ELIGIBILITY:
- Postmenopausal, hormone receptor positive, HER-2 negative advanced breast cancer after recurrence or progression on a non-steroidal aromatase inhibitor (anastrozole or letrozole)
- Note: Patients are eligible to receive palbociclib plus letrozole/anastrozole (UBRAVPALAI) or everolimus plus exemestane (BRAVEVEX), but not sequential use of these combination regimens.
- ECOG status 0-2

EXCLUSIONS:
- Premenopausal
- 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:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>everolimus</td>
<td>10 mg</td>
<td>PO on an empty stomach or after a fat-free meal daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do not crush or chew tablets.</td>
</tr>
<tr>
<td>exemestane</td>
<td>25 mg</td>
<td>PO daily</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>ANC (x10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>Dose Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 1.0 and greater than or equal to 75</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>less than 1.0 or less than 75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 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

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Warning: The information contained in these documents are a statement of consensus of BC Cancer professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is at your own risk and is subject to BC Cancer’s terms of use available at [www.bccancer.bc.ca/legal.htm](http://www.bccancer.bc.ca/legal.htm)
Dose levels:

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Dose level – 1</td>
<td>5 mg daily</td>
</tr>
<tr>
<td>Dose level – 2</td>
<td>5 mg every other day</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Grade of everolimus related adverse events</th>
<th>Everolimus Dose Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0-2</td>
<td>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.</td>
</tr>
<tr>
<td>Grade 3-4 First occurrence</td>
<td>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.</td>
</tr>
<tr>
<td>Grade 3-4 toxicity or intolerable grade 2 toxicity Second occurrence</td>
<td>If toxicity re-occurs at a lower dose level, therapy should be stopped until resolution. Therapy can be resumed at the lowest dose level.</td>
</tr>
<tr>
<td>Grade 3-4 toxicity or intolerable grade 2 toxicity Third occurrence</td>
<td>Discontinue everolimus</td>
</tr>
</tbody>
</table>
3. Everolimus induced pneumonitis:

<table>
<thead>
<tr>
<th>Grade of everolimus related pneumonitis</th>
<th>Dose Adjustments</th>
</tr>
</thead>
</table>
| 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 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: