Protocol Contains CHECKPOINT INHIBITOR IMMUNOTHERAPY	
Indication	For use in treatment-naïve patients with intermediate or poor risk advanced renal cell carcinoma for whom combination treatment with either nivolumab plus ipilimumab or lenvatinib plus pembrolizumab would otherwise be suitable. NB if the patient has received prior systemic immune-modulatory therapy in the context of adjuvant/neoadjuvant therapy, then such treatment was completed 12 or more months previously.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days Continue nivolumab until progressive disease or unacceptable toxicity or patient choice to discontinue treatment or completion of 2 calendar years of treatment, whichever is sooner. Cabozantinib monotherapy can continue until loss of clinical benefit or excessive toxicity or withdrawal of patient consent. A formal medical review as to whether treatment with cabozantinib in combination with nivolumab should continue or not will be scheduled to occur at least by the start of 3rd 4 weekly cycle.
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 and U&Es** at each cycle. In particular monitor potassium, calcium, phosphate, sodium & magnesium. • Prior to treatment neuts must be >/=1.5 and PLT >/= 100, otherwise d/w consultant. During treatment if neuts <1.0 and/or PLT <50 d/w consultant. • **LFTS** (ALT, AST and bilirubin) baseline and at each cycle. Closer monitoring is recommended in patients with mild or moderate hepatic impairment. • **Monitor blood glucose** prior to treatment and then at each cycle during nivolumab therapy and then as clinically indicated. • **Thyroid function & urinalysis for proteinuria** at baseline, then every cycle. Discontinue cabozantinib in the event of nephrotic syndrome. If cabozantinib is discontinued monitor thyroid function every 8 weeks. • 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. • **ECG** prior to treatment and then as clinically indicated. • **Blood pressure** should be well controlled before starting cabozantinib. If blood pressure exceeds 150/90mmHg please discuss with consultant. Blood pressure to be measured weekly for first cycle, then at every cycle. In the case of persistent hypertension despite use of anti-hypertensives, treatment should be interrupted until blood pressure is controlled, after which cabozantinib can be resumed at a reduced dose. Cabozantinib should be discontinued if hypertension is severe, persistent despite anti-hypertensive therapy and dose reduction. • Osteonecrosis of jaw (ONJ) has been observed with cabozantinib. An **oral examination** should be performed prior to initiation and periodically during therapy. Patients should be advised on oral hygiene practice. Cabozantinib treatment should be held at least 28 days prior to scheduled dental surgery or invasive dental procedures, if possible. Cabozantinib should be discontinued in patients who experience ONJ.

- Reference should be made to the UK chemotherapy board guidance on medication related osteonecrosis of the jaw: https://www.rcplondon.ac.uk/guidelines-policy/medication-related-osteonecrosis-jawguidance-oncology-multidisciplinary-team.
- 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.
- **Hepatic impairment (prior to treatment):**
  - Cabozantinib: No dose adjustment is required in mild hepatic impairment. Limited data are available in moderate impairment (Child-Pugh B) no dose recommendation available, clinician's decision to dose reduce. Patients should be monitored for adverse events and dose adjustment or treatment interruption should be considered as needed. Cabozantinib is not recommended for use in patients with severe hepatic impairment (Child-Pugh C).
  - Nivolumab: 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.
- **Hepatic Impairment during treatment see table 1.**
- **Renal impairment:**
  - Cabozantinib: Dose adjustment is not required, but use with caution in patients with mild or moderate renal impairment. Not recommended for patients with severe renal impairment (CrCl<30ml/min).
  - Nivolumab: No specific dose adjustment is necessary in patients with mild to moderate renal impairment. Severe renal impairment d/w consultant.
- **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.
- **Dose modification: If toxicity can be related to either cabozantinib or nivolumab, treatment can continue with either cabozantinib or nivolumab whilst the other is held whilst toxicity resolves.**
  - **Nivolumab:**
  - Dose escalation or reduction is not appropriate. Dosing delay or discontinuation may be required based on individual safety and tolerability
  - **Cabozantinib:**
  - Suspected adverse drug reactions may require treatment interruption and/or dose reduction (see table 1).
  - When a dose reduction of cabozantinib is necessary, it is recommended to reduce to 20mg daily then 20mg every other day daily. Dose interruptions are recommended for grade 3 or greater toxicities or intolerable grade 2 toxicities.
  - Cabozantinib should be permanently discontinued if there is: development of unmanageable fistula or GI perforation, severe haemorrhage, arterial thromboembolic event (e.g., myocardial infarction, cerebral infarction), hypertensive crisis or severe hypertension despite optimal medical management, nephrotic syndrome or reversible posterior leukoencephalopathy syndrome.
- If nivolumab has to be discontinued as a consequence of toxicity, cabozantinib can be continued as monotherapy as long as there is no evidence of progressive disease, and vice versa (up to 2 years of nivolumab treatment).
- **Cabozantinib adverse reactions and cautions:**
- Patients who have inflammatory bowel disease, have tumour infiltration in the GI tract, or have complications from prior GI surgery should be carefully evaluated before initiating cabozantinib therapy and subsequently they should be monitored closely for symptoms of perforations and fistulas including abscesses. Persistent or recurring diarrhoea while on treatment may be a risk factor for the development of anal fistula.
- Patients should be monitored for signs and symptoms of hepatic encephalopathy.

- Cabozantinib should be used with caution in patients who are at risk for, or who have a history of venous thromboembolism, including pulmonary embolism, and arterial thromboembolism.
- Cabozantinib should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances.
- Severe haemorrhage, sometimes fatal, has been observed with cabozantinib. Patients who have a history of severe bleeding prior to treatment initiation should be carefully evaluated before initiating cabozantinib therapy. Cabozantinib should not be administered to patients that have or are at risk for severe haemorrhage.
- Posterior reversible encephalopathy syndrome (PRES) has been observed with cabozantinib. This syndrome should be considered in any patient presenting with multiple symptoms, including seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in patients with PRES.
- Wound complications have been observed with cabozantinib. Cabozantinib treatment should be stopped at least 28 days prior to scheduled surgery, including dental surgery, if possible. The decision to resume cabozantinib therapy after surgery should be based on clinical judgment of adequate wound healing. Cabozantinib should be discontinued in patients with wound healing complications requiring medical intervention.
- Patients should be advised to use regular emollients on their skin (particularly their hands and feet).
- **Nivolumab Immune-related reactions and cautions:**
  - 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.
  - 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.
  - 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/ ○ **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. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** ○ **Cabozantinib** is a CYP3A4 substrate. Concomitant medicinal products that are **strong inhibitors** of CYP3A4 (e.g. ketoconazole, itraconazole, clarithromycin, grapefruit juice) should be used with caution, and concomitant use of **strong inducers** of CYP3A4 (e.g. rifampicin, dexamethasone, phenytoin, and carbamazepine) should be avoided. ○ Concomitant use of MRP2 inhibitors (e.g. cyclosporine, efavirenz, emtricitabine) may increase cabozantinib plasma concentrations. ○ Cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan). ○ Because of high plasma protein binding levels of cabozatinib interaction with warfarin is possible, monitor INR. ○ Caution should be used in patients receiving agents associated with ONJ, such as bisphosphonates. • **Missed dose**: If a dose of cabozantinib is missed, the missed dose should not be taken if it is less than 12 hours before the next dose. • **Driving and operating machinery:** Cabozantinib and nivolumab can potentially cause fatigue and weakness in some patients therefore patients should be advised to be cautious when driving or operating machines. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet. • 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). • 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.
References	SPC accessed online 12.03.2024 CDF list accessed online 11.03.2024, NHSE CDF List v1.296

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

Table 1: Recommended cabozantinib dose modifications for adverse reactions

Adverse reaction and severity	**Treatment modification**
Grade 1 and grade 2 adverse reactions which are tolerable and easily managed	Dose adjustment is usually not required. Add supportive care as indicated.
Grade 2 adverse reactions which are intolerable and cannot be managed with a dose reduction or supportive care	Interrupt treatment until the adverse reaction resolves to grade ≤1. Add supportive care as indicated. Consider re-initiating at a reduced dose.
Grade 3 adverse reactions (except clinically nonrelevant laboratory abnormalities)	Interrupt treatment until the adverse reaction resolves to grade ≤1. Add supportive care as indicated. Re-initiate at a reduced dose.
Grade 4 adverse reactions (except clinically nonrelevant laboratory abnormalities)	Interrupt treatment. Institute appropriate medical care. If adverse reaction resolves to grade ≤1, re-initiate at a reduced dose. If adverse reaction does not resolve, permanently discontinue the treatment.
Liver enzymes elevations for RCC patients treated with cabozantinib in combination with nivolumab	
ALT or AST > 3 times ULN but ≤10 times ULN without concurrent total bilirubin ≥ 2 times ULN	Interrupt cabozantinib and nivolumab until these adverse reactions resolves to Grade≤1 Corticosteroid therapy may be considered if immune-mediated reaction is suspected (refer to nivolumab SmPC). Re-initiate with a single medicine or sequential re-initiating with both medicines after recovery may be considered. If re-initiating with nivolumab, refer to nivolumab SmPC.
ALT or AST > 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN	Permanently discontinue cabozantinib and nivolumab. Corticosteroid therapy may be considered if immune-mediated reaction is suspected (refer to nivolumab SmPC).

Cycles 1 to 26 (nivolumab should stop after 2 calendar years) - combination therapy repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		
	NIVOLUMAB	**480mg**	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	**CABOZANTINIB (Cabometyx®)**	**40mg**	PO	OD Swallow whole, do not crush. To be taken on an empty stomach (do not eat anything for at least 2 hours before dose and for 1 hour after). Available as 20mg and 40mg tablets.	
	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 days continuously.	
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. **Do not take for longer than 3 days without contacting the oncology team.** Dispense 30 capsules on cycle 1 then only if required	

NB Nivolumab may be given at a dose of 240mg iv every 14 days is clinically necessary. 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.

Cycle 27 onwards - monotherapy repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**CABOZANTINIB (Cabometyx®)**	**40mg**	PO	OD Swallow whole, do not crush. To be taken on an empty stomach (do not eat anything for at least 2 hours before dose and for 1 hour after). Available as 20mg and 40mg tablets
	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Loperamide	2mg-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.