BC Cancer Protocol Summary for Treatment of Advanced RET-Mutant Medullary Thyroid Cancer using Selpercatinib

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

ELIGIBILITY:

Patients must have:

- Rearranged during transfection (RET)-mutant medullary thyroid cancer,
- Advanced unresectable or metastatic disease, and
- Progressed on, or intolerance or contraindication to vandetanib (HNOTVAN)

Patients should have:

- Good performance status,
- Adequately controlled: blood pressure, renal and liver function, and
- Electrolytes within normal range (potassium, magnesium, and calcium)

Note: TSH suppression not required. TSH to be maintained in normal range.

EXCLUSIONS:

Patients must not have:

- Differentiated thyroid cancer (see protocol HNOTDSEL),
- QTc greater than 470 ms, or
- Combination treatment. This protocol is monotherapy only.

TESTS:

- Baseline: CBC & Diff, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, sodium, potassium, magnesium, calcium, albumin, TSH, CEA, calcitonin, blood pressure, ECG
- Seven days after start of treatment: sodium, potassium, magnesium, calcium, blood pressure, ECG
- Every two weeks for first 3 months: ALT and total bilirubin
- Months 1 to 6: CBC & Diff, platelets, creatinine, ALT, total bilirubin, sodium, potassium, magnesium, calcium, albumin, TSH, CEA, calcitonin, blood pressure, ECG monthly
- After 6 months, before each doctor's appointment: CBC & Diff, platelets, creatinine, ALT, total bilirubin, sodium, potassium, magnesium, calcium, albumin, TSH, CEA, calcitonin, blood pressure
- If clinically indicated: random glucose, uric acid, phosphorus, total cholesterol, ECG, chest x-ray, BUN

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PREMEDICATIONS:

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

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
selpercatinib	160 mg twice daily (for body weight 50 kg or greater)	PO
	120 mg twice daily (for body weight less than 50 kg)	

Repeat every 30 days (one cycle) until deterioration of symptoms or functional status, radiological evidence of disease progression, or unacceptable toxicity

Dose Reduction at Initiation for Severe Hepatic Impairment:

Hepatic Impairment at Baseline	Selpercatinib Dose	
	Body weight 50 kg or greater	Body weight less than 50kg
Child-Pugh Class C	80 mg twice daily	

DOSE MODIFICATIONS:

Dose Levels for Adverse Reactions During Treatment:

Dose Level	Selpercatinib Dose	
	Body weight 50 kg or greater	Body weight less than 50kg
0	160 mg twice daily	120 mg twice daily
-1	120 mg twice daily	80 mg twice daily
-2	80 mg twice daily	40 mg twice daily
-3	40 mg twice daily	40 mg **once** daily

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1. **Hematological:**

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
Greater than or equal to 1.0	and	Greater than or equal to 75	100%
Less than 1.0	or	Less than 75	Hold until ANC greater than or equal to 1.0, and platelets greater than or equal to 75, then restart at reduced dose

2. **QT prolongation:**

Toxicity	Selpercatinib Dose
QTc greater than or equal to 501 ms	• Hold until QTc 450 to 480 ms or baseline, then restart at next lower dose. • If recurrence after 2 dose reductions, discontinue.
QTc greater than or equal to 501 ms or greater than 60 ms from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Discontinue

3. **Elevated LFTs During Treatment:**

Toxicity	Selpercatinib Dose
ALT or AST elevation greater than 5 to 20 x ULN	• Hold* until ALT and AST 3 x ULN or less or baseline • Once recovered, restart dose **2 dose levels lower** • If no elevation in ALT or AST 2 weeks after re-initiation, consider increasing by 1 dose level. • If no elevation in ALT or AST 4 weeks later, consider increasing to dose taken prior to onset of ALT/AST elevation. • If recurrence of ALT or AST elevation despite dose reduction, discontinue.

* Monitor LFTs weekly upon LFT elevation. Continue weekly LFTs until 4 weeks after final dose escalation

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4. **Hypersensitivity Reactions:**

Toxicity	Selpercatinib Dose
Hypersensitivity: All grades	• Hold until resolution • Initiate prediSONE 1 mg/kg (or equivalent) • Once recovered, restart dose **3 levels lower.** Continue predniSONE • May escalate selpercatinib dose by 1 level weekly if no recurrence of hypersensitivity reactions, increasing to dose taken prior to hypersensitivity. Continue predniSONE without taper • If no recurrence after a minimum of 7 days at final selpercatinib dose, taper predniSONE • If recurrence of hypersensitivity reactions despite dose reduction, discontinue selpercatinib

5. **Hypertension:**

Blood Pressure Elevation	Selpercatinib Dose
Greater than 160 mmHg systolic or greater than 100 mmHg diastolic	• Hold until hypertension is controlled • 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

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6. **Hemorrhagic events:**

Hemorrhagic Event	Selpercatinib Dose
Grade 3 (Bleeding requiring transfusion, radiologic, endoscopic, or elective operative intervention)	• Hold until recovery to baseline or Grade 1 (Mild; intervention not indicated) • Discontinue if severe or life-threatening
Grade 4	• Discontinue

7. **Pulmonary Toxicity:**

Interstitial Lung Disease/Pneumonitis	Selpercatinib Dose
Grade 2 (Symptomatic; medical intervention indicated; limiting instrumental ADL)	• Hold until recovery • Once recovered, restart at reduced dose. • Discontinue if recurrent
Grade 3 or 4	Discontinue

8. **Drug Interactions:** Selpercatinib is a substrate of CYP3A4, and inhibits CYP2C8 and P-glycoprotein and MATE1. Dose adjustment may be required during concomitant use with other medications. See Cancer Drug Manual.

PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
2. **Hemorrhagic events** including fatalities are reported during treatment with selpercatinib, including cerebral hemorrhage, tracheostomy site hemorrhage, hemoptysis, epistaxis, hematemesis, hematuria, post-procedural hemorrhage, and hemorrhage at various organ sites**.**
3. **Wound healing** may be impaired due to inhibition of vascular endothelial growth factor (VEGF) pathway by selpercatinib. Stop treatment at least 7 days prior to elective surgery, and do not restart for at least 2 weeks after major surgery and until wound is adequately healed.

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4. **Hypersensitivity** has been reported in 4-6% of patients being treated with selpercatinib. Patients may experience maculopapular rash often preceded by fever, accompanied by arthralgia or myalgia. Concurrent signs and symptoms may include hypotension, tachycardia and lab abnormalities (e.g., decreased platelets, increased AST/ALT, or increased creatinine). Stop selpercatinib for hypersensitivity reactions and initiate corticosteroids. Rechallenge with dose escalation may be considered in some cases. See Dose Modifications, above.
5. **Hypertension** may occur during treatment with selpercatinib**.** Blood pressure should be controlled before treatment is initiated. Monitor regularly and instruct patients to hold treatment for greater than 160 mmHg systolic or greater than 100 mmHg diastolic. Antihypertensive treatment may be required (see hypertension.ca). Dose reduction upon reinitiation may be required. See Dose Modifications, above.
6. Selpercatinib can cause **prolongation of the QTc interval**. Correct electrolyte disturbances prior to initiation. Do not initiate selpercatinib in patients with QTc interval >470 ms. Avoid combination of selpercatinib with other medications known to prolong QT interval. Caution when combining with medications that cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin), or drugs that can decrease electrolytes (e.g., loop diuretics, thiazide and related diuretics, laxatives, high-dose corticosteroids, proton pump inhibitors). Monitor electrolytes and follow ECGs during treatment. Hold selpercatinib for QTc greater than or equal to 501 ms. Dose reduction or discontinuation may be required. See dose modifications, above.
7. **Tumor Lysis Syndrome** has occurred in 1% of patients using selpercatinib for medullary thyroid carcinoma. Dehydration, renal dysfunction, or rapidly growing tumours may increase the risk. Consider prophylaxis including hydration. Monitor and treat as clinically indicated.
8. **Hepatotoxicity** including increases in ALT and AST occur during treatment with selpercatinib. Dose adjustment, interruption, or discontinuation may be required. See Dose Modifications, above.
9. **Increased creatinine** has been observed during treatment with selpercatinib, secondary to inhibition of renal tubular transporter MATE1 (multidrug and toxin extrusion protein 1) by selpercatinib. Selpercatinib can decrease the renal tubular secretion of creatinine, which is a substrate of MATE1. Glomerular function is unaffected.
10. **Pulmonary toxicity**: Severe or life-threatening interstitial lung disease/pneumonitis may occur during treatment with selpercatinib. Fatalities have been reported. Monitor for signs/symptoms of pulmonary toxicity (eg, dyspnea, cough, fever). Promptly evaluate for interstitial lung disease for acute or worsening respiratory symptoms. See Dose Modifications, above.
11. **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.
12. Symptoms of **hypothyroidism** may be managed by monitoring TSH levels and treated with thyroid replacement therapy accordingly.

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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. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. Lancet Oncol. 2022 Oct;23(10):1261-1273.
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7. Geller G, Laskin J, Cheung WY, Ho C. A retrospective review of the multidisciplinary management of medullary thyroid cancer: eligibility for systemic therapy. Thyroid Res. 2017 Sep 19;10:6.
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