BC Cancer Protocol Summary for Therapy for Advanced Breast Cancer Using Everolimus and Exemestane

Protocol Code	*BRAVEVEX*
Tumour Group	*Breast*
Contact Physician	*Dr. Caroline Lohrisch*

ELIGIBILITY:

Patients must be:

- Post-menopausal women with hormone receptor positive, HER-2 negative advanced breast cancer after recurrence or progression on a non-steroidal aromatase inhibitor (anastrozole or letrozole) (including women with chemically induced menopause with LHRH agonists)

Patients should have:

- ECOG status 0-2

Notes:

- Patients are eligible to receive any of the following, but not their sequential use:
  - Palbociclib plus fulvestrant (BRAVPBFLV) or ribociclib plus fulvestrant (BRAVRBFLV),
    OR
  - Ribociclib plus letrozole/anastrozole (BRAVRIBAI) or palbociclib plus letrozole/anastrozole (BRAVPALAI)
    OR
  - Everolimus plus exemestane (BRAVEVEX)

EXCLUSIONS:

Patients must not have:

- Major surgery within the last 4 weeks

CAUTIONS:

- Pre-existing significant lung compromise due to the risk for pneumonitis
- Concomitant immunosuppressive therapies excluding corticosteroids as antiemetic or anaphylactic prophylaxis
- History of hypersensitivity reaction to everolimus or other rapamycin derivatives (i.e. sirolimus, temsirolimus)
- Diabetic patients as everolimus may elevate blood sugar
- Hepatitis B or C carriers as everolimus may induce an active hepatitis in carriers

TESTS:

- **Baseline**: CBC & Diff, creatinine, urea, random glucose, HbA1c, total bilirubin, ALT, alkaline phosphatase, LDH, albumin, INR
- **Baseline** (required but results do not need to be available to proceed with first cycle): sodium, potassium, calcium, phosphate, total cholesterol, triglycerides
- **Baseline, if clinically indicated:** total protein, GGT, HBsAg, HBsAb, HBcoreAb, chest X-ray, oxygen saturation
- **Prior to cycle 2, then prior to each doctor's visit:** CBC & Diff
- **If clinically indicated:** total protein, albumin, GGT, total bilirubin, INR, 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 treatment.

Alcohol-free Dexamethasone 0.1 mg/mL solution. Use 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). May continue up 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	PO
exemestane	25 mg once daily	PO

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

Patients should be evaluated within 4 weeks after initiation of therapy to monitor for serious toxicity such as pneumonitis, hyperglycemia, rash, mucositis, infection. Thereafter, patients tolerating the combination well can be seen less frequently (up to every 2 months), at the physician's discretion.

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. **Exemestane** - continue exemestane regardless of everolimus interruptions or dose modifications

2. **Hematological Toxicity: Everolimus**

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Everolimus 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 PLT 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 progression or if patient with Grade 3-4 toxicities fail to recover to Grade 0-2 within three weeks

3. Hepatic Impairment: Everolimus

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

4. 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

5. Stomatitis:

- Use of prophylactic medicated mouthwash for stomatitis is recommended during the first two cycles of treatment.

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

6. Other Everolimus-Related Non-Hematologic Toxicity:

- Dose modification required for everolimus.
- Common toxicities reported with everolimus include mucositis, rash, diarrhea.
- Supportive medications such as medicated mouth wash, topical steroid cream, non-sedating oral antihistamine 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% dose • 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. 50% dose reduction in mild to moderate hepatic failure is suggested. No data exists for everolimus in patients with severe hepatic impairment.
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 Dr. Caroline Lohrisch or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. 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.
2. Yardley DA, Noguchi S, Pritchard KI, et al: Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther 30:870-884, 2013.
3. Baselga J, Campone M, Piccart M, et al: Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 366:520-529, 2012.
4. Rugo HS, Hortobagyi GN, Yao J, et al: Meta-analysis of stomatitis in clinical studies of everolimus: Incidence and relationship with efficacy. Ann Oncol 27:519-525, 2016.
5. Rugo HS, Pritchard KI, Gnant M, et al: Incidence and time course of everolimus-related adverse events in postmenopausal women with hormone receptor-positive advanced breast cancer: Insights from BOLERO-2. Ann Oncol 25:808-815, 2014.