

BC Cancer Protocol Summary for Treatment of Advanced C-Kit Positive and C-Kit Negative Gastrointestinal Stromal Cell Tumours (GISTs) Using iMAtinib

Protocol Code: SAAVGI
Tumour Group: 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.
- No contraindication 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 CAUTION:

- 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.
- Follow up: Clinical evaluation associated with imaging as below
 - Chest X-ray yearly
 - CT scan abdomen and pelvis
 - On drug: every 3 to 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 daily	PO

- Evaluate for response with clinical measures or evaluation of disease at 3 months then every 3 months.
- Continue drug until evidence of disease progression at which time the patient may be started on a higher dose of drug (see SAAVGIDD)
- In cases of localized progression, surgery or radiofrequency ablation might be appropriate and the patient maintained on lower dose of iMAtinib – discuss with contact physician.

DOSE MODIFICATIONS:

- Monitor for side effects using physical and laboratory evaluations monthly for 3 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	or	greater than LLN to 75	400 mg daily
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	400 mg daily
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 Grade 1, then resume at 300 mg daily. For second occurrence, hold until toxicity less than Grade 1, then resume at 200 mg daily.

Toxicity	ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose
Grade 4	less than 0.5	or	less than 10	Hold until toxicity less than or equal to Grade 1, then resume at 300 mg daily. For second occurrence, hold until toxicity less than or equal to Grade 1, then resume at 200 mg daily.

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

2. 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 daily ▪ If Grade 2 toxicity recurs again, hold until toxicity less than or equal to Grade 1, then resume at 200 mg daily
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 daily ▪ If Grade 3 or 4 toxicity recurs, hold until toxicity less than or equal to Grade 1, then resume at 200 mg daily

- **Hemorrhage:** Intra-tumoral hemorrhage or tumor related intra-abdominal bleeding early in the course of treatment 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. Patients should be supported fully during the episode as generally that side effect is associated with early tumor necrosis and a good response. 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 (greater 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. Peng B, Hayes M, Racine-Poon A, et al. Clinical investigation of the pharmacokinetic/pharmacodynamic relationship for glivec (STI571): a novel inhibitor of signal transduction. Proc Am Soc Clin Oncol 2001;20(Part 1 of 2):abstr 280.
2. Blackstein ME, Rankin C, Fletcher C, et al. Clinical benefit of imatinib in patients with metastatic gastrointestinal stromal tumors negative for the expression of CD117 in the S0033 trial. J Clin Oncol (Meeting Abstracts) 2005;23(16_suppl):9010-.
3. van Oosterom AT, Judson I, Verweij J, et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. Lancet 2001;358(9291):1421-23.

4. Van den Abbeele AD, for the GIST Collaborative PET Study Gro OHSU. F18-FDG-PET provides early evidence of biological response to STI571 in patients with malignant gastrointestinal stromal tumors (GIST). *Proc Am Soc Clin Oncol* 2001;20(Part 1 of 2):abstr 1444.
5. Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001;344(14):1052-6.
6. Zalcberg JR, Verweij J, Casali PG, et al. Outcome of patients with advanced gastro-intestinal stromal tumors (GIST) crossing over to a daily imatinib dose of 800mg (HD) after progression on 400mg (LD) - an international, intergroup study of the EORTC, ISG and AGITG. *J Clin Oncol (Meeting Abstracts)* 2004;22(14_suppl):9004-.
7. Kerkela R, Grazette L, Yacobi R, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med* 2006;12(8):908-16.
8. Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. *J Clin Oncol* 2005;23(23):5357-64.
9. Mauro MF, O'Dwyer M, Heinrich MC, Druker BJ. STI571: A paradigm of new agents for cancer therapeutics. *J Clin Oncol* 2002;20(1):325-34.
10. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose Imatinib: randomised trial. *Lancet* 2004;364(9440):1127-34.