BC Cancer Protocol Summary for Therapy for Locally Recurrent or Metastatic, RAI-refractory Differentiated Thyroid Cancer Using Lenvatinib

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

ELIGIBILITY:

- Locally recurrent or metastatic differentiated thyroid cancer refractory to radioiodine
- Treatment naïve or one prior TKI therapy (SORAfenib, SUNItinib, or PAZOpanib)
- ECOG 0 to 2
- Adequately controlled: blood pressure, renal and liver function
- TSH less than or equal to 0.5 mIU/L

EXCLUSIONS:

- Anaplastic or medullary thyroid cancer
- Significant cardiovascular or gastrointestinal dysfunction
- Proteinuria greater than or equal to 1 g/24h
- History of significant thrombosis
- Pre-existing significant QTc prolongation

TESTS:

- Baseline: CBC/differential, serum creatinine, alkaline phosphatase, ALT, total bilirubin, albumin, potassium, calcium, magnesium, urine protein, TSH, blood pressure, ECG
- Every two weeks for first 2 months: blood pressure, alkaline phosphatase, ALT, total bilirubin, albumin
- Before each Doctor's appointment: CBC/differential, serum creatinine, alkaline phosphatase, ALT, total bilirubin, albumin, potassium, calcium, magnesium, urine protein, TSH, blood pressure
- If clinically indicated: ECG

PREMEDICATIONS:

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

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
lenvatinib	24 mg	PO once daily

- Repeat every 30 days (one cycle). Continue until toxicity or disease progression.
- Consider starting at 20 mg/day and escalate or de-escalate as tolerated.

DOSE MODIFICATIONS

Table 1 – Persistent or intolerable Grade 2 or 3 adverse reactions or Grade 4 lab abnormalities

Adverse Reaction	Modification	Adjusted Dose*
First occurrence	Hold dose until resolved to Grade 0 to 1 or baseline	20 mg one daily
Second occurrence**		14 mg once daily
Third occurrence**		10 mg once daily

* Reduce dose in succession based on prior dose level (24 mg, 20 mg, or 14 mg daily); do not increase dose after dose reductions have been made.
** refers to the same or a different adverse reaction that requires dose modification

Table 2 – Hematology

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	Delay

Table 3 – Hepatotoxicity: No dose modifications with mild or moderate hepatic impairment (Child-Pugh A or B). With severe impairment (Child-Pugh C), use 14 mg once daily.

Adverse event	Alkaline Phosphatase		AST		ALT		Total bilirubin	Dose
Grade 1	greater than ULN to 2.5 X ULN	and/ or	greater than ULN to 3 X ULN	or	greater than ULN to 3 X ULN	and/ or	greater than ULN to 1.5 X ULN	No adjustment
Grade 2	greater than 2.5 to 5 X ULN	and/ or	greater than 3 to 5 X ULN	or	greater than 3 to 5 X ULN	and/ or	greater than 1.5 to 3 X ULN	No adjustment
Grade 3	greater than 5 to 20 X ULN	and/ or	greater than 5 to 20 X ULN	or	greater than 5 to 20 X ULN	and/ or	greater than 3 to 10 X ULN	reduce to 14 mg (max.) daily or lower
Grade 4	greater than 20 X ULN	and/ or	greater than 20 X ULN	or	greater than 20 X ULN	and/ or	greater than 10 X ULN	discontinue

Table 4 – Renal impairment:

Adverse event	eGFR or CrCl	Dose
Grades 1 and 2	greater than or equal to 30 mL/min	Maintain dose or physician's discretion
Grade 3	15 to less than 30 mL/min	14 mg once daily or physician's discretion
Grade 4	less than 15 mL/min; dialysis indicated	discontinue

Table 5 - Diarrhea: See **Table 1** for dose modifications

Adverse event	Diarrhea
Grade 1	Increase of less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4 to 6 stools per day over baseline; moderate increase in output compared to baseline
Grade 3	Increase of greater than or equal to 7 stools per day over baseline; incontinence; hospitalization indicated
Grade 4	Life-threatening

Table 6 - Proteinuria:

Proteinuria	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 2 g/24 h, monitor every 2 weeks. Hold until proteinuria less than 2 g/24h; resume at reduced dose*
24 hour urine protein: greater than or equal to 3.5 g/24h	discontinue

* see Table 1

Table 7 – QT Prolongation:

Adverse event	QT Prolongation	Dose
Grade 1	QTc 450 to 480 ms	Maintain dose
Grade 2	QTc 481 to 500 ms	Assess risk for developing TdP; maintain dose or reduce dose*
Grade 3	QTc greater than or equal to 501 ms on 2 separate ECGs	Hold until Grade 1 or baseline; resume at reduced dose*
Grade 4	QTc greater than or equal to 501 ms or greater than 60 ms from baseline or signs and symptoms of serious arrhythmia	discontinue

* see Table 1

PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines. There are no dose modifications for lenvatinib.
2. **Hypertension:** Patients with hypertension should exercise caution while on Lenvatinib. Rigorous treatment of blood pressure is necessary, since Lenvatinib can cause a rapid onset of high blood pressure. Temporary suspension of Lenvatinib is recommended for patients with severe hypertension (greater than 160 mmHg systolic or greater than 100 mmHg diastolic). Treatment with Lenvatinib may be resumed once hypertension is controlled (see also http://www.hypertension.ca).

   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 keep a journal of their blood pressure measurements that can be submitted to the physician at the next appointment.
3. **Renal toxicity:** Primary risk factor was dehydration/hypovolemia secondary to diarrhea and vomiting; encourage oral hydration.
4. **Hepatotoxicity:** Liver enzymes should be monitored before treatment, every two weeks for the first two months, then monthly thereafter during treatment. Lenvatinib is neither a strong inducer nor inhibitor of cytochrome P450 3A in the liver. It may be co-administered without dose adjustment with CYP3A inhibitors and inducers, P-glycoprotein inhibitors and inducers, BCRP inhibitors.
5. **Posterior Reversible Encephalopathy Syndrome (PRES)**: MRI to confirm diagnosis. If patients present with headache, seizure, lethargy, confusion, altered mental function, blindness, or other visual or neurological disturbances, consider dose interruptions, adjustments, or discontinuation.
6. **Risk of nosebleeds** would require dose interruptions, adjustments or discontinuation.

7. **Gastrointestinal perforation and fistula formation**: Upon development, discontinue.
8. **Arterial or venous thromboembolic event**: Assess a patient's risk for myocardial infarction or hemorrhagic stroke prior to initiation of treatment. Discontinue lenvatinib following an arterial thrombotic event.
9. **Weight loss** secondary to decreased appetite, diarrhea; patients with body weight below 60 kg appear to have reduced tolerability.
10. Risk of **prolonged QT interval**; monitor ECG and electrolytes regularly. Hold lenvatinib for QTc greater than or equal to 501 ms.

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. Schlumberger M, Tahara M, Wirth LJ, et.al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 2015;372:621-30.
2. Schlumberger M, Tahara M, Wirth LJ, et.al. Supplementary Appendix to Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 2015;372:621-30.
3. Pan-Canadian Oncology Drug Review. Lenvatinib.Final Recommendation_September 2016.
4. Shumaker RC, Zhou M, Ren M, et.al. Effect of lenvatinib (E7080) on QTc interval: results from a thorough QT study in healthy volunteers. Cancer Chemother Pharmacol 2014;73:1109-17.