BC Cancer Protocol Summary for Therapy of Advanced Hepatocellular Carcinoma using Lenvatinib

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

ELIGIBILITY:
Patients must have:
- Hepatocellular carcinoma not amenable for local regional therapy, and
- No prior systemic therapy, or
- Progression on first-line atezolizumab and bevacizumab (GIATZB) or tremelimumab and durvalumab (GITREMDUR)

Note: Patients who are intolerant to SORAfenib may switch to GILEN

Patients should have:
- ECOG 0 to 1
- Child-Pugh A liver function
- Adequately controlled blood pressure and renal function

EXCLUSIONS:
Patients must not have:
- History of significant thrombosis
- Pre-existing significant QTc prolongation or unable to discontinue medications that can prolong QTc

CAUTIONS:
- Significant cardiovascular or gastrointestinal dysfunction
- Proteinuria greater than or equal to 1 g/24h

TESTS:
- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, albumin, sodium, potassium, INR, TSH, urinalysis, blood pressure measurement
- Baseline if clinically indicated: AFP, GGT, ECG, MUGA scan or echocardiogram
- Every two weeks for first 2 months: blood pressure, ALT, total bilirubin
- Prior to each cycle: CBC & Diff, creatinine, total bilirubin, ALT, INR, albumin, blood pressure
- If clinically indicated: AFP, urine protein, alkaline phosphatase, GGT, sodium, potassium, TSH, ECG, MUGA scan or echocardiogram
- 24 hour urine for protein if laboratory urinalysis for protein is greater than or equal to 1 g/L or dipstick urinalysis shows 2+ or 3+ proteinuria
- Blood pressure monitoring at home: See Precautions
- For patients on warfarin, weekly INR during lenvatinib therapy until stable warfarin dose established, then INR prior to each cycle

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

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
lenvatinib	8 mg once daily continuously (for body weight less than 60 kg) 12 mg once daily continuously (for body weight more than or equal to 60 kg)	PO

Repeat every 30 days (one cycle) until progression or unacceptable toxicity.

DOSE MODIFICATIONS:

1. **Table 1 - Persistent or intolerable Grade 2 or 3 adverse reactions or Grade 4 lab abnormalities* (lenvatinib)**

Adverse Reaction	Modification	Dose	
		(Greater than or equal to 60 kg body weight) **Starting dose = 12 mg**	**(Less than 60 kg body weight)** **Starting dose = 8 mg**
First occurrence	Hold dose until resolved to Grade 0 to 1 or baseline	8 mg once daily	4 mg once daily
Second occurrence**		4 mg once daily	4 mg every other day
Third occurrence**		4 mg every other day	Discontinue

* excluding laboratory abnormalities judged to be non-life-threatening, which could be managed as Grade 3
** same reaction or new reaction

2. **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

3. **Hepatotoxicity -** No dose modifications with mild hepatic impairment (Child-Pugh A). Patients with mild hepatic impairment may require additional monitoring of adverse reactions requiring dose adjustments. Further dose adjustment may be necessary based on individual tolerability. The available very limited data in moderate hepatic impairment (Child-Pugh B) are not sufficient to allow for a dosing recommendation. Lenvatinib has not been studied in patients with severe hepatic impairment (Child-Pugh C).

4. **Renal impairment -** No dose modifications are required on the basis of renal function in patient with mild or moderate renal impairment. The available data does not allow for a dosing recommendation for patients with severe renal impairment.

5. **Table 3 - 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

6. **Table 4 - Proteinuria:** See **Table 1** for dose modifications

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

7. **Table 5 – QT Prolongation:** See **Table 1** for dose modifications

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 Torsades de pointes (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

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.

   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. Blood pressure should be monitored monthly thereafter while on treatment.

   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 at a reduced dose once hypertension is controlled (see also http://www.hypertension.ca)**.**

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, Pglycoprotein 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

10. Risk of **prolonged QT interval**; use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Monitor ECG, and electrolytes regularly. Correct electrolyte disturbances prior to treatment. Hold lenvatinib for QTc greater than or equal to 500 ms.

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. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018; 391: 1163-1173.