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

Protocol Code	*LUNETEV*
Tumour Group	*Lung*
Contact Physician	*Dr. Christopher Lee*

ELIGIBILITY:

- Well differentiated, non-functional, neuroendocrine tumours of lung origin
- Unresectable, locally advanced or metastatic disease
- ECOG 0 – 2
- Adequate hematologic, renal and hepatic function

EXCLUSIONS:

- Carcinoid syndrome
- Major surgery within the last 4 weeks
- Caution is advised for patients with pre-existing significant lung compromise due to risk for pneumonitis
- Concomitant immunosuppressive therapies excluding corticosteroids as antiemetic or anaphylactic prophylaxis
- History of hypersensitivity to everolimus or other rapamycin derivatives (i.e. sirolimus, temsirolimus)
- Caution is advised for hepatitis B or C carriers; everolimus may induce active hepatitis in carriers – *obtain HBsAg/HBcoreAb for patients considered at high risk*

TESTS:

- **Baseline**: CBC, differential, platelets, sodium, potassium, creatinine, BUN, random glucose, calcium, phosphate, ALT, LDH, total bilirubin, alkaline phosphatase, total cholesterol, triglycerides, appropriate radiographic evaluations including Chest X-ray, O2 saturation
- **Prior to each treatment**: CBC, differential, platelets, creatinine, bilirubin, ALT, alkaline phosphatase, sodium, potassium, random glucose
- **If clinically indicated:** any abnormal baseline tests

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	PO on an empty stomach or after a fat-free meal daily.* Do not crush or chew tablets.

*Note: 4 weeks of treatment comprise 1 cycle

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	and	greater than or equal to 75	100%
less than 1	or	less than 75	• Hold until ANC greater than or equal to 1 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 tumour progression or if patient with Grade 3-4 toxicities fails to recover to Grade 0-2 within three weeks.

2. Non-Hematologic:

Common toxicities reported with everolimus include mucositis, rash, and 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	Dose Adjustments
Grade 0-2	• 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 3-4	• Hold therapy until recovery to grade 0-2 • If recovery within 3 weeks, dose reduce by one dose level for subsequent treatment.

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 • Consider short course of prednisone 20 mg/day for 10-14 days • Treatment break for 4-14 days • If improved to grade less than or equal to 1 within 2 weeks restart treatment • If it is a second occurrence , treat as above and restart at one dose level lower 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 than1 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 clinician's discretion.
Grade 4	• All of the above • Ventilator therapy • Termination of treatment

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 2.5mg if not tolerated
Severe (Child-Pugh C)	Max 2.5mg (If the potential benefit outweighs the risk.)

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

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. **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 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)

Call Dr. Christopher Lee or tumour group delegate at (604) 877-6000 or 1-800-670-3322 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.