BC Cancer Protocol Summary for Second Line Treatment of Advanced C-kit Positive Gastrointestinal Stromal Cell Tumours (GIST) After iMAtinib Using SUNItinib

Protocol Code: *SAAVGS*

Tumour Group: *Sarcoma*

Contact Physician: *Dr. Christine Simmons*

ELIGIBILITY:

- Progression after previous treatment with imatinib for advanced gastrointestinal stromal tumour, or intolerance of imatinib
- Unequivocal diagnosis of Gastrointestinal Stromal Tumour: Demonstration of c-kit protein using DAKO immunohistochemistry
- Advanced disease status – not amenable to surgery or other local therapy.
- No contra-indication to use of SUNItinib, 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)

* Fresh/frozen tissue is preferable to paraffin block for mutation analyses though either specimen is acceptable. Specimens to be sent to Dr. Doug Horsley's Lab at BC Cancer Agency – Vancouver Clinic

EXCLUSIONS:

- Significant cardiovascular disease and/or LVEF less than 55%
- Uncontrolled hypertension

TESTS:

- Baseline: CBC, differential, platelets, sodium, potassium, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, GGT, ALT, urine analysis, TSH.
- Before each cycle: CBC, differential and platelets, urine analysis, creatinine, uric acid, ALT, bilirubin. TSH every other cycle or if clinically indicated.
- MUGA scan or echocardiogram if clinically indicated or if history of cardiac problems

PREMEDICATIONS:

- Antiemetic not usually required

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
SUNItinib	50 mg daily for days 1 to 28 followed by 2 weeks' rest*	PO
Alternatively:		
SUNItinib	37.5 mg once daily continuously	If patients show rapid progression during the 2 week break

Repeat every 42 days (i.e., 6 weeks) until progression or intolerance.
*Each cycle consists of 6 weeks.

Dose reduction:
- Dose level -1: 37.5 mg
- Dose level -2: 25 mg

DOSE MODIFICATIONS:

1. Hematological:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose (all drugs)
greater than or equal to 1.0	and	greater than or equal to 100	100%
less than 1.0	or	less than 100	Delay

2. Non-Hematological toxicity:

CTC-Grade	Dose
1 to 2	100%
3 to 4	Delay until less than or equal to grade 1 Dose reduce by 1 dose level

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
2. **Cardiac Toxicity:**

Asymptomatic Patients – SUNItinib continuation based on serial LVEFs

Relationship of LVEF to LLN	Absolute Decrease Of Less Than 10%	Absolute Decrease Of 10 to 15%	Absolute Decrease Of Greater Than or Equal to 16%
Within Normal Limits	Continue	Continue	Hold *
1 to 5% below LLN	Continue	Hold *	Hold *
greater than or equal to 6 % below LLN	Continue *	Hold *	Hold *

- *Repeat LVEF assessment after 4 weeks
- If criteria for continuation are met – resume SUNItinib
- If 2 consecutive holds or a total of 3 holds occur, discontinue SUNItinib

Symptomatic Patients

- Symptomatic patients with evidence of cardiac dysfunction should have SUNItinib discontinued

3. **Renal dysfunction:** Only a very small percentage of SUNItinib and its metabolites are excreted by the kidney. SUNItinib appears safe in patients with mild renal impairment (creatinine less than or equal to 2x upper limit of normal). No data exist for SUNItinib in patients with moderate to severe kidney failure.
4. **Hepatic dysfunction**: SUNItinib is mainly metabolized and excreted through the liver. SUNItinib appears safe in patients with mild hepatic impairment (bilirubin less than or equal to 1.5x upper limit of normal). No data exist for SUNItinib in patients with moderate to severe hepatic impairment
5. **Caution:**
   - SUNItinib is predominantly metabolized and excreted through cytochrome P4503A4 in the liver. Potential drug interactions with cytochrome P4503A4 interacting agents must be considered. see also: http://medicine.iupui.edu/flockhart/table.htm
   - Patients with hypertension should exercise caution while on SUNItinib. Rigorous treatment of blood pressure is necessary, since SUNItinib can cause a rapid onset of high blood pressure. Temporary suspension of SUNItinib is recommended for patients with severe hypertension (greater than 200 mmHg systolic or greater than110 mmHg diastolic). Treatment

with SUNItinib may be resumed once hypertension is controlled (see also http://www.hypertension.ca).

- It is recommended that for at least the first 2 cycles of treatment patients monitor their blood pressure daily (home measurements, GP's office…) and keep a journal of their blood pressure measurements that can be submitted to the physician.

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. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006; 368: 1329-1338.
2. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. JAMA 2006; 295: 2516-2524.