BC Cancer Protocol Summary for Treatment of Advanced Systemic Mastocytosis using Avapritinib

Protocol Code	*UMLASMAVA*
Tumour Group	*Myeloid*
Contact Physician	*Dr. Lynda Foltz*

ELIGIBILITY:
Patient must have:
- Advanced systemic mastocytosis, including patients with:
  - aggressive systemic mastocytosis,
  - systemic mastocytosis with an associated hematological neoplasm,
  - mast cell leukemia
- Good performance status
- A BC Cancer Compassionate Access Program (CAP) approval prior to treatment

Note: combination with other systemic therapy for advanced systemic mastocytosis is not funded

EXCLUSIONS:
Patient must not have:
- Platelets less than 50 x 10^9/L
- High risk or history of intracranial bleeding
- Primary brain malignancy or metastasis

TESTS:
- Baseline: CBC & Diff, ALT, total bilirubin, alkaline phosphatase, albumin, INR, creatinine, tryptase
- Baseline**:** (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): HBsAg, HBsAb, HBcoreAb
- Baseline, if clinically indicated: calcium, phosphate, sodium, potassium
- Every 2 weeks during Cycles 1 and 2: CBC & Diff, ALT, total bilirubin, creatinine,
- Prior to Cycles 2 to 6: tryptase ALT, total bilirubin
- Cycle 3 onwards:
  - If platelets are greater than or equal to 75 x 10^9/L prior to Cycle 3: CBC & Diff prior to each cycle
  - If platelets are less than 75 x 10^9/L prior to Cycle 3: CBC & Diff every 2 weeks
  - Prior to each cycle: ALT, total bilirubin
- If clinically indicated: tryptase, creatinine, alkaline phosphatase, calcium, phosphate, sodium, potassium, albumin, HBV viral load (see protocol SCHBV)

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

SUPPORTIVE MEDICATIONS:

- Moderate risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
avapritinib	200 mg once daily	PO

- In patients with severe hepatic impairment (Child Pugh class C), reduce starting dose to 100 mg once daily
- 1 cycle = 28 days. Repeat until disease progression or intolerable toxicity

DOSE MODIFICATIONS:

Starting Dose	Dose Level -1	Dose Level -2	Dose Level -3
200 mg	100 mg	50 mg	25 mg*

- Permanently discontinue avapritinib in patient unable to tolerate a dose of 25 mg once daily

1. Hematological:

Thrombocytopenia:

Platelets ($x10^9$/L)	Dose
Greater than or equal to 50	100%
Less than 50	Withold treatment until platelets recover to greater than or equal to 50, then resume at next lower dose level

2. Cognitive Effects:

Severity*	Management
Grade 1	At provider discretion, may continue with same dose, reduce or withhold treatment until recovery to baseline or resolution. When resuming treatment, may resume treatment at same dose or reduced dose.
Grade 2 or 3	Withold treatment until resolution to Grade 1 or baseline. At provider discretion, may resume treatment at same dose or reduced dose.
Grade 4	Permanently discontinue avapritinib

*Graded per CTCAE v5.0

3. **Intracranial Hemorrhage:** permanently discontinue avapritinib if intracranial hemorrhage occurs, regardless of severity.

4. **Other Toxicity:**

Severity*	Management
Grade 3 or 4	Withold treatment until improvement to Grade 2 or lower. At provider discretion, may resume treatment at same dose or reduced dose.

*Graded per CTCAE v5.0

PRECAUTIONS:

1. **Cognitive Effects** of avapritinib treatment have been observed, and may present as memory impairment, confusion, somnolence, delirium, dementia, disorientation and speech disturbance. Avapritinib may influence a person's ability to drive or use machines. Median time to onset of cognitive effects is 13 weeks. Management of cognitive effects may include treatment interruption, dose reduction or discontinuation, depending on severity.
2. **Fluid retention:** Localized (facial, periorbital, peripheral, pulmonary, pericardial/pulmonary effusion) or generalized edema have been observed. Ascites have also been reported. Symptoms suggestive of fluid retention such as unexplained rapid weight gain or respiratory symptoms should be investigated. Management may include supportive care or therapeutic measures such as diuretics.
3. **Intracranial hemorrhage**, including subdural hematoma and cerebral hemorrhage, has been reported with avapritinib. Platelet count less than 50 x 10^9/L is a risk factor for intracranial hemorrhage. Symptoms may include headache, nausea, vomiting, vision changes or altered mental status. Use of avapritinib should be avoided in patients at high risk or recent history of intracranial hemorrhage. Monitor patients closely for signs of intracranial hemorrhage and permanently discontinue for any grade intracranial hemorrhage.
4. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **Drug interactions**: avapritinib is a substrate of CYP3A4, and concomitant use with strong or moderate CYP3A inhibitors should be avoided. If use with a moderate CYP3A inhibitor is unavoidable, the starting dose should be reduced to 50 mg once daily.
6. **Hepatitis B Reactivation:** See SCHBV protocol for more details.
7. **Hepatic Impairment:** No dose adjustment is recommended for patients with mild hepatic to moderate hepatic impairment. A reduced starting dose of 100 mg daily is recommended for patients with severe hepatic impairment.
8. **Photosensitivity Reactions:** Avapritinib may cause photosensitivity reactions. Patients should minimize exposure to direct sunlight and use protective measures during treatment and or one week after treatment discontinuation

Call Dr. Lynda Foltz or Myeloid Tumour Group delegate at (236) 317-3083 with any problems or questions regarding this treatment program.

References:

1. Gotlib J, Reiter A, Radia DH, et al. Efficacy and Safety of Avapritinib in Advanced Systemic Mastocytosis: Interim Analysis of the Phase 2 PATHFINDER Trial. Nat.Med. ; 2021;27(12):2192–2199.
2. Reiter, A. Efficacy and Safety of Avapritinib in Previously Treated Patients with Advanced Systemic Mastocytosis. Blood Advances 2022: 6 (21); 5750-5762.
3. Avapritinib (Ayvakyt) CDA-AMC Canada's Drug Agency Reimbursement Recommendation. Canadian Journal of Health Technologies. Nov 2024: 4(11); 1-25.