BC Cancer Protocol Summary for Therapy for Advanced Hepatocellular Carcinoma using SORAfenib

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

ELIGIBILITY:

Patients must have:

- Inoperable advanced hepatocellular carcinoma, and
- No prior systemic therapy and intolerant of lenvatinib, or
- Progression on first-line atezolizumab and bevacizumab (GIATZB) or tremelimumab with durvalumab (GITREMDUR) and intolerant of lenvatinib

Patients should have:

- ECOG performance status less than or equal to 2
- Child-Pugh A status

EXCLUSIONS:

- Significant cardiovascular disease and/or known LVEF less than 50%
- Uncontrolled hypertension

TESTS:

- Baseline: CBC, differential, platelets, sodium, potassium, magnesium, calcium, phosphate, creatinine, albumin, bilirubin, ALT, alkaline phosphatase, INR, TSH, and optional AFP.
- Prior to each cycle: CBC, differential and platelets, creatinine, ALT, bilirubin.
- If clinically indicated: sodium, potassium, magnesium, calcium, phosphate, albumin, lipase, TSH, AFP
- For patients on warfarin: regular INR monitoring. See Precautions.
- MUGA scan or echocardiogram if clinically indicated or if history of cardiac problem.
- Baseline and routine ECG for patients at risk of developing QT prolongation (at the discretion of the ordering physician) and consider monitoring sodium, potassium, magnesium, and calcium. See Precautions.

PREMEDICATIONS:

- Antiemetic not usually required

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
SORAfenib	400 mg BID continuously	PO

One cycle is 28 days

Dose reduction:
Dose level -1: 400 mg **once** a day continuously
Dose level -2: 400 mg **every other day** continuously
If dose level -2 not tolerated then discontinue.

DOSE MODIFICATIONS:

1. **Hematological**

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose (all drugs)
greater than or equal to 1.0	and	greater than or equal to 50	100%
0.5 to less than 1.0	and	greater than or equal to 50	Decrease one dose level
less than 0.5	or	less than 50	Delay until ANC greater than 0.5 and platelets greater than 50 then decrease one dose level. If no recovery after 4 weeks, treatment should be discontinued.

2. **Non-Hematological toxicity:**

CTC-Grade	Dose
1-2	100%
3	Delay until less than or equal to Grade 2 then decrease one dose level
4	Discontinue therapy

3. **Renal dysfunction:**

Only a very small percentage of SORAfenib and its metabolites are excreted by the kidney. No dose adjustment is required in patients with mild, moderate, or severe renal impairment not requiring dialysis.
However, to reduce the risk of adverse events, a small pharmacokinetic trial (Miller 2009) suggested the initial dose of SORAfenib may be reduced based on CrCl:

CrCl	SORAfenib starting dose
>40 mL/min	400 mg twice daily
20 to 40 mL/min	200 mg twice daily
< 20 mL/min	No information found

SORAfenib has not been studied extensively in patients undergoing dialysis. However, the trial also suggested that it can be initiated at a reduced dose (such as 200 mg once daily) under close monitoring.

4. **Hepatic dysfunction**:

SORAfenib is mainly metabolized and excreted through the liver.

Product Monograph: Patients with Child-Pugh B hepatic impairment had greater systemic exposure than those with Child-Pugh A hepatic impairment. Sorafenib has not been studied in patients with Child Pugh C hepatic impairment.

A small pharmacokinetic trial (Miller 2009) suggested initial dose of SORAfenib may be reduced based on hepatic function:

Bilirubin	SORAfenib starting dose
≤ 1.5 x ULN	400 mg twice daily
>1.5 x ULN to ≤ 3 x ULN	200 mg twice daily
>3 to 10 x ULN	Not recommended

The trial also suggested if Albumin falls below 25 g/L (with any bilirubin or ALT) then SORAfenib initial dose be reduced to 200 mg once daily.

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BCCA Febrile Neutropenia Guidelines.

2. **Cardiac Toxicity:** Symptomatic patients with evidence of cardiac dysfunction should have SORAfenib discontinued.

3. SORAfenib is predominantly metabolized and excreted through cytochrome P4503A4 in the liver. Potential drug interactions with cytochrome P4503A4 interacting agents must be considered. see also: http://medicine.iupui.edu/flockhart/table.htm. Possible drug interaction with SORAfenib and warfarin has been reported. Patients taking warfarin concurrently with sorafenib should be monitored regularly for changes in prothrombin time, INR, and for clinical bleeding episodes.

4. Patients with hypertension should exercise caution while on Sorafenib. Rigorous treatment of blood pressure is necessary, since SORAfenib can cause a rapid onset of high blood pressure. Temporary suspension of SORAfenib is recommended for patients with severe hypertension (greater than 200 mmHg systolic or greater than 110 mmHg diastolic). Treatment with SORAfenib 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.

5. QT prolongation has been reported with SORAfenib: Use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Correct electrolyte disturbances prior to treatment and monitor periodically. Baseline and periodic ECG monitoring is suggested in patients with cardiac disease, arrhythmias, concurrent drugs known to cause QT prolongation, and electrolyte abnormalities.

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. Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib improves survival in advanced hepatocellular carcinoma (HCC): results of a Phase III randomized placebo-controlled trial (SHARP trial). Proc Am Soc Clin Oncol 2007;25: abstract LBA1.
2. Abou-Alfa GK, Schwartz L, Ricci S, et al. Phase II Study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2006; 24(26):4293-300.
3. Miller AA, Murry DJ, Owzar K, et al, Phase I and Pharmacokinetic Study of Sorafenib in Patients With Hepatic or Renal Dysfunction: CALGB 60301, J Clin Oncol 2009, 27(11):1800-5.