BC Cancer Protocol Summary for Palliative Treatment of Advanced Pancreatic Neuroendocrine Tumours using SUNItinib

Protocol Code	*GIPNSUNI*
Tumour Group	*Gastrointestinal*
Contact Physician	*GI Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Well to moderately differentiated, unresectable or metastatic pancreatic neuroendocrine tumours (PNET)

Patients should have:

- ECOG performance status 0 to 2
- Adequate hematologic, hepatic and renal function

Note: Approvals will only be given for one of GIPNSUNI or GIPNEVER – not both, unless due to intolerance within the first month of therapy

EXCLUSIONS:

Patients must not have:

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

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, albumin, sodium, potassium, random glucose, dipstick or laboratory urinalysis for protein, TSH
- Baseline if clinically indicated: GGT, ECG
- Before each cycle: CBC & Diff, creatinine, sodium, potassium, magnesium, phosphate, calcium, random glucose, total bilirubin, ALT
- If clinically indicated: alkaline phosphatase, albumin, GGT, lipase, 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

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

Activated: 1 Jun 2011 Revised: 1 Aug 2024 (Eligibility clarified, tests updated, antiemetic risk category clarified, physician contact updated)

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
SUNItinib	37.5 mg once daily continuously	PO

- Note: 4 weeks of treatment comprise 1 cycle
- Continue until disease progression or unacceptable toxicity

DOSE MODIFICATIONS (A, B & C):

A. Dose Modifications for HEMATOLOGIC Toxicity
B. Dose Modifications for NON-HEMATOLOGIC Toxicity
C. Dose ESCALATION

Table 1: Dose Modification Levels for All Toxicity

Agent	Dose Level -1	Starting Dose	Dose Level +1
SUNItinib	25 mg PO once daily	37.5 mg PO once daily	50 mg PO once daily

A. Hematological Toxicity:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
Greater than or equal to 1.0	and	Greater than or equal to 75	100%
Less than 1.0	or	Less than 75	Delay

B. Non-Hematologic Toxicity:

Grade	Diarrhea	Nausea	Dose
1	Increase of 2-3 stools/day, or mild increase in loose watery colostomy output	Lose of appetite without alteration in eating habits.	Maintain dose level
2	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	
3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Delay until less than or equal to grade 1. Dose reduce by - 1 dose level.
4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	Life-threatening consequences.	

Other Non-Hematologic Toxicity:

Grade of SUNItinib-related adverse events	Dose Adjustments
Grade 0 to 2	100%
Grade 3 to 4	Delay until less than or equal to grade 1 Dose reduce by 1 dose level

C. Dose Escalation:

- May increase to +1 dose level if no response after 8 weeks, with grade 1 or lower non-hematologic or grade 2 or lower hematologic treatment related adverse events.

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 16% or Greater
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 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 years with cardiac disease:	Usual starting dose of: **Levothyroxine 25 to 50 mcg PO daily**
For adults over the age of 50 years without cardiac disease:	Usual starting dose of: **Levothyroxine 25 to 50 mcg PO daily**
For adults over the age of 50 years with cardiac disease:	Usual starting dose of: **Levothyroxine 12.5 to 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** (See BC Cancer Drug Manual and see also: http://medicine.iupui.edu/flockhart/table.htm).

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.

Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

References:

1. Raymond, E et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumours. N Engl J Med 2011;364;6:501-513.
2. Di Lorenzo G, et al. Toxicities of targeted therapy and their management in kidney cancer. Eur Urol 2011;59(4):526-540.
3. Kollmannsberger C, et al. Sunitinib in metastatic renal cell carcinoma: recommendations for management of noncardiovascular toxicities. The Oncologist 2011;16(5):543-553.