CABOZANTINIB (Cabometyx) NIVOLUMAB (Opdivo)

INDICATION (ICD10) C64

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (CABNIV1)

1. For use in treatment-naïve patients with intermediate or poor risk advanced unresectable locally advanced or metastatic renal cell carcinoma renal cell carcinoma for whom combination treatment with either nivolumab plus ipilimumab or lenvatinib plus pembrolizumab would otherwise be suitable but not in patients suitable for single agent TKI therapy. No symptomatic brain metastases or leptomeningeal metastases currently requiring steroids for symptom control. Karnofsky performance status of at least 70 (PS 0 or 1). (TA964)

REGIMEN SC

Day 1	NIVOLUMAB	1200mg subcutaneous over 3 to 5 minutes
Days 1-28	CABOZANTINIB	40mg orally daily

REGIMEN IV

Day 1	NIVOLUMAB	480mg in 100ml sodium chloride IV infusion over 30 minutes
Days 1-28	CABOZANTINIB	40mg orally daily

CYCLE FREQUENCY AND NUMBER OF CYCLES

Cabozantinib daily continuously as long as clinical benefit or toxicity.
Nivolumab every 28 days up to maximum 2 calendar years from first dose.
A formal medical review to assess the tolerability of treatment with cabozantinib plus nivolumab will be scheduled to occur at least by the start of the 3rd 4-weekly cycle of treatment and thereafter on a regular basis.

ANTI-EMETICS

Minimal risk all days

CONCURRENT MEDICATION REQUIRED

Cabozantinib	Loperamide

ADMINISTRATION

Cabozantinib	Available as 20mg, 40mg and 60mg tablets Swallow whole. Not to eat anything for at least 2 hours before until 1 hour after taking cabozantinib Grapefruit and grapefruit juice should be avoided while on cabozantinib.
Nivolumab	SC administer in the abdomen or thigh over 3 to 5 minutes. Alternate injection sites.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Nivolumab IV - neutral

IV use low protein binding 0.2 to 5micron in-line or add-on filter.
Peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs minimum monthly
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Thyroid function tests baseline, then every cycle
Random cortisol baseline, then every cycle
Random glucose every cycle
Blood pressure weekly for cycle 1 then every month
Viral screening as per national guidance
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Carbonatitic	Diarrhoea Hand-foot syndrome Haemorrhage Hypertension Hypothyroidism Proteinurea Wound healing delayed
Nivolumab	Immune related toxicities - pneumonitis, colitis or hepatitis etc

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS

(not exhaustive list check SPC/BNF/Stockleys)

Cabozantinib	Lots of interactions, causing bleeding, QT prolongation and hypokalaemia etc. Check interactions carefully.

DOSE MODIFICATIONS

Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities. Dose reductions are recommended for events that, if persistent, could become serious or intolerable.

Cabozantinib dose

Recommended dose	40mg daily
First dose adjustment	20mg daily
Second dose adjustment	20mg alternate days

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	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	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
ALT or AST >3xULN but ≤10xULN without concurrent total bilirubin ≥2xULN	Interrupt cabozantinib and nivolumab until these adverse reactions resolves to grade≤1 Corticosteroid therapy may be considered if immune-mediated reaction is suspected. 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 immuno-oncology guidelines.
ALT or AST >10xULN or >3xULN with concurrent total bilirubin ≥2xULN	Permanently discontinue cabozantinib and nivolumab. Corticosteroid therapy may be considered if immune-mediated reaction is suspected.

Non-haematological

Cabozantinib

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.
Hypertension	Blood pressure should be well-controlled prior to initiating cabozantinib. During treatment with cabozantinib, all patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensives, the cabozantinib dose should be reduced. 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.
Palmar plantar	When PPES is severe, interruption of treatment with cabozantinib should be considered. Cabozantinib should be restarted with a lower dose when PPES has been resolved to grade 1.
Perforations and fistulas	Cabozantinib should be discontinued in patients who experience a GI perforation or a fistula that cannot be adequately managed.
Posterior reversible encephalopathy syndrome	Cabozantinib treatment should be discontinued in patients with PRES.
Proteinuria	Proteinuria has been observed with cabozantinib. Urine protein should be monitored regularly during cabozantinib treatment. Cabozantinib should be discontinued in patients who develop nephrotic syndrome.
Thrombocytopenia	Platelet levels should be monitored during cabozantinib treatment and the dose modified according to the severity of the thrombocytopenia
Thromboembolic events	Cabozantinib should be discontinued in patients who develop an acute myocardial infarction or any other clinically significant thromboembolic complication.
Wound healing and osteonecrosis	Cabozantinib treatment should be stopped at least 28 days prior to scheduled surgery, including dental surgery or invasive dental procedures, 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. Cabozantinib treatment should be held at least 28 days prior to scheduled dental surgery or invasive dental procedures, if possible. Caution should be used in patients receiving agents associated with ONJ, such as bisphosphonates. Cabozantinib should be discontinued in patients who experience ONJ.

Nivolumab

Immune-related adverse reactions - refer to TV immune-oncology agent immune related adverse event clinical guideline

Hepatic impairment

Cabozantinib

Child-Pugh scores are based on ascites, encephalopathy, INR, albumin, total bilirubin

Severe hepatic impairment (Child-Pugh C).	Not recommended

Nivolumab

Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions. Nivolumab should be administered with caution in patients with moderate or severe hepatic impairment ie bilirubin >1.5xULN and any AST.

Renal impairment

Cabozantinib

Cabozantinib should be used with caution in patients with mild or moderate renal impairment. Cabozantinib is not recommended for use in patients with severe renal impairment.

Nivolumab

Data from patients with severe renal impairment (CrCl <30ml/min) are too limited to draw conclusions.

REFERENCES

1. CDF