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

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

ELIGIBILITY:

- 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).

** Note: Patients are eligible to receive any of the following, but not their sequential use:*

- *Palbociclib plus fulvestrant (UBRAVPBFLV) or Ribociclib plus fulvestrant (UBRAVRBFLV), OR*
- *Ribociclib plus letrozole/anastrozole (UBRAVRIBAI) or Palbociclib plus letrozole/anastrozole (UBRAVPALAI).*

Patients who have received the above regimens are NOT eligible for subsequent use of everolimus plus exemestane (BRAVEVEX).

- ECOG status 0-2

EXCLUSIONS:

- Major surgery within the last 4 weeks
- Caution is advised for patients with 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)
- Caution is advised for diabetic patients as everolimus may elevate blood sugar
- Caution is advised for Hepatitis B or C carriers as everolimus may induce an active hepatitis in carriers.

TESTS:

- **Baseline**: CBC, differential, platelets, creatinine, BUN, random glucose, total bilirubin, ALT, alkaline phosphatase, LDH, appropriate radiographic evaluations including Chest X-ray, O2 saturation. Obtain HBsAg, HBcoreAb for patients considered at high risk.
- **Baseline** (required but results do not need to be available to proceed with first cycle): sodium, potassium, calcium, phosphorus, total cholesterol, triglycerides
- **Prior to cycle 2:** CBC, differential, platelets, ALT, LDH, alkaline phosphatase, total bilirubin, albumin, random glucose
- **At each subsequent visit**: CBC, differential, platelets, random glucose
- **If clinically indicated:** any abnormal baseline tests, total protein, albumin, GGT

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 daily	PO
exemestane	25 mg 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:

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

2. **Hematological: Everolimus**

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose Everolimus
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

Dose levels:

Standard	10 mg daily
Dose level – 1	5 mg daily
Dose level – 2	5 mg every other day

2. Everolimus Related 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, 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 of everolimus related adverse events	Everolimus Dose Adjustments
Grade 0-2	Maintain dose, add supportive medications as needed If adverse event is persistent and/or intolerable hold therapy until resolution and then resume at one dose level lower.
Grade 3-4 First occurrence	Hold therapy until recovery to grade 0-2 If recovery within 3 weeks, dose reduce by one dose level for subsequent treatment. If no resolution, consider permanent discontinuation
Grade 3-4 toxicity or intolerable grade 2 toxicity Second occurrence	If toxicity re-occurs at a lower dose level, therapy should be stopped until resolution. Therapy can be resumed at the lowest dose level
Grade 3-4 toxicity or intolerable grade 2 toxicity Third occurrence	Discontinue everolimus

3. Everolimus induced pneumonitis:

Grade of everolimus related pneumonitis	Dose Adjustments
Grade 1 (Asymptomatic, radiographic changes only)	• Establish absence of symptoms • Continue treatment with close observation for development of symptoms and repeat chest CT/CXR • Exceptions to be considered e.g. underlying ILD
Grade 2 (Symptomatic; not interfering with the activities of daily living)	• Rule out infection or co-existing infection • Consider referral to Respirology • Stop everolimus for 10-14 days or until resolution to grade 0 or 1 • Consider short course of prednisone 20 mg/day for 10-14 days • If improved to grade less than or equal to 1 within 2 weeks, restart treatment at one dose level lower • If it is a second occurrence, treat as above and restart at lowest dose level or discontinue everolimus

Grade of everolimus related pneumonitis	Dose Adjustments
Grade 3 (Symptomatic; interfering with the activities of daily living; oxygen indicated)	• Stop everolimus until resolution to grade 0 or 1 • Rule out infection or co-existing infection • Refer to Respirology • High-dose prednisone (greater than 1 mg/kg/day) if impending respiratory failure • Lower prednisone dose may be adequate for less severe cases • Consider permanent discontinuation of everolimus. • If clinical benefit is being observed on therapy, it may be resumed at a reduced dose with caution and close monitoring at the physician's discretion.
Grade 4	• As for grade 3 • Ventilator therapy • Permanently discontinue everolimus

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**: For reactions with everolimus refer to BC Cancer Hypersensitivity Guidelines.
3. 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 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)

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.