Nivolumab and Cabozantinib (RCC)

Please note this protocol has been produced in a new format that is currently being piloted. Any feedback on this new format should be sent to SSGMeetings@uhbw.nhs.uk

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Indication

Untreated advanced renal cell carcinoma that is intermediate or poor risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria in those who would have otherwise been offered nivolumab with ipilimumab or Lenvatinib with pembrolizumab.

(NICE TA964)

Response Rates

Phase III CheckMate 9ER trial:

- Nivolumab plus cabozantinib (n=323) vs sunitinib (n=328)
- ORR: Nivolumab plus cabozantinib 55.7% vs sunitinib 27.1%
- PFS: Nivolumab plus cabozantinib 16.6 months vs sunitinib 8.3 months HR 0.51

Regimen details

Day	Drug	Dose	Route
1	Nivolumab	480mg every 4 weeks Or 240mg every 2 weeks	IV infusion
Continuous	Cabozantinib	40mg OD	Oral

Cycle frequency
Every 14 or 28 days (see above)

If patients need to switch nivolumab from 2 weekly dosing to 4 weekly dosing, the first 480mg dose should be administered 2 weeks after the last 240mg dose. If patients need to switch from the 4 weekly dosing to the 2 weekly dosing, the first 240mg dose should be administered 4 weeks after the last 480mg dose.

Number of cycles
Continue until disease progression or unacceptable toxicity (NB. Nivolumab may be continued for up to a maximum of 2 years but cabozantinib monotherapy may be continued beyond this in the absence of disease progression or unacceptable toxicity).

Pre-medication
Nil

Supportive medication
Loperamide if required.
Patients should be advised to apply regular moisturiser to their hands and feet throughout treatment to minimise the risk of developing PPE.
Mouthwash as per local policy.

Emetogenicity
This regimen has low emetogenic potential (no routine antiemetics required)

Administration
Nivolumab may be administered without dilution as a 10mg/mL solution or in sodium chloride 0.9% or glucose 5% at a concentration between 1-10mg/mL over 30 minutes (240mg dose) or 60 minutes (480mg dose). Nivolumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 1.2µm).

Patients should be monitored (blood pressure, pulse and temperature) every 30 minutes during the infusion for infusion related reactions. For mild to moderate reactions, decrease the infusion rate and closely monitor. Premedication with paracetamol and chlorphenamine should be used for further doses. For severe infusion related reactions discontinue treatment.

Cabozantinib is available as 20mg and 40mg tablets. Tablets should be swallowed whole and not crushed. Patients should not eat for at least two hours before or one hour after administration. If a dose is missed the patient should not take it if it is less than 12 hours before the next dose is due.

Cabozantinib tablets are available as the Cabometyx® brand. Cabozantinib capsules (Cometriq®) are not bioequivalent and should not be used for this indication.

Grapefruit and grapefruit juice should be **avoided** whilst taking cabozantinib.

Extravasation

Nivolumab is neutral (Group 1)

Mandatory investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+Es (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
Magnesium	14 days
Thyroid function	14 days
Glucose	14 days
Cortisol	14 days
Blood pressure	Must be controlled before initiating treatment
ECG	Baseline

Additional investigations advised pre-first cycle

- ECG if patient has significant cardiac history.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	Monitor 2 weekly for the first 8 weeks. Within 7 days thereafter.
U+E (including creatinine)	Monitor 2 weekly for the first 8 weeks. Within 7 days thereafter.
LFTs	Monitor 2 weekly for the first 8 weeks. Within 7 days thereafter.
Calcium	Monitor 2 weekly for the first 8 weeks. Within 7 days thereafter.
Magnesium	Monitor 2 weekly for the first 8 weeks. Within 7 days thereafter.
Thyroid function	Every 12 weeks
Glucose	As clinically indicated
Cortisol	At consultant discretion
Blood pressure	Weekly for first 4 weeks then monthly

Patients should be monitored for up to 5 months after last dose of Nivolumab for adverse reactions.

Additional investigations advised pre subsequent cycles

- Periodic urinalysis to monitor for proteinuria. Consider 4 weekly initially and then as clinically indicated.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer must be given by prescriber/ consultant

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine Clearance (CrCl)	≥ 60mL/min
Bilirubin	≤ 1.5 x ULN
ALT/AST	< ULN
Alkaline Phosphatase	< 5 x ULN

Dose modifications

Cabozantinib:

Dose level	Dose
Starting dose	40mg OD
Dose level -1	20mg OD
Dose level -2	20mg on alternate days

Nivolumab: Dose reductions are not recommended. Doses should be delayed until an adverse reaction resolves to ≤ grade 1.

Haematological toxicity

Discuss with the consultant if:
Neutrophils <1.0 x 10^9/L
Platelets <75 x 10^9/L

Renal impairment

Nivolumab: No dose modifications required in mild or moderate renal impairment (CrCl>30ml/min). No dose modification is expected in severe renal impairment (CrCl<30ml/min) but use with caution – consultant decision. See below for management of nephritis emergent on treatment.

Cabozantinib: Cabozantinib should be used with caution in mild-moderate renal impairment (CrCl 30-60mL/min) and is not recommended for use in severe renal impairment (CrCl < 30mL/min) due to a lack of safety data.

Hepatic impairment

Nivolumab: No dose modification is required for mild hepatic impairment. There is limited data on the use of Nivolumab in moderate or severe hepatic impairment but no need for dose modification is expected. Use with caution if bilirubin > 1.5 x ULN – consultant decision. See below for management of LFT derangement on treatment.

Cabozantinib: In mild-moderate hepatic impairment (Child-Pugh A or B) the recommended starting dose is 40mg OD and patients should be monitored closely for adverse events. Cabozantinib is not recommended for use in severe hepatic impairment (Child Pugh C) due to a lack of safety data. See below for management of LFT derangement on treatment.

Other toxicities

LFT derangement

Toxicity	Action
ALT/AST > 3 x ULN and ≤ 10 x ULN *without* concurrent bilirubin ≥ 2 x ULN	Interrupt cabozantinib and nivolumab until adverse reaction resolves to ≤ grade 1. Corticosteroid therapy may be considered if immune-mediated reaction is suspected. Once toxicity resolves, re-initiation with a single agent or sequential re-initiation of both agents may be considered.
ALT/AST > 10 x ULN Or ALT/AST > 3 x ULN with concurrent bilirubin ≥ 2 x ULN	Permanently discontinue both drugs Corticosteroid therapy may be considered if immune-mediated reaction is suspected.

Immune-related adverse reactions

Immune-related adverse reactions can be severe or life-threatening and may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. While most immune-related adverse reactions reported occurred during the induction period, onset months after the last dose have also been reported. Unless an alternate aetiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and treatment-related. Early diagnosis and appropriate management are essential to minimise life-threatening complications.

Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions. Specific management guidelines for immune-related adverse reactions are described in full in the summary of product characteristics for nivolumab. Management of immune-related adverse reactions may require a dose delay or permanent discontinuation of treatment and initiation of systemic high-dose corticosteroid or, in some cases, the addition of other immunosuppressive therapy. Dose reduction is not recommended.

Toxicity	Definition	Action
Colitis	Grade 1	Continue and closely monitor
	Grade 2-3	Withhold until symptoms resolve to ≤ grade 1
	Grade 4 or recurrent grade 3	Permanently discontinue nivolumab
Pneumonitis	Grade 1	Continue and closely monitor
	Grade 2	Withhold until symptoms resolve to ≤ grade 1
	Grade 3-4 or recurrent grade 2	Permanently discontinue nivolumab
Nephritis	Grade 2 (creatinine 1.5-3 x ULN) or Grade 3 (creatinine > 3 x ULN)	Withhold until symptoms resolve to ≤ grade 1
	Grade 4 (creatinine > 6 x ULN)	Permanently discontinue
Endocrine	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grade 3 or 4 adrenal insufficiency or symptomatic hypophysitis	Withhold until symptoms resolve to ≤ grade 1
	Type 1 diabetes with grade > 3 hyperglycaemia (glucose > 13.9 mmol/L) or ketoacidosis	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hyperthyroidism ≥ grade 3	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hypothyroidism	Continue and manage with replacement therapy

Toxicity	Definition	Action
Skin	Grade 3 rash	Withhold until resolves to ≤ grade 1
	Grade 4 rash or Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis	Permanently discontinue nivolumab
Cardiac	Grade 2 myocarditis	Withhold until resolves to ≤ grade 1
	Grade 3 or 4 myocarditis	Permanently discontinue nivolumab
Neurological	Grade 2 motor or sensory neuropathy	Withhold until resolves to ≤ grade 1
	Grade 3 or 4 motor or sensory neuropathy	Permanently discontinue nivolumab
	Grade 3 or 4 encephalitis	Permanently discontinue nivolumab
	Grade 3 or 4 Guillain-Barré syndrome	Permanently discontinue nivolumab
Infusion-related reactions	Grade 3-4	Permanently discontinue nivolumab
Any other toxicity	Grade 3 (first occurrence)	Withhold until resolves to ≤ grade 1
	Grade 4 or recurrent Grade 3	Permanently discontinue nivolumab

Cabozantinib specific toxicities:

Adverse reaction	Cabozantinib dose
Grade 1 and Grade 2 - tolerable	Dose adjustment is usually not required. Add supportive care as indicated.
Grade 2 - intolerable and cannot be managed with a dose reduction or supportive care	Interrupt treatment until resolves to Grade ≤1. Add supportive care as indicated. Consider re-commencing at dose reduction.
Any Grade 3	Interrupt treatment until resolves to Grade ≤1. Add supportive care as indicated. Re-commence at reduced dose.
Any Grade 4	Interrupt treatment. Institute appropriate medical care. If adverse reaction resolves to Grade ≤1, re-commence at reduced dose. If adverse reaction does not resolve, permanently discontinue treatment.

Side Effects

CheckMate 9ER study:

Toxicity		Any grade (%)	Grade 3 or 4 (%)
Haematological	Anaemia	15.0	1.9
	Thrombocytopenia	7.8	0.6
	Neutropenia	4.7	0.6
Non-haematological	Diarrhoea	63.8	6.9
	Palmar-plantar erythrodysaethesia	40.0	7.5
	Hypertension	34.7	12.5
	Hypothyroidism	34.1	0.3
	Fatigue	32.2	3.4
	Increased ALT	28.1	5.3
	Decreased appetite	28.1	1.9
	Nausea	26.6	0.6
	Increased AST	25.3	3.4
	Dysgeusia	23.8	0
	Asthenia	22.2	4.4
	Rash	21.6	1.9
	Mucosal inflammation	20.6	0.9

Specific drug related side effects:

Nivolumab:

Common (>10%)	Uncommon (1-10%)	Rare (<1%)
Respiratory tract infections	Infusion related reactions	Aseptic meningitis
Decreased appetite	Hypothyroidism/Hyperthyroidism	Histiocytic necrotising lymphadenitis
Hyperglycaemia	Pneumonia	Eosinophilia
Headache	Hypoglycaemia	Sarcoidosis
Dyspnoea, cough	Dizziness	Adrenal insufficiency, hypopituitarism, hypophysitis,
Nausea, vomiting	Peripheral neuropathy	Diabetes mellitus
Diarrhoea, constipation	Blurred vision, dry eye	Uveitis
Rash, pruritis	Tachycardia, AF	Autoimmune neuropathy, Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis
Arthralgia	Pneumonitis	Toxic epidermal necrolysis, Stevens-Johnson syndrome
Fatigue	Colitis	Myocarditis
Deranged LFTs	Stomatitis	Vasculitis
Deranged electrolytes	Dry skin	Pancreatitis
Increased lipase/amylase	Arthritis	Gastritis
	Renal failure, acute kidney injury	Hepatitis
		Polymyalgia rheumatica
		Sjogren's syndrome
		Myositis, rhabdomyolysis

Cabozantinib:

Common (>10%)	Uncommon (1-10%)	Rare (<1%)
Anaemia	Neutropenia	Convulsions
Thrombocytopenia	Pneumonia	Posterior reversible encephalopathy syndrome
Hypothyroidism	Peripheral neuropathy	Acute myocardial infarction
Decreased appetite	Tinnitus	Hypertensive crisis
Hypomagnesaemia, Hypokalaemia	Hypophosphataemia, hyponatraemia, hypocalcaemia, hyperkalaemia, hyperbilirubinemia, hyperglycaemia, hypoglycaemia	Arterial thrombosis
Dysgeusia	Venous thrombosis, pulmonary embolism	Pneumothorax
Headache	GI perforation, fistula	Glossodynia
Dizziness	Pancreatitis	Hepatitis cholestatic
Hypertension	Dysphagia	Osteonecrosis of the jaw
Haemorrhage	Hepatic encephalopathy	Wound complications
Dysphonia	Dry skin, pruritis, hyperkeratosis	
Dyspnoea, cough	Alopecia, hair colour change	
Diarrhoea, constipation	Arthralgia	
Nausea, vomiting	Muscle spasms	
Dyspepsia	Proteinuria	
Stomatitis	Increased cholesterol/triglycerides	
Rash	Increased GGT/ALP	
Palmar-plantar erythrodysaesthesia	Increase lipase/amylase	
Fatigue	Increased creatinine	
Peripheral oedema		
Raised transaminases		

Osteonecrosis of the jaw (ONJ):
Patient should have a full dental assessment and management of pre-existing dental disease prior to starting cabozantinib. If extractions are required wait 4 weeks before starting cabozantinib treatment. Dental check-up should be performed 6 monthly during cabozantinib treatment. Patients should be advised regarding oral hygiene practice and advised to contact their dentist promptly if dental issues arise. Cabozantinib should be held at least 28 days prior to scheduled dental surgery or invasive dental procedures and discontinued in patients who develop ONJ.

Hypertension:
Blood pressure should be well controlled prior to commencing treatment. All patients must be monitored for hypertension and should be treated with anti-hypertensives as appropriate. If hypertension is persistent a dose reduction of cabozantinib may be required. Cabozantinib should be discontinued if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of cabozantinib. In case of hypertensive crisis, cabozantinib should be discontinued.

Haemorrhage:
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.

Proteinuria
Proteinuria has been observed with cabozantinib. Urine protein should be monitored regularly during cabozantinib treatment and treatment should be discontinued in patients who develop nephrotic syndrome.

Cardiovascular:
Cabozantinib should be used with caution in patients with cardiac impairment or a history of QT prolongation. Treatment should be discontinued in patients who develop an acute MI.

Additional information

Surgery:
Cabozantinib treatment should be stopped at least 28 days prior to scheduled surgery, if possible. The decision to resume cabozantinib therapy after surgery should be based on clinical judgment of adequate wound healing
Patients should be issued with a Nivolumab Patient Alert Card and advised to carry the card at all times.

Contraception: Adequate methods of contraception should be used during therapy and for at least 5 months after last dose of nivolumab and 4 months after stopping cabozantinib.

Significant drug interactions – for full details consult product literature/ reference texts

Nivolumab:
Corticosteroids: use of systemic corticosteroids at baseline, before starting nivolumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of the agent. However, systemic corticosteroids or other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions.

Cabozantinib:
CYP3A4 inhibitors (e.g. ketoconazole, voriconazole, itraconazole, clarithromycin, ritonavir): avoid co-administration - may increase plasma concentrations of cabozantinib.
Grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of cabozantinib.
Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration - may reduce exposure to cabozantinib.
MRP 2 inhibitors (e.g. cyclosporine, efavirenz, emtricitabine): administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations.
Bile salt-sequestering agents (e.g. cholestyramine and cholestagel): may interact with cabozantinib resulting in potentially decreased exposure.
P-gp substrates (e.g. fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan): cabozantinib may have the potential to increase plasma concentrations therefore P-gp substrates should be used with caution.
Contraceptives: The effect of cabozantinib on contraceptive steroids has not been investigated. As contraceptive effect may not be guaranteed, an additional contraceptive method, such as a barrier method, is recommended.

References

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1	July 2024	July 2027	New protocol	Written/reviewed: J Dunn (Pharmacist, Somerset NHS Foundation Trust), Dr M Sephton (Consultant Oncologist, Somerset NHS Foundation Trust) Checked: Kate Gregory, Pharmacist, SWAG Cancer Alliance Authorised: Dr J Braybrooke, Consultant Oncologist UHBW NHS Trust and SWAG Cancer Alliance