

BC Cancer Protocol Summary for Treatment of Advanced c-kit positive Gastrointestinal Stromal Cell Tumours (GIST) Using 800 mg Dosing of iMAtinib

Protocol Code: SAAVGIDD

Tumour Group: GI / Sarcoma

Contact Physician: Dr. Christine Simmons

ELIGIBILITY:

- Diagnosis of Gastrointestinal Stromal Tumour: demonstration of c-kit protein and/or DOG1 confirmation of diagnosis.
- Diagnosis of c-kit negative Gastrointestinal Stromal Tumour: Mutation analysis (if possible) should show one of the mutations known to respond to iMAtinib
- Advanced disease status - not amenable to surgery or other local therapy that has
 - progressed on iMAtinib 400 mg po daily, **or**
 - demonstrated exon-9 mutation
- No contra-indication to use of iMAtinib, but it may not be indicated for patients with significant co-morbid illnesses which preclude quality of life etc (i.e., not appropriate for elderly patients with other life-limiting diseases or significantly impaired cognitive states)

EXCLUSIONS:

- Pregnancy

SPECIAL PRECAUTIONS:

- Concurrent warfarin therapy

TESTS:

- Baseline (required before first treatment): CBC & diff, platelets, creatinine, bilirubin, alkaline phosphatase, **ALT**, LDH.
- 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, HBcoreAb
- Every 4 weeks **for cycles 1, 2 and 3, then at least every 3 months**: CBC and diff, platelets, creatinine, bilirubin, alkaline phosphatase, **ALT**, LDH
- Patients on warfarin should have more frequent INR monitoring at treatment initiation by physician who is managing the anticoagulation.
- Followup: Clinical evaluation associated with imaging as below
 - Chest X-ray yearly
 - CT scan abdomen and pelvis
 - On drug: every 3 - 4 months – frequency of imaging may be modified after stability of disease for 6 months at the discretion of the treating oncologist

PREMEDICATIONS:

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

SUPPORTIVE MEDICATIONS:

- If HBsAg or HBcoreAb positive, start lamivudine 100 mg/day PO for the duration of chemotherapy and for six months afterwards.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
iMAtinib	400 mg twice daily	PO

- Continue drug until evidence of disease progression.

DOSE MODIFICATIONS:

- Monitor for side effects using physical and laboratory evaluations monthly for 5 months, then every 3 months.

1. Hematological:

Toxicity	ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose
Grade 1	greater than or equal to 1.5 to less than 2.0	or	less than LLN to 75	No change required
Grade 2	greater than or equal to 1.0 to less than 1.5	or	greater than or equal to 50 to less than 75	No change required
Grade 3	greater than or equal to 0.5 to less than 1.0	or	greater than or equal to 10 to less than 50	Hold until toxicity less than or equal to Grade 1, then resume at same dose For <u>second</u> occurrence, hold until toxicity less than or equal to Grade 1, then resume at 300 mg two times a day
Grade 4	less than 0.5	or	less than 10	Hold until toxicity less than or equal to Grade 1, then resume at same dose For <u>second</u> occurrence, hold until toxicity less than or equal to Grade 1, then resume at 300 mg two times a day

- No dose reductions for Grade 3 or 4 anemia. Patients can be transfused or treated with erythropoietin (EPREX®).

Non-Hematological:

Toxicity	Dose
Grade 2	<ul style="list-style-type: none"> - Hold until toxicity less than or equal to Grade 1, then resume at the same daily dose - If Grade 2 toxicity recurs, hold until toxicity less than or equal to Grade 1, then resume at 300 mg two times a day - If Grade 2 toxicity recurs again, hold until toxicity less than or equal to Grade 1, then resume at 200 mg two times a day
Grade 3 or 4	<ul style="list-style-type: none"> - Hold until toxicity less than or equal to Grade 1, then resume at 300 mg two times a day - If Grade 3 or 4 toxicity recurs, hold until toxicity less than or equal to Grade 1, then resume at 200 mg two times a day

2. Hepatotoxicity

Bilirubin		ALT	Dose
less than or equal to 3 x ULN	AND	less than or equal to 5 x ULN	100%
greater than 3 x ULN	OR	greater than 5 X ULN	Hold until Bilirubin is less than 1.5 x ULN and ALT less than 2.5 x ULN Then resume at 300 mg two times a day

ULN = upper limit of normal

- **Hemorrhage** Intra-tumoral hemorrhage or tumor related intra-abdominal bleeding has been reported in an estimated 5% of cases and may be life threatening. This may not be manifested as obvious gastrointestinal bleeding as blood may be confined to the tumor, within the hepatic capsule, peritoneum or otherwise sequestered. Signs and symptoms of such an event may include hypotension, signs of hypovolemia, fall in hematocrit, localized pain, apparent rapid increase in size of mass, and CT results suggestive of bleeding. CT results should be evaluated carefully in light of this so that this syndrome is not mistaken for progressive disease.
- **Vomiting** In the case of emesis related loss of iMAtinib, the dose should **NOT** be replaced.

PRECAUTIONS:

1. **Edema** Facial and generalized body swelling commonly occurs and may be dose related. Track weight gain and use diuretics if excessive (more than 2 Kg in one week).
2. **Rash** is frequent and is not a reason to discontinue drug. Rarely toxic epidermolysis syndrome can occur.
3. **Congestive heart failure (CHF) with decreased left ventricular ejection fraction (LVEF)** has been reported in a very small proportion of patients treated with iMAtinib. Careful clinical evaluation of patients who might be predisposed by reason of age or co-morbidities is recommended. If clinically CHF occurs: measure LVEF, start treatment of CHF and follow carefully. If further deterioration then discontinue iMAtinib.
4. **Hepatotoxicity** with severe elevations of transaminases or bilirubin may be life threatening. Risk may be increased when iMAtinib is combined with other potentially hepatotoxic drugs. Management is dose reduction, interruption (median duration one week) or discontinuation (less than 0.5%) of iMAtinib.
5. **Drug interactions** may occur as iMAtinib is a potent competitive inhibitor of Cytochrome P450 enzymes (see BC Cancer Drug Manual). Warfarin's effect may be increased; monitor INR more closely especially at treatment initiation and at dose modifications of iMAtinib.
6. **Pregnancy:** Women of childbearing potential must be advised to use highly effective contraception during treatment.
7. **HBV infection reactivation risk:** Risk of Hepatitis B Reactivation can occur in chronic HBV carriers after they receive BCR-ABL TKIs. All patients should be tested for both HBsAg and HBcoreAb. If either test is positive, such patients should be treated with lamivudine during chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.
8. **Progressive renal dysfunction:** loss of function may be greatest in first year and may contribute to development or worsening of some kidney diseases

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

References:

1. Van Glabbeke MM, Owzar K, Rankin C, et al. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors (GIST): A meta-analysis based on 1,640 patients. J Clin Oncol (Meeting Abstracts) 2007;25(18_suppl):10004.
2. Heinrich MC, Owzar K, Corless CL, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. J Clin Oncol 2008;26(33):5360-7.
3. Gleevec Product Monograph. Novartis Pharmaceuticals Canada: Dorval, Quebec; 17 February 2011.
4. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010;8 (Suppl 2):S1–S41.