

BC Cancer Protocol Summary for Palliative Therapy for Renal Cell Carcinoma Using SUNItinib

Protocol Code

GUSUNI

Tumour Group

Genitourinary

Contact Physician

Dr. C. Kollmannsberger

ELIGIBILITY:

- Advanced renal cell carcinoma
- Any histology and IMDC risk group
- ECOG performance status less than or equal to 2
- No prior therapy or after failure of first-line immunotherapy
- If patient exhibits poor prognosis criteria, consider Temsirolimus.
Poor prognosis defined if at least 3 out of 6 risk factors are present (minimum of 3 poor-risk features required):
 - LDH greater than 1.5 X upper limit of normal
 - Hemoglobin less than lower limit of normal
 - Corrected calcium greater than 10 mg/dL
 - Time from diagnosis to first treatment less than 1 yr
 - Karnofsky Performance Status 60-70
 - Multiple organ sites of metastasis

EXCLUSIONS:

- Pregnancy
- 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 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 protocol for low emetogenic chemotherapy protocols (see SCNAUSEA)

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
SUNItinib	50 mg once daily for 4 weeks followed by 2 weeks rest*	PO
Alternatively:		
SUNItinib	37.5 mg once daily continuously (If patients show rapid progression during the 2 week break)	PO

*Each cycle consists of 6 weeks.

Dose reduction:

Dose level -1: 37.5 mg

Dose level -2: 25 mg

DOSE MODIFICATIONS:**1. Hematological**

ANC ($\times 10^9/L$)		Platelets ($\times 10^9/L$)	Dose (all drugs)
Greater than or equal to 1.0	and	Greater than or equal to 75	100%
Less than 1.0	or	Less than 75	Delay

2. Non-Hematological toxicity:

CTC-Grade	Dose
1-2	100%
3-4	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 -15%	Absolute Decrease Of \geq 16%
Within Normal Limits	Continue	Continue	Hold *
1-5% below LLN	Continue	Hold *	Hold *
Greater than or equal to 6% below LLN	Continue *	Hold *	Hold *

LLN = Lower Limit of Normal

- *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. **Sunitinib-Induced hypothyroidism:** All patients on SUNItinib should be observed closely for signs and symptoms of thyroid dysfunction (such as fatigue). Patients should have thyroid function laboratory monitoring done (TSH every cycle for cycles 1-4 then every 2-3 months). Patients with minor TSH elevations (up to 20 mU/L), no symptoms and no pre-existing heart disease can be managed with observation. Patients with TSH elevation and symptoms and/or pre-existing heart conditions should be treated as per current recommended guidelines.

Thyroid hormone replacement therapy should be initiated and maintained as follows:

For adults under the age of 50 yr <u>with</u> cardiac disease:	Usual starting dose of: Levothyroxine 25 – 50 mcg PO daily
For adults over the age of 50 yr <u>without</u> cardiac disease:	Usual starting dose of: Levothyroxine 25 – 50 mcg PO daily
For adults over the age of 50 yr <u>with</u> cardiac disease:	Usual starting dose of: Levothyroxine 12.5 – 25 mcg PO daily

Dose adjustments are needed every 6-8 weeks, based on clinical and laboratory parameters. Close observation of liver function tests and thyroid function is required when patients are receiving both SUNItinib and thyroid hormone replacement therapy.

6. Drug Interaction: SUNItinib is predominantly metabolized and excreted through cytochrome P450 3A4 in the liver. Potential drug interactions with cytochrome P450 3A4 interacting agents must be considered.

7. Hypertension:

- 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 than 110 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, etc.) and keep a journal of their blood pressure measurements that can be submitted to the physician.

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

References:

1. Motzer R, et al: Phase III randomized trial of sunitinib malate (SU11248) versus interferon-alfa (IFN-a) as first-line systemic therapy for patients with metastatic renal cell carcinoma. N Engl J Med 2007;356(2):115-24.
2. Motzer R, et al: Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma: J Clin Oncol 2006;24:16-24.
3. Di Lorenzo G, et al. Toxicities of targeted therapy and their management in kidney cancer. Eur Urol 2011;59(4):526-40.
4. Kollmannsberger C, et al. Sunitinib in metastatic renal cell carcinoma: recommendations for management of noncardiovascular toxicities. Oncologist 2011;16 (5):543-53.

APPENDIX – Renal Cell Carcinoma Funding Algorithm

