

BCCA Protocol Summary for Treatment of Advanced c-kit positive Gastrointestinal Stromal Cell Tumours (GIST's) Using 800 mg Dosing of Imatinib (GLEEVEC®)

Protocol Code: SAAVGIDD

Tumour Group: GI / Sarcoma

Contact Physician: Dr. Charles Blanke/ Dr. Meg Knowling

ELIGIBILITY:

- Unequivocal diagnosis of Gastrointestinal Stromal Tumour: demonstration of c-kit protein using DAKO immunohistochemistry
- Diagnosis of c-kit negative Gastrointestinal Stromal Tumour: Must be reviewed at central lab and diagnosis confirmed. Mutation analysis – if possible – should show one of the mutations known to respond to Imatinib*– please provide path review.
- Advanced disease status - not amenable to surgery or other local therapy
 - that has progressed on Imatinib 400 mg po daily.
 - or
 - that has 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)
- A “Class II Drug Registration Form” must be submitted at the time of initiation of treatment. For other indications, an “Individual use of Benefit Drug List Medication for an Undesignated Indication” form must be approved.

* Fresh/frozen tissue is preferable to paraffin block for mutation analyses though either specimen is acceptable. Please use GIST mutation analysis form previously circulated and FAX forms to originating lab as well as to Dr. [Sean Young's Lab](#) at BC Cancer Agency – Vancouver Clinic
<H:\EVERYONE\Sarcoma\Forms\Gist Mutation analysis request>

EXCLUSIONS:

- Concurrent warfarin therapy

TESTS:

- **Baseline and ongoing care:**

TESTS	Months	1		2		3		4		5		6 +	
	baseline	WEEKS											EVERY 3 MONTHS
		2	4	6	8	10	12	14	16	18	20		
HPE ^b	X		X		X		X		X		X	X	
Weight	X		X		X		X		X		X	X	
Assess Toxicity			X		X		X		X		X	X	
Assess Disease ^c	X				X						X	X	
CBC ^d	X	X	X	X	X	X	X	X	X	X	X	X	
LFT's ^e	X		X		X		X		X		X	X	
Creatinine	X		X		X		X		X		X	X	
Pregnancy test	X												
Tumour c-kit	X												

*Full history and physical examination

PREMEDICATIONS:

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

TREATMENT:

Drug	Dose	BCCA Administration Guideline
Imatinib (GLEEVEC®)	400 mg twice daily Or 800 mg once daily	PO

- Evaluate for response with clinical measures or evaluation of disease every 3 months.
- Continue drug until evidence of disease progression.
- 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 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 – less than 2.0	or	less than LLN – 75	No change required
Grade 2	greater than or equal to 1.0 – less than 1.5	or	greater than or equal to 50 – less than 75	No change required
Grade 3	greater than or equal to 0.5 – less than 1.0	or	greater than or equal to 10 – less than 50	Hold until toxicity less than or equal to Grade 1, then resume at same dose For second 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 second 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®).

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 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

3. Hepatotoxicity

Bilirubin		ALT or AST	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/AST 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 BCCA Cancer Drug Manual).

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

Date activated: 1 Mar 2009

Date revised: 1 Jun 2011 (dose reduction for hematological and non hematological toxicities)

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 (pts). 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):5360-5367.
3. Gleevec Product Monograph, Novartis Pharmaceuticals Canada, Dorval, Quebec, Feb 17, 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 Nat'l Compr. Canc Netw 2010 Apr;8 Suppl 2: S-1 –S41.