BC Cancer Protocol Summary for Therapy for Tuberous Sclerosis Complex-Associated High Risk Renal Angiomyolipomas using Everolimus

Protocol Code	*GUOTEVER*
Tumour Group	*Genitourinary*
Contact Physician	*Dr. Richard Gagnon*

ELIGIBILITY:

Patients must have:

- Tuberous sclerosis complex (TSC), and
- Renal angiomyolipoma with at least one lesion being 3 cm or larger on imaging (CT, MRI, or ultrasound)

Patients should have:

- Adequate hematologic and hepatic function

EXCLUSIONS:

Patients must not have:

- Major surgery within the last 4 weeks
- History of hypersensitivity reaction to everolimus or other rapamycin derivatives (i.e., SIrolimus, temsirolimus)
- Pregnancy

CAUTIONS:

- Pre-existing significant lung compromise due to risk of pneumonitis
- Concomitant immunosuppressive therapies excluding corticosteroids as antiemetic or anaphylactic prophylaxis
- Diabetic patients
- Hepatitis B or C carriers

TESTS:

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

triglycerides, sodium, potassium, magnesium, calcium, phosphate, creatine kinase, 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
- Consider regular monitoring of blood pressure, lipid profile, and blood glucose

PREMEDICATIONS:
- Antiemetic protocol for low emetogenic chemotherapy protocols (see SCNAUSEA)
- Stomatitis prophylaxis: see Precautions

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
everolimus	10 mg	PO

- 1 cycle is 4 weeks of treatment
- Continue until disease progression or unacceptable toxicity

DOSE MODIFICATIONS:

Everolimus Dose Levels:

Starting Dose	Dose Level -1	Dose Level -2
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 Grade 3 to 4 toxicities fail to recover to Grade 2 or lower 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
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 once 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

* 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
- Proteinuria can be indicative of disease status or everolimus toxicity. If proteinuria present, discuss with provider

Grade	Management
0 to 2	• 100% everolimus dose • Grade 2 adverse events that are persistent and intolerable can result in dose delays or dose reductions to the next lower dose level
3 to 4	• Hold everolimus until recovery to Grade 0 to 2 • If recovery within 3 weeks, 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: https://drug-interactions.medicine.iu.edu/Home.aspx)
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. **Lung dysfunction**: Caution is advised for patients with significant lung dysfunction due to the risk for pneumonitis (mTOR inhibitor class effect)
6. **Stomatitis Prophylaxis:** Dexamethasone mouthwash 0.1 mg/mL (alcohol-free) can significantly reduce the incidence of stomatitis caused by everolimus:
   - 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.
7. Metabolic effects such as **hyperglycemia, hypercholesterolemia**, and **hypertriglyceridemia** can occur in patients taking everolimus, with Grade 3 and 4 events reported. Monitoring is suggested during treatment.

Call Dr. Richard Gagnon or tumour group delegate at (250) 519-5500 or 1-800-670-3322 with any problems or questions regarding this treatment program.

References:

1. Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus long-term use in patients with tuberous sclerosis complex: Four-year update of the EXIST-2 study. PLoS One. 2017 Aug 9;12(8):e0180939.
2. Sasongko TH, Kademane K, Chai Soon Hou S, Jocelyn TXY, Zabidi-Hussin Z. Rapamycin and rapalogs for tuberous sclerosis complex. Cochrane Database Syst Rev. 2023 Jul 11;7(7):CD011272.
3. Tuberous Sclerosis Canada. Consensus Guidelines for Diagnosis, Surveillance, and Management of Tuberous Sclerosis Complex. TSC Canada; 2014. Available from: https://www.tscanada.ca/wp-content/uploads/2014/12/TSCanada-TREATMENT-CONSENSUS-GUIDELINES.pdf
4. Everolimus (Afinitor) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies Sep 2013