Cabozantinib & Nivolumab

Indication

Cabozantinib with nivolumab for untreated, intermediate or poor risk (as assessed by the International Metastatic RCC Database Consortium system), advanced renal cell carcinoma

Regimen Details

Day	Drug	Dose	Route
1	Nivolumab	480mg	Intravenous
1-28	Cabozantinib	40mg OD	Oral

Cycle frequency

Every 4 weeks

Number of cycles

Continue cabozantinib until disease progression or unacceptable toxicity
Continue nivolumab until loss of clinical benefit or excessive toxicity or withdrawal of patient consent or completion of a total treatment duration of 2 calendar years*, whichever occurs first

Note: if cabozantinib is permanently discontinued on account of toxicity, treatment with nivolumab can be continued as monotherapy as long as there is no evidence of progressive disease and the patient has not already completed 2 years of treatment with nivolumab

*2 calendar years of treatment is defined as a duration of treatment which does not have any cycles of nivolumab in the period commencing on or after a date which is 2 years after the date of first nivolumab treatment.

Note: if nivolumab is permanently discontinued on account of toxicity, treatment with cabozantinib can be continued as monotherapy as long as there is no evidence of progressive disease.

Administration

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.

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

Nivolumab should be administered intravenously in 100ml 0.9% sodium chloride over 30 minutes via a 0.2micrometre filter

Patients should be monitored every 30 minutes during the infusion (blood pressure, pulse and temperature) 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

Pre-medication

Nil

Emetogenicity

This regimen has mild emetic potential (no routine antiemetics required)

Additional 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.

Extravasation

Neutral

Investigations – pre first cycle

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

Blood pressure must be well controlled before initiating treatment with cabozantinib

The use of vascular endothelial growth factor (VEGF) pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating cabozantinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm

Temporary interruption of cabozantinib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume cabozantinib therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery

Investigations – pre subsequent cycles

FBC, U&Es, LFTs (including AST), calcium, magnesium, thyroid function, blood pressure
Periodic urinalysis to monitor for proteinuria.
ECG if patient has significant cardiac history

Standard limits for administration to go ahead

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

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
Creatinine clearance (CrCl)	> 60mL/min (see advice below)
AST/ALT	< ULN (refer to advice below and IRAE guidance)
Bilirubin	< ULN (refer to advice below and IRAE guidance)

Dose modifications

If dose reductions are required the dose should be reduced as per table below:

Dose level	Cabozantinib dose
Full dose	40mg OD
1st dose reduction	20mg OD
2nd dose reduction	20mg alternate days

- **Immune Related Adverse Events (IRAEs)**

Immunotherapy toxicities should be aggressively managed as they can cause permanent and life-threatening complications.
Consider immunotherapy driven toxicity as a potential reason for all changing laboratory results and discuss with a consultant if any concerns.
Refer to network guidelines for management of IRAEs

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L or platelets < 50 x 10^9/L discuss with consultant.

- **Renal impairment**

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**

In mild-moderate hepatic impairment the recommended dose is 40mg OD and patients should be monitored closely for adverse events. Cabozantinib is not recommended for use in severe hepatic impairment due to a lack of safety data

ALT or AST > 3 x ULN but ≤10 x ULN without concurrent total bilirubin ≥ 2 x 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 x ULN or > 3 x ULN with concurrent total bilirubin ≥ 2 x ULN	Permanently discontinue cabozantinib and nivolumab. Corticosteroid therapy may be considered if immune-mediated reaction is suspected (refer to nivolumab SmPC).

- **Other 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 reduced dose.
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.

- **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.

- **Surgery/dental work**

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.

- **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 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.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
RPLS (reversible posterior leukoencephalopathy syndrome)
GI perforation, fistula

QT interval prolongation
Thyroid dysfunction
Proteinuria, nephrotic syndrome
Arterial and venous thrombotic events
Haemorrhage
Impaired wound healing
Hepatic encephalopathy, abnormalities of LFTs
Immune related adverse effects

- **Frequently occurring side effects**

Myelosuppression
Epistaxis
Hypertension
Electrolyte disturbances
Diarrhoea, constipation
Nausea, vomiting
Stomatitis
PPE
Arthralgia

- **Other side effects**

Skin and hair changes
Taste disturbances
Anorexia
Fatigue
Headache
Dizziness
Tinnitus
Infusion reaction

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

CYP3A4 inhibitors Concomitant medicinal products that are strong inhibitors of CYP3A4 should be used with caution, and chronic use of concomitant medicinal products that are strong inducers of CYP3A4 should be avoided

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.

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 nivolumab. However, systemic corticosteroids or other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions

Additional comments

Women of childbearing potential must be advised to avoid pregnancy while on cabozantinib. Female partners of male patients taking cabozantinib must also avoid pregnancy. Effective methods of contraception should be used by male and female patients and their partners during therapy, and for at least 4 months after completing therapy. Because oral contraceptives might possibly not be considered as effective methods of contraception (see above), they should be used together with another method, such as a barrier method.

References

- NICE guidance cabozantinib and nivolumab (Accessed 11/3/24): https://www.nice.org.uk/guidance/indevelopment/gid-ta11158/documents
- Nivolumab SPC (Accessed 11/3/24): https://www.medicines.org.uk/emc/product/6888/smpc
- Cabozantinib SPC (Accessed 11/3/24): https://www.medicines.org.uk/emc/product/7631/smpc
- Choueiri et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma N Engl J Med 2021; 384:829-841

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