BC Cancer Protocol Summary for Treatment of Relapsed or Refractory Advanced Osteosarcoma using Regorafenib

Protocol Code	*SAAVOR*
Tumour Group	*Sarcoma*
Contact Physician	*Dr. Alannah Smrke*

ELIGIBILITY:

Patients must have:

- Histologic diagnosis of osteosarcoma,
- Documented evidence of unresectable, recurrent or metastatic disease,
- Progression after at least one line of chemotherapy for advanced, recurrent or metastatic disease.

Patients should have:

- Adequate organ function.

EXCLUSIONS:

- Uncontrolled hypertension
- Hypersensitivity to regorafenib or sorafenib

Special caution:

- Concurrent warfarin therapy
- Patients at risk for or who have a history of cardiac events 2) patients with mild or moderate hepatic impairment, 3) patients 65 years or older

TESTS:

- Baseline: CBC & diff, platelets, creatinine, albumin, bilirubin, alkaline phosphatase, ALT, GGT, urinalysis, TSH
- Before each cycle: CBC & diff, platelets, creatinine, bilirubin, alkaline phosphatase, ALT, urinalysis. TSH prior to each odd numbered cycle or if clinically indicated.

PREMEDICATIONS:

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

TREATMENT:

Drug	Dose	BCCA Administration Guideline
regorafenib	160 mg once daily* on days 1 to 21 followed by 1 week rest** (may start with 120 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)

*round dose to the nearest 40 mg
** Each cycle consists of 4 weeks

Repeat every 28 days until progression or unacceptable toxicity.

DOSE MODIFICATIONS:

1. **Hematological**

ANC (x10^9/L)		Platelets (x10^9/L)	Dose*
greater than or equal to 1.5	or	greater than or equal to 75	100%
1.0 to less than 1.5	or	50 to less than 75	100%
0.5 to less than 1.0	or	25 to less than 50	Delay then 75%
less than 0.5	or	less than 25	Delay then 50% (if recurrent, then discontinue)

*round dose to the nearest 40 mg

2. **Hepatotoxicity**

Bilirubin		ALT	Dose
-		Greater than 3 X ULN	Delay then resume at 120 mg PO daily
-		Greater than 5 X ULN Recurrent despite dose reduced to 120 mg PO daily	Discontinue
-		Greater than 20 X ULN	Discontinue
Greater than 2 X ULN	And	Greater than 3 X ULN	Discontinue

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 (eg, numbness, dysesthesia, paresthesia, tingling, erythema) not disrupting normal activities	100%	100%	100%	100%
2	Skin changes with pain (eg, erythema, swelling) affecting activities of daily living	delay* then 100%	delay* then 75%	delay* then 50%	discontinue
3	Severe skin changes with pain (eg, moist desquamation, ulceration, blistering) causing severe discomfort and inability to work or perform activities of daily living	delay* then 75%	discontinue or delay* then 50%	discontinue	discontinue

*stop treatment immediately and delay until resolved to grade 0-1
**round dose to the nearest 40 mg

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

CTC-Grade	Dose
1 to 2	100%
3 to 4	Delay until less than or equal to Grade 2 then resume at reduced dose
4 recurrent	Delay until less than or equal to Grade 2 then reinitiate only after consideration of potential benefits and risks. Discontinue if patient is unable to tolerate 80 mg dose.

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:** respiratory, genitourinary and gastrointestinal tract 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:** usually occurs in the first cycle of treatment. Monitor blood pressure weekly for the first 6 weeks of treatment and regularly thereafter. Hypertension may be treated with a combination of standard anti-hypertensive therapy and regorafenib dose reduction or interruption. Discontinue regorafenib for hypertensive crisis, or severe and persistent hypertension despite anti-hypertensive therapy.
4. **Renal dysfunction:** No dose modification is required in pre-existing mild to moderate renal impairment. Regorafenib has not been studied in severe renal impairment or 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. **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 Dr. Alannah Smrke or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Duffaud F, Mir O, Boudou-Rouquette P, et al. Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study. Lancet Oncol 2019;20(1):120-33.