BC Cancer Protocol Summary for Treatment of Advanced Hepatocellular Carcinoma Using Regorafenib

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

ELIGIBILITY:

Patients must have:
- Advanced hepatocellular carcinoma with disease progression on first-line SORAfenib or lenvatinib.
- Tolerated SORAfenib dose at least 400 mg/day for 20 of 28 days if prior SORAfenib
- Not amenable to surgery or other local therapy

Patients should have:
- ECOG 0-1
- Child-Pugh A liver function
- No major surgery within 14 days of administration of therapy

EXCLUSIONS:

Patients must not have:
- Uncontrolled hypertension
- Hypersensitivity to regorafenib or SORAfenib
- Prior first-line atezolizumab with bevacizumab or tremelimumab and durvalumab followed by second-line SORAfenib or lenvatinib

CAUTION:

- Concurrent warfarin therapy
- Patients at risk for or who have a history of cardiac events, including those with bradycardia, have a history of arrhythmia, or are taking heart rate lowering drugs
- Asian patients
- Mild or moderate hepatic impairment
- 65 years or older

TESTS:

- Baseline: CBC & diff, platelets, creatinine, sodium, potassium, calcium, magnesium, phosphate, albumin, bilirubin, alkaline phosphatase, ALT, GGT, TSH, urinalysis, Blood Pressure measurement. If clinically indicated: AFP.
- Prior to each cycle: CBC & diff, platelets, creatinine, sodium, potassium, calcium, magnesium, phosphate, bilirubin, alkaline phosphatase, ALT, urinalysis, Blood Pressure measurement.
- TSH prior to each odd numbered cycle or if clinically indicated.
- If clinically indicated: 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 ordering physician) and monitor sodium, potassium, magnesium and calcium. See Precautions.

PREMEDICATIONS:

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

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
regorafenib	160 mg once daily* on days 1 to 21 followed by 7 day rest (at physician discretion, may start with 120 mg or 80 mg daily and escalate to 160 mg once daily if tolerated)	PO at the same time each day after a light, low-fat, low-calorie meal (less than 30% fat, ~300-550 calories)

Repeat every 28 days until progression or unacceptable toxicity.

DOSE MODIFICATIONS:

Table 1 - Dose Reduction Levels for All Toxicities:

Agent	Starting Dose	Dose Level -1	Dose Level -2
regorafenib	**160 mg**	**120 mg**	**80 mg**

Dose can be re-escalated to a maximum of 160 mg at the physician's discretion once the toxicities are resolved

1. **Hematological**

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
greater than or equal to 1.0	or	greater than or equal to 50	100%
0.5 to less than 1.0	or	25 to less than 50	Delay then reduce one dose level*†
less than 0.5	or	less than 25	Delay then reduce one dose level**†

* If stable, dose re-escalation can be considered at physician's discretion.
** Permanent discontinuation can be considered at physician's discretion.
† If no recovery after a 4-week delay, discontinue treatment.

2. **Hepatotoxicity**

		1st episode	2nd episode	3rd episode
ALT	Less than 5 times upper limit or normal/baseline	No cycle delay No dose reduction		
	5 to 20 times upper limit of normal/baseline	Delay cycle until recovery. Then dose reduce one level and weekly ALT and bilirubin for at least 4 weeks.*	Delay cycle until recovery. Then dose reduce one level and weekly ALT and bilirubin for at least 4 weeks.*	Discontinue
	More than 20 times upper limit of normal/baseline	Discontinue	-	-
Bilirubin	Less than 3 times upper limit or normal/baseline	No cycle delay No dose reduction		
	3 to 10 times upper limit of normal/baseline	Delay cycle until recovery. Then dose reduce one level and weekly ALT and bilirubin for at least 4 weeks.*	Delay cycle until recovery. Then dose reduce one level and weekly ALT and bilirubin for at least 4 weeks.*	Discontinue
	More than 10 times upper limit of normal/baseline	Discontinue	-	-
ALT & Bilirubin	ALT more than 3 times upper limit of normal/baseline with a concomitant rise in bilirubin more than 2 times upper limit of normal/baseline	Delay cycle until recovery. Then dose reduce one level and weekly ALT and bilirubin for at least 4 weeks.* In case of negative risk-benefit assessment, consider permanent discontinuation at the first occurrence. †	Discontinue	-

* If all values remain stable for two full cycles, dose re-escalation may be considered at the discretion of physician. After re-escalation ALT and bilirubin should be checked weekly for at least 4 weeks.

† Patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations.

3. **Hand-Foot Skin Reaction (HFSR)**

Grade	Hand-Foot Skin Reaction	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
1	Skin changes with discomfort the hands or feet (eg, numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema) not disrupting normal activities	100%	100%	100%	100%
2	Skin changes with pain (eg, erythema, swelling) affecting activities of daily living	Reduce one dose level. If no improvement, delay until symptoms resolve to Grade 1 and then resume treatment at the reduced dose level.*	Delay until symptoms resolve to grade 1 and then reduce one dose level.*	Delay until symptoms resolve to grade 1 and then reduce one dose level.* †	Discontinue
3	Severe skin changes (eg, moist desquamation, ulceration, blistering) causing severe pain or discomfort and inability to work or perform activities of daily living	Delay until symptoms resolve to grade 1 and then reduce one dose level.*	Delay until symptoms resolve to grade 1 and then reduce one dose level.* †	Discontinue	-

* If symptoms resolve to Grade 1 after dose reduction, dose escalation may be considered at physician's discretion.

† Patients requiring more than 2 dose level reductions (less than 80 mg), discontinue regorafenib therapy.

4. **Non-Hematological toxicity** (not related to HFSR, hypertension or abnormal liver function tests)**:**

NCI-CTCAE	Dose	Dose for subsequent cycles
Grade 0-2	100%	100%
Grade 3	Delay until symptoms resolve to grade 2 and then reduce one dose level.*	If symptoms remain at grade 2 or less, dose re-escalation can be considered at physician's discretion. If toxicity recurs, institute permanent dose reduction.
Grade 4	Delay until symptoms resolve to grade 2 and then reduce one dose level.* Permanent discontinuation can be considered at physician's discretion.	-

* If no symptom recovery after a 4-week delay, discontinue treatment.

PRECAUTIONS:

1. **Cardiac Toxicity**: Regorafenib has been associated with cardiac adverse events including myocardial ischemia and/or infarction and must be used with caution in patients with history of ischemic heart disease. For new or acute onset cardiac ischemia and/or infarction, hold regorafenib until resolution; reinitiate therapy only after consideration of potential benefits and risks to the patient. Permanently discontinue therapy if there is no resolution.
2. **Hemorrhagic events:** Cerebral, respiratory, genitourinary and gastrointestinal tract hemorrhagic events have been reported with regorafenib. Patients on warfarin should be closely monitored. Discontinue regorafenib in patients with severe or life-threatening hemorrhage.
3. **Hypertension:** The onset of hypertension usually occurs in the first cycle of treatment. Blood pressure should be controlled prior to initiation of treatment with regorafenib. Hypertension may be treated with a combination of standard antihypertensive therapy and regorafenib dose reduction or interruption. Temporary suspension of regorafenib is recommended for patients with severe hypertension (greater than 160 mmHg systolic or greater than 100 mmHg diastolic). Treatment with regorafenib may be resumed once hypertension is controlled. Discontinue regorafenib for hypertensive crisis, or severe and persistent hypertension despite anti-hypertensive therapy.
   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 regularly thereafter. Keep a journal of their blood pressure measurements that can be submitted to the physician at the next appointment.
4. **Renal dysfunction:** No dose modification is required in pre-existing mild to severe impairment. Regorafenib has not been studied in end-stage renal disease.
5. **Hepatic dysfunction**: No dose modification is required for pre-existing mild to moderate hepatic impairment. Regorafenib has not been studied in severe hepatic dysfunction
6. **Neutropenia (uncommon)**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
7. **Wound Healing complications**: Regorafenib may suppress wound healing. Hold treatment at least 2 weeks prior to scheduled surgery. The decision to resume after surgery should be based on clinical judgement of adequate wound healing. Discontinue treatment in patients with wound dehiscence.
8. **Infections**: Increased incidence of urinary tract infections, nasopharyngitis, mucocutaneous and systemic fungal infections and pneumonia have been reported with regorafenib. In case of worsening infection event, hold regorafenib.
9. **Reversible posterior leukoencephalopathy syndrome (RPLS) (rare)**: Symptoms may include seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without

associated hypertension. Brain imaging is necessary to confirm diagnosis. Discontinue regorafenib when signs/symptoms or RPLS are present and provide supportive management of symptoms. The safety of reinitiating treatment is not known.

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 JM et al. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329-338.
2. Llovet JM et al SHARP Investigation Study Group. Sorafenib in advanced helpatocellular carcinoma. N Engl J Med 2008;359:378-390.
3. Cheng AL et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, placebo-controlled trial Lancet Oncol 2009;10:25-34.
4. Bruix J et al Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE) a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;389:56-66.
5. Ogasawara S et al Characteristics of patients with sorafenib-treated advanced hepatocellular carcinoma eligible for second-line treatment. Invest New Drugs 2018;36(2):332-339.
6. Manufacturer's monograph: Stivarga, https://www.bayer.ca/omr/online/stivarga-pm-en.pdf