BC Cancer Protocol Summary for Fourth-Line Therapy of Advanced Gastrointestinal Stromal Cell Tumours (GIST) using Ripretinib

Protocol Code	*SAAVGRIP*
Tumour Group	*Sarcoma*
Contact Physician	*Dr. Howard Lim*

ELIGIBILITY:

Patients must have:
- Advanced gastrointestinal stromal tumour (GIST), and
- Disease progression on or intolerance to iMAtinib, SUNItinib, and regorafenib

Patients should have:
- Adequate hematological, renal and hepatic function,
- Good performance status,
- Adequately controlled blood pressure

EXCLUSIONS:

Patients must not have:
- Active central nervous system metastases,
- Clinically significant cardiac conditions or other comorbidities,
- Gastrointestinal problems preventing the ingestion or absorption of oral medications,
- Combination treatment. This protocol is monotherapy only

CAUTIONS:

- Hypersensitivity to any previous tyrosine kinase inhibitor,
- Recent surgery. Ensure adequate wound healing prior to initiation

TESTS:

- Baseline: CBC & Diff, platelets, creatinine, albumin, total bilirubin, alkaline phosphatase, ALT, blood pressure
- Baseline if clinically indicated: cardiac MUGA or echocardiogram
- Every 4 weeks: CBC & Diff, platelets, total bilirubin, ALT, blood pressure
- If clinically indicated: cardiac MUGA or echocardiogram, creatinine, alkaline phosphatase, lipase, calcium, albumin, phosphate, sodium, potassium, creatine kinase, LDH

PREMEDICATIONS:

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

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
ripretinib	150 mg* once daily *dose escalation to 150 mg PO BID permitted after disease progression at physician discretion	PO

- **Repeat every 28 days as long as clinical benefit**

DOSE MODIFICATIONS:

Dose Levels:

Dose Level	Standard Ripretinib Dose
	150 mg PO once daily
Dose Level -1	100 mg PO once daily
Dose Level -2	50 mg PO once daily

Dose Levels:

Dose Level	Escalated Ripretinib Dose
	150 mg PO BID
Dose Level -1	100 mg PO BID
Dose Level -2	150 PO **once** daily*

*no further dose reduction for patients previously escalated

1. Hematological:

ANC ($x\ 10^9$/L)		Platelets ($x\ 10^9$/L)	Dose
Greater than or equal to 1.0	and	Greater than or equal to 50	100%
Less than or equal to 0.99	or	Less than or equal to 49	Hold until ANC 1.0 or greater and platelets 50 or greater ▪ If no recovery after 28 days, discontinue ▪ If recovery within 28 days, then restart but at next lower dose level ▪ Consider re-escalating dose if neutropenia/thrombocytopenia does not worsen after 28 days at reduced dose ▪ If recurrence at reduced dose, discontinue

2. Palmar plantar erythrodysesthesia syndrome (PPES):

Grade 1	Grade 2	Grade 3
Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL

Severity	Ripretinib Dose
Grade 2	Hold for 7 days minimum, and until Grade 1 or baseline, then: ▪ If recovery takes 7 days or less, restart at same dose. ▪ If recovery takes more than 7 days, restart but at next lower dose level ○ Consider re-escalating dose if PPES does not worsen after 28 days ▪ If recurrent, hold until recovery to Grade 1 or baseline, then restart at next lower dose, regardless of time to recovery
Grade 3	Hold for 7 days minimum (maximum of 28 days), and until Grade 1 or baseline ▪ If not resolved after 28 days, consider discontinuation ▪ If resolution within 28 days, then restart but at next lower dose level ▪ Consider re-escalating dose if PPES does not worsen after 28 days at reduced dose

3. Hypertension:

Blood Pressure in mmHg			
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Systolic 120 to 139 or diastolic 80 to 89	Systolic 140 to 159 or diastolic 90 to 99; medical intervention indicated; recurrent or persistent (24 h or longer); symptomatic increase by more than 20 mmHg (diastolic) or to more than 140/90 if previously within normal limits; monotherapy indicated	Systolic 160 or higher or diastolic 100 or higher; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated

Severity	Ripretinib Dose
Grade 3	▪ Asymptomatic: continue at current dose, and manage hypertension to achieve Grade 1 or lower blood pressure ▪ Symptomatic: ○ Hold until Grade 1 or lower and asymptomatic, then restart at previous dose ○ If blood pressure remains higher than Grade 1 but symptoms resolved, restart but at next lower dose level ▪ Discontinue if recurrent despite dose reduction and medical management of hypertension
Grade 4	▪ Discontinue

4. Arthralgia or Myalgia:

Grade 1	Grade 2	Grade 3
Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL

Severity	Ripretinib Dose
Grade 2	Hold for 7 days minimum, and until Grade 1 or baseline, then: ▪ If recovery takes 7 days or less, restart at same dose. ▪ If recovery takes more than 7 days, restart but at next lower dose level ○ Consider re-escalating dose if arthralgia/myalgia does not worsen after 28 days ▪ If recurrent, hold until recovery to Grade 1 or baseline, then restart at next lower dose, regardless of time to recovery
Grade 3	Hold for 7 days minimum (maximum of 28 days), and until Grade 1 or baseline ▪ If not resolved after 28 days, discontinue ▪ If resolution within 28 days, then restart but at next lower dose level ○ Consider re-escalating dose if arthralgia/myalgia does not worsen after 28 days at reduced dose

5. Left ventricular systolic dysfunction:

Grade 3	Grade 4
Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated

- Discontinue for Grade 3 or 4 left ventricular systolic dysfunction

6. **Isolated total bilirubin increased:**

Severity	Ripretinib Dose
Greater than 1.5 x ULN Or Greater than 3 x ULN	▪ Hold until total bilirubin 1.5 x ULN or lower or baseline. ▪ If not resolved after 28 days, discontinue ▪ If resolution within 28 days, restart but at next lower dose level Consider re-escalating dose if total bilirubin does not increase after 28 days ▪ If recurrence of total bilirubin greater than 3 x ULN, discontinue

7. **Drug Interactions:** ripretinib is a substrate of CYP3A4. Dose adjustment may be required during concomitant use with other medications. Grapefruit and grapefruit juice may increase the plasma level of ripretinib. See Cancer Drug Manual.

PRECAUTIONS:

1. **Cardiac toxicity:** ripretinib has been associated with cardiac ischemic events including cardiac arrest, acute coronary syndrome, and myocardial infarction. Fatal outcomes have been reported. Use with caution in patients with history of ischemic heart disease. For new or acute onset cardiac ischemia and/or infarction, hold ripretinib until resolution; reinitiate therapy only after consideration of potential benefits and risks to the patient. Permanently discontinue therapy if there is no resolution.

   Left ventricular systolic dysfunction can occur during treatment with ripretinib. Assess prior to starting treatment and monitor as indicated throughout treatment. Discontinue for Grade 3 or 4 left ventricular systolic dysfunction. See Dose modifications, above.
2. **New primary cutaneous malignancies** including squamous cell carcinoma and melanoma have been reported in patients receiving ripretinib. Median time to event was 4.6 months (range: 3.8 to 6 months). Begin screening for suspicious lesions prior to initiating ripretinib and monitor throughout treatment.
3. **Dermatologic effects**, including palmar-plantar erythrodysesthesia syndrome (PPES), and alopecia can occur during ripretinib treatment. Dose reduction, interruption, or discontinuation may be necessary. See dose modifications, above.
4. Ripretinib is potentially **phototoxic**; exposure to strong sunlight, sunlamps, and other sources of ultraviolet radiation should be avoided or minimized during treatment. All patients should be advised to wear protective clothing and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF 30 or higher) when outdoors to help protect against sunburn.
5. **Wound healing may be impaired** with ripretinib; in patients undergoing minor and major surgical procedures, temporary interruption of ripretinib is recommended. Consider withholding ripretinib for a minimum of one week prior to elective surgery and for at least two weeks following major surgery or until adequate wound healing.

6. **Hypertension:** has been associated with ripretinib treatment. Pre-existing hypertension should be adequately controlled prior to starting treatment. Monitor prior to treatment initiation and during treatment. Dose interruption, adjustment, or discontinuation may be required. See dose modifications, above.
7. **Musculoskeletal toxicity:** arthralgia and/or myalgia have been reported during ripretinib treatment and may require dose interruption, adjustment, or discontinuation. See dose modifications, above.
8. **Drug-drug and drug-food interactions** can occur during treatment with ripretinib. Dose interruption or modification may be required. See Cancer Drug Manual for more information.
9. **Hypersensitivity:** has been reported during ripretinib treatment in a patient with previous hypersensitivity to another tyrosine kinase inhibitor. Use caution when initiating and increase monitoring during treatment with ripretinib in patients with previous hypersensitivity reaction to other tyrosine kinase inhibitors.

Call Dr. Howard Lim or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2020 Jul;21(7):923-934.
2. Ripretinib (Qinlock) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies 2022; 2(5):1-15.