BC Cancer Protocol Summary for the Treatment of Malignant Pheochromocytoma and Secretory Paraganglioma Using SUNItinib

Protocol Code	*GUOTSUNI*
Tumour Group	*Genitourinary*
Contact Physician	*GU Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Unresectable malignant pheochromocytoma or secretory paraganglioma, and
- Documented progression on most recent imaging, or
- Symptomatic disease or risk of end-organ compromise

Patients should have:

- ECOG 0 to 2
- Adequate marrow, renal and hepatic function
- Life expectancy of at least 6 months
- No signs or symptoms of cardiac disease

Note:

- All patients with confirmed secretory tumours must receive appropriate alpha-adrenergic blockade at least 7 to 14 days prior to initiating therapy

EXCLUSIONS:

Patients must not have:

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

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, random glucose, sodium, potassium, magnesium, phosphate, calcium, dipstick or laboratory urinalysis for protein, TSH, blood pressure measurement
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with Cycle 2): 24-hour urine metanephrines and catecholamines
- Baseline, if clinically indicated: ECG

- Cycle 2, prior to Day 1: CBC & Diff, creatinine, total bilirubin, ALT, albumin, random glucose, sodium, potassium, magnesium, phosphate, calcium
- Cycles 3 onwards, prior to Day 1 of each cycle: CBC & Diff, creatinine, total bilirubin, ALT, random glucose, sodium, potassium
- If clinically indicated: alkaline phosphatase, albumin, GGT, magnesium, phosphate, calcium, 24-hour urine metanephrines and catecholamines, TSH, dipstick or laboratory urinalysis for protein, 24-hour urine for protein if laboratory urinalysis for protein is greater than or equal to 1 g/L or dipstick urinalysis shows 2+ or 3+ proteinuria, ECG, MUGA scan or echocardiogram

PREMEDICATIONS:

- Antiemetics not usually required
- If antiemetics are required, note that dopamine receptor antagonists such as metoclopramide and prochlorperazine should be avoided in patients with pheochromocytoma and other catecholamine-releasing paragangliomas due to increased risk of hypertensive crisis

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	PO

Repeat every 42 days (i.e., 6 weeks) until disease progression or unacceptable toxicity
*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 75	100%
Less than 1.0	or	Less than 75	Delay

2. Non-Hematological Toxicity:

CTC-Grade	Dose
0 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 *

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 2 times the 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 (total bilirubin less than or equal to 1.5 times the upper limit of normal). No data exists 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 to 4 then every 2 to 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 with cardiac disease:	Usual starting dose of: **Levothyroxine 25 – 50 mcg PO daily**
For adults over the age of 50 without cardiac disease:	Usual starting dose of: **Levothyroxine 25 – 50 mcg PO daily**
For adults over the age of 50 with cardiac disease:	Usual starting dose of: **Levothyroxine 12.5 – 25 mcg PO daily**

   Dose adjustments are needed every 6 to 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 SUNItinb 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.

Contact the GU Systemic Therapy physician at your regional cancer centre or the GU Systemic Therapy Chair with any problems or questions regarding this treatment program.

References:

1. Baudin E, Goichot B, Berruti A, Hadoux J, Moalla S, et. al. Sunitinib for metastatic progressive phaeochromocytomas and paragangliomas: results from FIRSTMAPPP, an academic, multicentre, international, randomised, placebo-controlled, double-blind, phase 2 trial. Lancet. 2024 Mar 16;403(10431):1061-1070.
2. O'Kane GM, Ezzat S, Joshua AM, et. al. A phase 2 trial of sunitinib in patients with progressive paraganglioma or pheochromocytoma: the SNIPP trial. Br J Cancer. 2019 Jun;120(12):1113-1119.