a break in immunotherapy treatment after 2 or more years. If such an option is chosen and if there is subsequent disease progression off treatment, NHS will commission the re-start of immunotherapy monotherapy as long as this re-start is the first treatment at that disease relapse. For adjuvant urothelial, adjuvant melanoma and adjuvant treatment of **completely resected** oesophageal (squamous or adenocarcinoma) carcinoma or adenocarcinoma of the GOJ until disease progression or unacceptable toxicity or withdrawal of patient consent or for a maximum of 12 months (or a maximum of 26 cycles if given 2-weekly or maximum of 13 cycles if given 4 weekly) from the start of treatment. 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 with nivolumab 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. • Monitor FBC, U&Es, LFTs, random blood glucose at each cycle. • If PLT <75 or neuts <1.0 d/w consultant. • **Pre-treatment cardiac assessment:** ○ **ECG** baseline and as clinically indicated. ○ Check **BNP**, and **Troponin T** prior to treatment.

	• 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 24hours of the last steroid dose. • **Renal impairment:** No specific dose adjustment is necessary in patients with mild to moderate renal impairment. Severe renal impairment d/w consultant. • **Hepatic impairment:** No dose adjustment in mild hepatic impairment. Use with caution in patients with moderate (total bilirubin > 1.5xULN to 3xULN and any AST) or severe (total bilirubin >3xULN and any AST) hepatic impairment. • Use with caution in patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression, after careful consideration of the potential risk-benefit. • 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. • Dose escalation or reduction is not appropriate. Dosing delay or discontinuation may be required based on individual safety and tolerability. • Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Patients on nivolumab who present with diarrhoea or other symptoms of colitis, and those who do not respond to steroid treatment for immune-related colitis, should be fully investigated. For further guidance see https://www.gov.uk/drug-safety-update/nivolumab-opdivo-reports-of-cytomegalovirus-cmv-gastrointestinal-infection-or-reactivation. • **Nivolumab Sub cutaneous administration and injection-related reactions:** o If SC Injection is being prepared on the ward Trust SOP should be followed. o Remove from fridge and allow to reach room temperature before administration. o The solution for injection should NOT be diluted or mixed with other medicinal products. o 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. o Administer the full contents of the syringe. o Inject into the subcutaneous tissue of the abdomen or thigh only, over 3 to 5 minutes. o Do not inject at other sites of the body. o Injection site should be alternated between left and right thigh/abdomen for successive injections. o 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. o During the treatment other medicinal products for subcutaneous administration should preferably be injected at different sites. • **Nivolumab Infusion-related reactions:** In the event of severe infusion-related reactions, discontinue 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:** o 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, 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. ○ Cases of myocarditis have been reported, if a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment. Once a diagnosis of myocarditis is established, nivolumab should be withheld or permanently discontinued. ○ Treatment must be permanently discontinued for any grade 4, recurrent grade 3 (or first occurrence of grade 3 if specified in guidance) or Grade 2 or 3 immune related adverse reactions that persist despite treatment modifications and any severe or life-threatening immune-related adverse reactions. Treatment must also be permanently discontinued if corticosteroid dosing cannot be reduced to < 10mg prednisolone or equivalent per day. ○ 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. ○ See guidelines for management of immune-related adverse reactions following immunotherapy: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/ • Careful consideration to the potential benefits of HSCT and the possible increased risk of transplant related complications following nivolumab in patients with Hodgkins lymphoma. Treatment with nivolumab may increase the risk of severe GVHD and death in patients who have had prior allogeneic HSCT, mainly in those with prior history of GVHD. The benefit of treatment with nivolumab versus the possible risk should be considered in these patients. • **Haemophagocytic lymphohistiocytosis (HLH)** has been observed with nivolumab. Caution should be taken when nivolumab is administered as monotherapy or in combination with ipilimumab. If HLH is confirmed, administration of nivolumab should be discontinued and treatment for HLH initiated. • Each ml of nivolumab contains 0.1 mmol (or 2.5mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet. • **Driving:** Nivolumab can potentially cause fatigue in some patients and therefore use caution when driving or using machines. • The patient should be provided with the appropriate OPDIVO® Patient Alert card with each prescription (to be carried until at least 5 months after the last dose 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.
Reference(s)	SPC accessed online 02.06.25 KMCC protocol MUTI-001 V12, CDF list V 1.364 accessed online 02.06.25 changes to NIV7, NIV 8a, NIV9, NIV15, NIV19 previous version 1.363 changes to NIV1 NIV6.

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

Schedule 1 IV administration: Every 14 days

Day	Drug	Dose	Route	Infusion Time	Administration Details
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.	

Schedule 2 IV administration - every 28 days (licensed for melanoma, adjuvant treatment of completely resected oesophageal (squamous or adenocarcinoma) carcinoma or adenocarcinoma of the GOJ and renal cell only. May be prescribed off license for ALL other indications

Day	Drug	Dose	Route	Infusion Time	Administration Details
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 240mg every 2 weeks schedule to the 480mg every 4 weeks schedule, the first 480mg dose should be administered two weeks after the last 240mg dose. Conversely, if patients need to be switched from the 480mg every 4 weeks schedule to the 240mg every 2 weeks schedule, the first 240mg dose should be administered four weeks after the last 480mg dose

Schedule 3 SC administration: Repeat 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.	

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.