BC Cancer Protocol Summary of Treatment for Locally Advanced or Metastatic Medullary Thyroid Cancer Using vanDETanib

Protocol Code	*HNOTVAN*
Tumour Group	*Head and Neck*
Contact Physician	*Dr. Cheryl Ho*

ELIGIBILITY:

- Patients with symptomatic or progressive unresectable, locally advanced, or metastatic medullary carcinoma of the thyroid
- ECOG performance status 0, 1 or 2.
- Registration of the prescribing physician and patient with the CAPRELSA Restricted Distribution Program (www.caprelsa.ca)

EXCLUSIONS:

- History of long QT_c syndrome, or QT_c interval greater than 500 ms
- Uncorrected hypokalemia, hypomagnesemia, or hypocalcemia
- Uncontrolled hypertension
- Pregnant or lactating women
- Prior treatment with selpercatinib (HNOTMSEL)

TESTS:

- **Baseline, two weeks after starting treatment, after any dose change, and prior to each Doctor's visit**: CBC & Diff, platelets, creatinine, potassium, calcium, magnesium, CEA, calcitonin, TSH, total bilirubin, ALT, alkaline phosphatase, ECG, blood pressure

PREMEDICATIONS:

- vanDETanib has low emetogenic potential. If antiemetics are required, avoid agents with potential for interaction (see below and Precautions).
- **NOTE**: dexamethasone, ondansetron, and prochlorperazine CANNOT be used with vanDETanib due to risk of increased QTc
- metoclopramide and dimenhyDRINATE can be used with vanDETanib

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
vanDETanib	300 mg	PO once daily

Continue until disease progression, or intolerable side effects.

DOSE MODIFICATIONS: (note: there are no dose modifications for hematology)

1. **QT_c Prolongation**

QT_c interval	Dose
greater than or equal to 500 ms	Hold until QT_c is less than 450 ms, then resume at 200 mg daily; may be reduced further to 100 mg daily

2. **Hypertension**

Blood Pressure	Dose
CTCAE Grade 3 or 4 Symptomatic increase greater than 20 mm Hg (diastolic) or greater than 140/90 if previously within normal limits	Hold until blood pressure is controlled; then may continue and adjust dose accordingly

3. **Renal dysfunction:**

Creatinine Clearance (mL/min)	Dose
Greater than or equal to 50	300 mg daily
30 to less than 50	200 mg daily
Less than 30	Proceed with caution

4. **Hepatic impairment:** vanDETanib is not recommended for use in patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment, as safety and efficacy have not been established

5. **Non-hematological toxicity**

CTCAE Grade	Dose
1-2	**100%**
3-4	Delay until less than or equal to Grade 1, then resume at 200 mg daily; may reduce dose further to 100 mg daily

PRECAUTIONS:

1. **QT prolongation,** leading to **Torsade de Pointes** and **sudden death,** has been reported. Serum potassium should be maintained in high normal range (≥ 4 mmol/L)

and serum magnesium and calcium levels should be within normal limits to reduce the risk of ECG QT prolongation.

2. **Caution to avoid concomitant use of drugs that prolong QT interval.** If no alternative therapy exists, ECG monitoring of the QTc interval should be done frequently. Drugs that may affect the QT interval include amiodarine, disopyramide, procainamide, sotalol, dofetilide, chloroquine, clarithromycin, dolasetron, granisetron, ondansetron, haloperidol, methadone, MOXIfloxacin, pimozide amongst others.
3. **Intractable diarrhea** may be due to high calcitonin levels. Anti-diarrheal agents are recommended for treatment of diarrhea. Serum electrolytes are to be maintained within normal limits. More frequent electrolyte and ECG monitoring may be required in cases of diarrhea.
4. **Hypertension, including hypertensive crisis** or **heart failure,** that may be irreversible, has been observed.
5. **Caution in patients with impaired renal function**. Suggested starting dose of 200 mg for creatinine clearance 30 to 50 mL/min. vanDETanib exposure may be increased up to 2-fold with creatinine clearance less than 30 mL/min.
6. **Caution in patients with impaired hepatic function** with serum bilirubin greater than 1.5 times ULN. Not recommended in patients with moderate to severe impairment (Child-Pugh class B or C).
7. **Blurred vision or corneal opacities** have been reported.
8. Symptoms of **hypothyroidism** may be managed by monitoring TSH levels and treated with thyroid replacement therapy accordingly.
9. **Mild to moderate skin reactions** (exfoliative rash, photosensitivity reactions, and palmar-plantar erythrodysaesthesia) may be managed symptomatically, or by dose reduction. More **serious skin reactions** (Stevens-Johnson Syndrome and toxic epidermal necrolysis) may require permanent discontinuation.
10. **Reverse Posterior Leukoencephalopathy syndrome (RPLS)** should be considered in any patient experiencing seizures, headache, visual disturbances, confusion, or altered mental function.
11. **Ischemic cerebrovascular events** have been observed in 1.3% of patients taking vanDETanib. vanDETanib should be discontinued in this setting.
12. **Hemorrhage** can occur with vanDETanib. Patients with greater than 2.5 mL of hemoptysis should not receive this agent.
13. **Interstitial lung disease or pneumonitis** should be ruled out in patients experiencing hypoxia, pleural effusion, cough, or dyspnea.
14. **Strong CYP3A4 inhibitors** may increase vanDETanib serum concentrations.
15. **Strong CYP3A4 inducers** may decrease vanDETanib serum concentrations. Examples include: dexamethasone, phenytoin, rifaMPin, carbamazepine, phenobarbital, St. John's Wort.

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

References:

1. Wells SA, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 2012;30(2):134-41.
2. Barbet J, et. al. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. J Clin Endocrinol Metab 2005;90(11):6077-6084.
3. Ton GN, et al. Vandetanib: a novel targeted therapy for the treatment of metastatic or locally advanced medullary thyroid cancer. Am J Health-Syst Pharm 2013;70:849-55.
4. Sanofi Genzyme. CAPRELSA Product Monograph 2 May 2017.
5. Duplomb S, et. al. Unusual adverse event with vandetanib in metastatic medullary thyroid cancer. J Clin Oncol 2012;30(2):e21-e23.
6. Robinson BG, et. al. Vandetanib (100 mg) in patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Endocrinol Metab 2010;95(6):2664-71.
7. Qi W, et. al. Incidence and risk of hypertension with vandetanib in cancer patients: a systematic review and meta-analysis of clinical trials. Br J Clin Pharmacol 2012;75(4):919-30.