

# BC Cancer Protocol Summary for Adjuvant Treatment of C-Kit Positive High Risk Gastrointestinal Stromal Cell Tumours Using iMAtinib

**Protocol Code:** SAAJGI  
**Tumour Group:** Sarcoma  
**Contact Physician:** Dr. Christine Simmons

## ELIGIBILITY:

- Unequivocal diagnosis of Gastrointestinal Stromal Tumour (GIST): Demonstration of c-kit protein using DOG1 confirmation of diagnosis
- Diagnosis of c-kit negative GIST: Mutation analysis (if possible) should show one of the mutations known to respond to iMAtinib.
- Patient with completely resected GIST and high risk for recurrence:
  - 5-year relapse-free survival less than 60% as calculated using Gold Nomogram (Lancet Oncology 2009) (80 points or more)

## EXCLUSIONS:

- Pregnancy

## SPECIAL CAUTION:

- Concurrent warfarin therapy

## TESTS:

- 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 anticoagulation
- Follow up: Clinical evaluation associated with imaging as below
  - Chest X-ray yearly
  - CT scan abdomen and pelvis
    - Years 1 – 3 (on drug): every 4 – 6 months
    - Years 4 – 5 (or 2 years off drug): every 3 – 4 months
    - Thereafter till 10 years: every 6 to 12 months at physicians discretion.

## 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

For 3 years after resection.

## 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 <sup>9</sup> /L)		Platelets (x 10 <sup>9</sup> /L)	Dose
<b>Grade 1</b>	greater than or equal to 1.5 to less than 2.0	or	less than LLN to 75	400 mg daily
<b>Grade 2</b>	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
<b>Grade 3</b>	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 300 mg daily. For second occurrence, hold until toxicity less than or equal to Grade 1, then resume at 200 mg daily.
<b>Grade 4</b>	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®).

### Non-Hematological:

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

- **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. DeMatteo R, Owzar K, Maki P. Adjuvant imatinib mesylate increases recurrence free survival (RFS) in patients with completely resected localized primary gastrointestinal stromal tumor (GIST): North American Intergroup Phase III trial ACOSOG Z90001. Proc Am Soc Clin Oncol 2007;25: abstract 10079.
2. Nilsson B, Sjolund K, Kindblom LG, et al. Adjuvant imatinib treatment improves recurrence-free survival in patients with high-risk gastrointestinal stromal tumours (GIST). Br J Cancer 2007;96(11):1656-8.
3. Zhan WH, China Gastrointestinal Cooperative G. Efficacy and safety of adjuvant post-surgical therapy with imatinib in patients with high risk of relapsing GIST. Proc Am Soc Clin Oncol 2007;25: abstract 10045.
4. Joensuu H, et al., Twelve versus 36 months of adjuvant imatinib (IM) as treatment of operable GIST with a high risk of recurrence: Final results of a randomized trial (SSGXVIII/AIO). Proc Am Soc Clin Oncol 2011;29(18 suppl):LBA1.
5. Gold JS, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol 2009;10(11):1045-52.