BC Cancer Protocol Summary for Therapy for Metastatic Renal Cell Carcinoma using Cabozantinib

Protocol Code	*GUCABO*
Tumour Group	*Genitourinary*
Contact Physician	*Dr. C. Kollmannsberger*

ELIGIBILITY:

Patients must have:

- Metastatic renal cell carcinoma,
- Any histology or IMDC risk group,
- One of the following indications for use:
  - Second-line therapy after first-line tyrosine kinase inhibitor (SUNItinib, SORAfenib, or PAZOpanib),
    OR
  - Second-line therapy after pembrolizumab plus axitinib or lenvatinib,
    OR
  - Third-line therapy after first-line tyrosine kinase inhibitor and second-line immunotherapy,
    OR
  - Third-line therapy after first-line immunotherapy and second-line tyrosine kinase inhibitor, or after everolimus (GUEVER) or axitinib (GUAXIT) if intolerant to everolimus or axitinib

Patients should have:

- Adequately controlled blood pressure, and
- Adequate hepatic and renal function

Note:

- Patients are eligible to receive everolimus (GUEVER) OR axitinib (GUAXIT) OR cabozantinib (GUCABO) but not sequential use of these agents except for intolerance or contraindications

EXCLUSIONS:

- Uncontrolled hypertension, and
- Pre-existing significant QTc prolongation or unable to discontinue medications that can prolong QTc

Activated: 1 Jan 2020 Revised: 1 Apr 2025 (Title, eligibility, exclusions, tests, treatment, dose modifications and precautions updated)

TESTS:

- Baseline: CBC & Diff, sodium, potassium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, ALT, dipstick or laboratory urinalysis for protein, uric acid, TSH, calcium, magnesium, blood pressure, heart rate, ECG
- Baseline if clinically indicated: MUGA scan or echocardiogram
- Before each cycle: CBC & Diff, dipstick or laboratory urinalysis for protein, creatinine, uric acid, ALT, total bilirubin, blood pressure, heart rate.
- If clinically indicated: total protein, albumin, GGT, alkaline phosphatase, LDH, calcium, magnesium, phosphate, sodium, potassium, TSH, ECG, MUGA scan or echocardiogram
- 24 hour urine for protein if laboratory urinalysis for protein is greater than or equal to 1 g/L or dipstick urinalysis shows 2+ or 3+ proteinuria
- For patients on warfarin: regular INR monitoring
- Blood pressure monitoring at home: See Precautions

PREMEDICATIONS:

Antiemetic protocol for moderate emetogenic chemotherapy protocols (see SCNAUSEA)

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
cabozantinib	60 mg once daily	PO

Duration: Continuous treatment, one cycle consists of 4 weeks of cabozantinib.
Dispense 30 day supply

DOSE MODIFICATIONS:

Hepatic Impairment at initiation:

- Reduce dose to 40 mg once daily for mild or moderate hepatic impairment. Cabozantinib is not recommended in patients with severe hepatic impairment.

Table 1 – Dose reduction levels for all toxicities:

Starting Dose	Dose Level -1	Dose Level -2
60 mg	40 mg	20 mg

1. Diarrhea:

Grade	Diarrhea	Cabozantinib Dose
1	Increase of less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Continue same dose
2	Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Hold until Grade 1 or less, then restart at next lower dose level
3	Increase of 7 or more stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	
4	Life-threatening consequences; urgent intervention indicated	

2. Palmar-Plantar Erythrodysesthesia (PPE):

Grade	Toxicity	Cabozantinib Dose
1	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Continue same dose
2 (Intolerable)	Skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Hold until Grade 1 or less, then restart at next lower dose level
3	Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self care ADL	

3. **Hypertension:**
   - Initiate antihypertensive therapy if clinically indicated
   - If cabozantinib is discontinued, a drop in blood pressure should be anticipated.
   - Antihypertensive dose adjustment or interruption may be required

Blood Pressure Elevation	Cabozantinib Dose
160 mmHg systolic or greater, or 100 mmHg diastolic or greater	▪ Hold until systolic less than 160 mmHg and diastolic less than 100 mmHg ▪ Once controlled, restart at next lower dose level
Elevated blood pressure with life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Discontinue

4. **Proteinuria:**

Proteinuria	Cabozantinib Dose
Negative or 1+ Dipstick, or less than 1 g/L lab urine protein	Maintain dose
2+ Dipstick or greater, or greater than or equal to 1 g/L lab urine protein	▪ Obtain 24 hour urine, hold treatment for greater than or equal to 1 g/24 h ▪ Repeat 24 hour urine prior to next treatment ▪ When proteinuria less than 1 g/24h; resume at reduced dose level
24 hour urine protein: greater than or equal to 3.5 g/24h	Discontinue

PRECAUTIONS:

1. **Diarrhea:** Consider dose reduction with severe diarrhea or short treatment breaks, if necessary. See Dose Modifications.
2. **Hypertension:** The onset of hypertension usually occurs early in treatment. Blood pressure should be controlled prior to initiation of treatment with cabozantinib. Temporary suspension of cabozantinib is recommended for patients with severe hypertension (greater than 160 mmHg systolic or greater than 100 mmHg diastolic). See dose modifications. Discontinue cabozantinib for severe and persistent hypertension despite anti-hypertensive therapy.

It is recommended that for at least the first 2 cycles of treatment, patients monitor their blood pressure daily (home measurements, GP's office, etc.) and regularly thereafter. Patients should keep a journal of their blood pressure measurements that can be submitted to the physician at the next appointment.

3. **Cardiac Toxicity**: cabozantinib can cause prolongation of the QTc interval, decreased heart rate and PR interval prolongation. Correct electrolyte disturbances prior to initiation. Use with caution in patients with baseline heart rate less than 60 beats per minute or history of conduction abnormalities, arrhythmia, ischemic heart disease, or congestive heart failure. Discontinue for arterial or venous thromboembolic events that require medical intervention (e.g., myocardial infarction, cerebral infarction). Monitor electrolytes and follow ECGs during treatment as indicated. Caution when combining with medications that cause bradycardia or drugs that can decrease electrolytes. See BC Cancer Drug Manual.
4. **Renal dysfunction:** Use with caution in patients with mild to moderate impairment. Cabozantinib has not been studied in severe renal impairment.
5. **Hemorrhagic events:** Severe and fatal hemorrhagic events have been reported with cabozantinib. Arterial aneurysm and artery dissection, including rupture, have been reported in patients with and without hypertension. Avoid cabozantinib in patients with recent hemorrhage. Discontinue cabozantinib in patients who experience severe hemorrhage.
6. **Hepatotoxicity**: Hepatitis, fatal hepatic failure and hepatic encephalopathy have been reported with cabozantinib treatment. Avoid in severe hepatic impairment.
7. **Wound healing complications**: cabozantinib may suppress wound healing. Hold treatment at least 4 weeks prior to scheduled surgery, including dental surgery. Treatment resumption is based on clinical judgement. Discontinue treatment in patients with wound dehiscence.
8. **Reversible posterior leukoencephalopathy syndrome (RPLS) (rare)**: Symptoms may include seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is necessary to confirm diagnosis. Discontinue cabozantinib when signs/symptoms or RPLS are present and provide supportive management of symptoms. The safety of reinitiating treatment is not known.
9. **Drug Interactions:** cabozantinib is predominantly metabolized by cytochrome P450 3A4. Potential drug interactions with cytochrome P450 3A4 interacting agents must be considered if combination cannot be avoided and cabozantinib dose modifications may be necessary. Avoid use with concomitant medications known to prolong the QT interval. See BC Cancer Drug Manual.
10. **Venous and arterial thromboembolic events:** are reported during cabozantinib treatment. Monitor and treat as clinically indicated.
11. **Gastrointestinal perforation and fistulas:** Have been reported during treatment with cabozantinib. Use caution in patients with a history of inflammatory bowel disease, prior GI surgery and/or metastases to the GI tract.
12. **Palmar-Plantar Erythrodysesthesia (PPE):** Is reported in patients taking cabozantinib. See dose modifications, above.

Call Dr. Kollmannsberger or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Cella D, Escudier B, Tannir NM, et al. Quality Life outcomes for Cabozantinib versus everolimus in patients with metastatic renal cell carcinoma: METEOR Phase III Randomized Trial. J Clin Oncol. 2018; 36(8):757-764
2. Choueiri TK, Escudier B, Powles T, et al. METEOR investigators. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015; 373:1814-23.
3. Choueiri TK, Escudier B, Powles T, et al. METEOR investigators. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomized, open-label phase 3 trial. Lancet Oncol. 2016; 17(7):917-927