BC Cancer Protocol Summary for Treatment of Advanced Neuroendocrine Tumours of Gastrointestinal Origin (Non-Functional) Using Everolimus

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

ELIGIBILITY:

Patients must have:

- Well differentiated, non-functional, neuorendocrine tumours of gastrointestinal origin, unknown primary or other origins (except for lung – see ULUNETEV),
- Unresectable, locally advanced or metastatic disease, and
- Compassionate Access Program (CAP) approval granted by BC Cancer

Patients should have:

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

Note: Patients with non-functional tumours are allowed sequential use of octreotide and everolimus, but not in combination

EXCLUSIONS:

Patients must not have:

- Carcinoid syndrome
- Major surgery within the last 4 weeks
- Concomitant immunosuppressive therapies excluding corticosteroids as antiemetic or anaphylactic prophylaxis
- History of hypersensitivity reaction to everolimus or other rapamycin derivatives (i.e., SIrolimus, temsirolimus)

CAUTIONS:

- Pre-existing significant lung compromise due to the risk for pneumonitis
- Hepatitis B or C carriers
- Diabetic patients

TESTS:

- Baseline: CBC & Diff, sodium, potassium, creatinine, urea, random glucose, calcium, phosphate, ALT, LDH, total bilirubin, albumin, INR, alkaline phosphatase, total cholesterol, triglycerides
- Baseline if clinically indicated: total protein, GGT, HBsAg, HBsAb, HBcoreAb, chest x-ray, oxygen saturation
- Prior to each cycle: CBC & Diff
- If clinically indicated: total protein, albumin, total bilirubin, INR, GGT, alkaline phosphatase, LDH, ALT, urea, random glucose, HbA1c, total cholesterol, triglycerides, creatinine, sodium, potassium, magnesium, calcium, phosphate, creatine kinase, 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

PREMEDICATIONS

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

Stomatitis Prophylaxis

The following mouthwash has been shown to significantly reduce the incidence of stomatitis and is recommended for all patients starting everolimus treatment.

- Dexamethasone mouthwash 0.1 mg/mL (alcohol-free) 10 mL four times a day, swish in mouth for 2 minutes then spit out. Do not eat or drink for 1 hour after using mouthwash.
- Start on Day 1 of everolimus treatment. Continue for 8 weeks (2 cycles) to a maximum of 16 weeks (4 cycles) at the discretion of the treating oncologist.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
everolimus	10 mg once daily continuously	PO

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

DOSE MODIFICATIONS:

Table 1: Dose Modification Levels

Agent	Starting Dose	Dose Level -1	Dose Level -2
everolimus	10 mg PO once daily	5 mg PO once daily	5 mg PO once every other day

1. Hematological

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	• Hold until ANC greater than or equal to 1.0 and/or platelets greater than or equal to 75 • If recovery within 10 days restart same dose level; if not, reduce dose by 1 dose level

Discontinue if tumour progression or if patient with Grade 3-4 toxicities fails to recover to Grade 0-2 within three weeks.

2. Everolimus induced pneumonitis:

Grade	Toxicity	Management
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• Continue everolimus at 100% dose • Monitor as clinically appropriate
2	Symptomatic; medical intervention indicated; limiting instrumental ADL	• Consider holding everolimus. Dose should be reduced by one dose level when restarted • Rule out infection • Consider treatment with corticosteroids until Grade 1 or lower, then restart everolimus at one dose level lower • If not recovered to Grade 1 or lower within 4 weeks, discontinue everolimus

Grade	Toxicity	Management
3	Severe symptoms; limiting self care ADL; oxygen indicated	• Hold everolimus until Grade 1 or lower • Rule out infection • Consider treatment with corticosteroids • Consider restarting everolimus. If restarting, start at one dose level lower ▪ If pneumonitis recurs at Grade 3, consider discontinuation of everolimus
4	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	• Discontinue everolimus • Rule out infection • Consider treatment with corticosteroids

3. Stomatitis:

- Consider use of prophylactic medicated mouthwash for stomatitis during first two cycles of treatment (see Precautions, below)

Grade	Toxicity	Everolimus Dose
1	Asymptomatic or mild symptoms, intervention not indicated	• Continue at same dose
2	Moderate pain; not interfering with oral intake; modified diet indicated	• Hold until Grade 1 or lower, then restart at previous dose • If Grade 2 stomatitis recurs, hold until Grade 1 or lower, then restart at one dose level lower
3	Severe pain; interfering with oral intake	• Hold until Grade 1 or lower, then restart at one dose level lower
4	Life-threatening consequences; urgent intervention indicated	• Discontinue

4. Hepatic impairment:

Degree of impairment	Dose (PO daily)*
Mild (Child-Pugh A)	7.5 mg Decrease to 5 mg if not tolerated
Moderate (Child-Pugh B)	5 mg Decrease to 2.5 mg if not tolerated
Severe (Child-Pugh C)	Max 2.5 mg (If the potential benefit outweighs the risk.)

*Note: Alternately a universal 50% dose reduction has been used in mild to moderate hepatic failure

5. Non-Hematologic Toxicity:

- Common toxicities reported with everolimus include rash and diarrhea
- Supportive medications such as topical steroid cream and anti-diarrheal agents may allow for continued dosing with or without dose adjustments
- Hyperglycemia resulting from everolimus use should be treated with oral hypoglycemics if persistent. Glucose levels should be monitored closely in diabetic patients

Grade	Management
Grade 0 to 2	• 100% • Grade 2 adverse events that are persistent and intolerable can result in dose delays or dose reductions to the next lower dose level
Grade 3 to 4	• Hold therapy until recovery to Grade 0 to 2 • If recovery within 3 weeks, dose reduce by one dose level for subsequent treatment

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
2. **Hypersensitivity**: reactions are reported including anaphylaxis, dyspnea, flushing, chest pain, or angioedema. Everolimus treatment should be discontinued for clinically significant reaction.
3. **Drug Interactions:** Everolimus is predominantly metabolized and excreted through cytochrome P450 3A4 in the liver. Potential drug interactions with cytochrome P4503A4 interacting agents must be considered. (See BC Cancer Drug Manual and see also: http://medicine.iupui.edu/flockhart/table.htm)

4. **Renal impairment:** Only a very small percentage of everolimus and its metabolites are excreted by the kidney. Everolimus appears safe in patients with mild renal impairment (creatinine less than or equal to 2x upper limit of normal). No data exist for everolimus in patients with moderate to severe kidney failure.
5. **Hepatic impairment:** Everolimus is mainly metabolized and excreted through the liver. See protocol for dose modifications.
6. **Lung dysfunction**: Caution is advised for patients with significant lung dysfunction due to the risk for pneumonitis (mTOR inhibitor class effect)
7. Metabolic effects such as **hyperglycemia, hypercholesterolemia**, and **hypertriglyceridemia** can occur in patients taking everolimus, with Grade 3 and 4 events reported.

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. Yao JC, Fazio N, Simron Singh S, et al. Everolimus for the treatment of advanced, non-functional. neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet 2016;387:968–77.
2. Rugo H, Seneviratne L, Beck J, et al: Prevention of everolimus/exemestane stomatitis in postmenopausal women with hormone receptor–positive metastatic breast cancer using a dexamethasone-based mouthwash: Results of the SWISH trial. MASCC/ISOO International Symposium on Supportive Care in Cancer. Abstract MASCC-0638. Presented June 23, 2016.