BC Cancer Protocol Summary for Therapy of Advanced Differentiated Thyroid Cancer using Cabozantinib

Protocol Code	*HNOTDCABO*
Tumour Group	*Head and Neck*
Contact Physician	*Dr. Nicole Chau*

ELIGIBILITY:

Patients must have:

- Advanced or metastatic differentiated thyroid cancer,
- No option for radioactive iodine therapy, or be refractory to prior radioiodine, and
- Prior progression on lenvatinib or intolerance to lenvatinib (HNOTLEN)

Patients should have:

- ECOG 0 to 2,
- Adequate renal and hepatic function,
- TSH less than or equal to 0.5 mIU/L prior to treatment initiation, and
- Electrolytes within normal range (potassium, magnesium, and calcium)

EXCLUSIONS:

Patients must not have:

- Pregnancy,
- Uncontrolled hypertension

CAUTIONS:

- Major surgery within 28 days of administration of therapy

TESTS:

- Baseline: CBC & Diff, platelets, creatinine, total bilirubin, ALT, alkaline phosphatase, sodium, potassium, magnesium, calcium, albumin, phosphate, total protein, thyroglobulin (Tg), thyroglobulin antibody (TgAb), TSH, blood pressure, urinalysis, ECG
- Prior to each cycle: CBC & Diff, platelets, creatinine, total bilirubin, ALT, alkaline phosphatase, TSH*, thyroglobulin (Tg), thyroglobulin antibody (TgAb), blood pressure
- If clinically indicated: Sodium, potassium, magnesium, calcium, albumin, phosphate, total protein, GGT, urinalysis, triglycerides, random glucose, ECG, MUGA scan or echocardiogram
- Consider weekly telephone nursing assessment for signs and symptoms of side effects for Cycle 1, or when increasing dose (Optional)

* TSH suppression during treatment to be individualized. Provider responsible for checking results.

PREMEDICATIONS:

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

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
cabozantinib	60 mg	PO daily

Repeat until progression or unacceptable toxicity. One cycle consists of 4 weeks of cabozantinib.

Dispense 30 day supply.

DOSE MODIFICATIONS:

Table 1 – Dose reduction levels for all toxicities:

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

1. **Hepatic impairment:**

Severity	Cabozantinib Dose
Child-Pugh class A	60 mg
Child-Pugh class B	40 mg
Child-Pugh class C	Do not use

2. **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

3. **Diarrhea:**
   - Initiate antidiarrheal therapy

Grade	Criteria	Cabozantinib Dose
1	Less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline	▪ No change
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	

4. **Palmar-Plantar Erythrodysesthesia (PPE)**

Grade	Criteria	Cabozantinib Dose
1	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	▪ No change
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	

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 at a reduced dose may be resumed once hypertension is controlled. Discontinue cabozantinib for hypertensive crisis, or severe and persistent hypertension despite anti-hypertensive therapy. If cabozantinib is discontinued, a drop in blood pressure should be anticipated. Antihypertensive dose adjustment or interruption may be required.

   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.

2. **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). Caution when combining with medications that cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin), or drugs that can decreased electrolytes (e.g., loop diuretics, thiazide and related diuretics, laxatives, high-dose corticosteroids, proton pump inhibitors). Monitor electrolytes and follow ECGs during treatment as indicated.
3. **Palmar-Plantar Erythrodysesthesia:** Is reported in patients taking cabozantinib. See dose modifications, above.
4. **Diarrhea:** GI perforations and fistulas (including fatal cases) have been reported. See dose modifications, above.
5. **Renal dysfunction/proteinuria:** Use with caution in patients with mild to moderate impairment. Cabozantinib has not been studied in severe renal impairment.
6. **Hemorrhagic events:** Severe and fatal hemorrhagic events have been reported with cabozantinib. Avoid cabozantinib in patients with recent hemorrhage. Discontinue cabozantinib in patients who experience severe hemorrhage.
7. **Wound healing complications**: Cabozantinib may suppress wound healing. Hold treatment at least 4 weeks prior to scheduled surgery, including dental surgery when possible. The decision to resume after surgery should be based on clinical judgement of adequate wound healing. 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. Avoid use with concomitant medications known to prolong the QT interval when possible. See BC Cancer Drug Manual.
10. **Hepatotoxicity**: Hepatitis, fatal hepatic failure and hepatic encephalopathy have been reported with cabozantinib treatment.

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

References:

1. Brose MS, Robinson B, Sherman SI, et al. Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2021 Aug;22(8):1126-1138.
2. Brose MS, Robinson BG, Sherman SI, et al. Cabozantinib for previously treated radioiodine-refractory differentiated thyroid cancer: Updated results from the phase 3 COSMIC-311 trial. Cancer. 2022 Dec 15;128(24):4203-4212.
3. CADTH Reimbursement Review Cabozantinib (Cabometyx). Canadian Journal of Health Technologies November 2022 Volume 2 Issue 11
4. CADTH Provisional Funding Algorithm: Differentiated Thyroid Carcinoma. Feb 2023