BC Cancer Protocol Summary for Treatment of Advanced Hepatocellular Carcinoma using Cabozantinib

Protocol Code	*UGICABO*
Tumour Group	*Gastrointestinal*
Contact Physician	*GI Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Advanced hepatocellular carcinoma with disease progression on first-line SORAfenib or lenvatinib; or intolerance to regorafenib,
- Not amenable to curative surgery or other local therapy, and
- BC Cancer Compassionate Access Program (CAP) approval

Patients should have:

- ECOG 0 or 1
- Child-Pugh A liver function

EXCLUSIONS:

Patients must not have:

- Progression on regorafenib
- Prior first-line atezolizumab with bevacizumab or tremelimumab with durvalumab followed by second-line SORAfenib or lenvatinib
- Pregnancy

CAUTIONS:

- Uncontrolled hypertension
- Baseline ALT or AST greater than 5 x ULN
- Major surgery within 28 days of administration of therapy

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, albumin, sodium, potassium, INR, TSH, blood pressure measurement
- Baseline if clinically indicated: AFP, GGT, urinalysis, ECG
- Prior to each cycle: CBC & Diff, creatinine, total bilirubin, ALT, INR, albumin, blood pressure measurement
- If clinically indicated: AFP, TSH, alkaline phosphatase, GGT, sodium, potassium, urinalysis, MUGA scan or echocardiogram, ECG
- For patients on warfarin, weekly INR during cabozantinib therapy until stable warfarin dose established, then INR prior to each cycle

PREMEDICATIONS:

- Antiemetic protocol for moderate emetogenic chemotherapy protocols (see SCNAUSEA)

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
cabozantinib	60 mg	PO daily

Repeat every 28 days until progression or unacceptable toxicity.

DOSE MODIFICATIONS:

Table 1 – Dose reduction levels for all toxicities:

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

1. **Hepatic Impairment:**
   In patients with mild to moderate hepatic impairment, reduce starting dose to 40 mg once daily. Use is not recommended in patients with severe hepatic impairment.

   In patients with ALT/AST and total bilirubin ≤ 3X ULN at baseline who develop ≥ Grade 3 elevated ALT/AST or total bilirubin, consider treatment interruption and dose reduction.

PRECAUTIONS:

1. **Hypertension:** The onset of hypertension usually occurs early in treatment. Blood pressure should be controlled prior to initiation of treatment with cabozantinib. Hypertension may be treated with a combination of standard antihypertensive therapy and cabozantinib dose reduction or interruption. Temporary suspension of cabozantinib is recommended for patients with severe hypertension (greater than 160 mmHg systolic or greater than 100 mmHg diastolic). Treatment with cabozantinib may be resumed once hypertension is controlled. Discontinue cabozantinib for hypertensive crisis, or 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. Keep a journal of their blood pressure measurements that can be submitted to the physician at the next appointment.
2. **Cardiac Toxicity**: Cabozantinib has been associated with bradycardia and PR interval prolongation. 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.
3. **QT interval prolongation:** Use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Correct electrolyte disturbances prior to treatment and monitor periodically. Baseline and periodic ECG monitoring is suggested in patients with cardiac disease, arrhythmias, concurrent drugs known to cause QT prolongation, and electrolyte abnormalities.
4. **Hand-Foot Skin Reaction (HFSR):** Consider dose reduction with intolerable symptoms, or short treatment breaks if necessary.

5. **Diarrhea:** Consider dose reduction with severe diarrhea, or short treatment breaks if necessary.
6. **Renal dysfunction/proteinuria:** Use with caution in patients with mild to moderate impairment. Cabozantinib has not been studied in severe renal impairment.
7. **Hemorrhagic events:** Severe hemorrhagic events have been reported with cabozantinib. Discontinue cabozantinib in patients with untreated or incompletely treated varices at high risk for bleeding.
8. **Wound healing complications**: Cabozantinib may suppress wound healing. Hold treatment at least 4 weeks prior to scheduled surgery. The decision to resume after surgery should be based on clinical judgement of adequate wound healing. Discontinue treatment in patients with wound dehiscence.
9. **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.
10. **Drug Interaction**: Cabozantinib is predominantly metabolized by cytochrome P450 3A4. Potential drug interactions with cytochrome P450 3A4 interacting agents must be considered.

Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

References:

1. Abou-Alfa GK, Meyer T, Cheng A-, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. New Engl J Med 2018;379(1):54-63
2. Ipsen Biopharmaceuticals Canada Inc. CABOMETYX® product monograph. Mississauga, Ontario; 7 November 2019.