Indication	As monotherapy for advanced renal cell cancer, which either has a clear cell component or is a papillary RCC, in adult patients after prior therapy. For the 1st line treatment of unresectable locally advanced or metastatic renal cell adenocarcinoma (intermediate or poor risk RCC) which either has a clear cell component or is a papillary RCC for the **SECOND PHASE** of treatment only (protocol RCC-010). The treatment of relapsed or refractory classical Hodgkin Lymphoma in adult patients who have received prior high-dose conditioning chemotherapy followed by autologous stem cell transplant (ASCT) and prior treatment with brentuximab vedotin. Nivolumab as monotherapy is recommended, within its marketing authorisation, as an option for treating advanced (unresectable or metastatic) melanoma and for the adjuvant treatment of newly diagnosed and completely resected stage III or IV melanoma in adults. Treatment of locally advanced or metastatic squamous or non-squamous stage IIIB or IV non-small cell lung cancer, in patients who have progressed after receiving at least two cycles of platinum containing chemotherapy and also a targeted treatment if the tumour is EGFR positive or ALK positive and would otherwise be potentially fit for docetaxel- based 2nd line chemotherapy. N.B. Non-squamous patients **must** have a PD-L1 tumour proportion score >/= 1%. Monotherapy 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. As monotherapy for the treatment of unresectable advanced, recurrent or metastatic squamous cell or adenosquamous oesophageal carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy. NB Nivolumab is available as an interim treatment option in certain other indications during the Covid 19 pandemic, see NICE Guidelines NG161. https://www.nice.org.uk/guidance/ng161/resources/nhs-england-interim-treatment-options-during-the-covid19-pandemic-pdf-8715724381
Treatment Intent	Palliative treatment for RCC, Melanoma, NSCLC, Oesophageal and Head and Neck Adjuvant treatment for melanoma. Disease modification / palliative treatment for Hodgkins disease.
Frequency and number of cycles	**Schedule 1:** Every 14 days **Schedule 2:** Every 28 days **NB** 4 weekly schedule is licensed for RCC 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. For RCC and Oesophageal continue until progressive disease or unacceptable toxicity. For NSCLC, Hodgkin Lymphoma and head and neck 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*

	*Where treatment is interrupted any restart and continuation of drug must be in line with the treatment break policy outlined in Specialised Services Circular (SSC) 1918. 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 melanoma, every 2 weeks 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. NB: a formal review should be performed by the end of the first 8 weeks of treatment to review whether treatment should continue or not. 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	• **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. • Monitor FBC, U&Es, LFTs, random blood glucose at each cycle. • If PLT <75 or neuts <1.0 d/w consultant. • Thyroid function must be assessed at baseline then every 6-8 weeks or as clinically indicated. • Random cortisol level must be assessed at baseline then as clinically indicated. • **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. • **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, and myalgia. ○ 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: http://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/sact-pathways-guidelines-for-the-management-of-sact-induced-adverse-reactions-and-nursing/ • 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. • 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 with each prescription (to be carried until at least 5 months after the last dose 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.
Reference(s)	SPC accessed online 10/06/21, KMCC protocol MUTI-001 v6, KMCC ,CDF list v1.181 MHRA update; https://www.gov.uk/drug-safety-update/nivolumab-opdivo-reports-of-cytomegalovirus-cmv-gastrointestinal-infection-or-reactivation

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

Schedule 1 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	
	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) Do not take for more than 5 days continuously.	
	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.	

Schedule 2 - every 28 days (licensed for melanoma and renal cell only can be prescribed off license for ALL other indications)

Day	Drug	Dose	Route	Infusion Time	Administration Details
1	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) Do not take for more than 5 days continuously.	
	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 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.