

# BCCA Protocol Summary for Palliative Treatment of Advanced Pancreatic Neuroendocrine Tumours using Everolimus

**Protocol Code**

*UGIPNEVER*

**Tumour Group**

*Gastrointestinal*

**Contact Physician**

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## ELIGIBILITY:

- Well to moderately differentiated, unresectable or metastatic pancreatic neuroendocrine tumours.
- ECOG 0 – 2.
- Adequate hematologic, renal and hepatic function.
- Compassionate Access Program (CAP)/Undesignated Indication approval granted by BCCA. **Note:** Approvals will only be given for one of UGIPNSUNI or UGIPNEVER – not both, unless due to intolerance within the first month of therapy.

## 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)

## TESTS:

- **Baseline:** CBC, differential, platelets, electrolytes, creatinine, BUN, random glucose, calcium, phosphorus, AST, LDH, total bilirubin, alkaline phosphatase, total cholesterol, triglycerides, appropriate radiographic evaluations including Chest X-ray, O<sub>2</sub> saturation.
- **Prior to each treatment:** CBC, differential, platelets, random glucose
- **If clinically indicated:** any abnormal baseline tests

## PREMEDICATIONS

- Antiemetic protocol for low emetogenic chemotherapy protocols (see [SCNAUSEA](#))

## TREATMENT:

Drug	Dose	BCCA 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 for All Toxicity**

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 <sup>9</sup> /L)		Platelets (x10 <sup>9</sup> /L)	Dose
greater than or equal to 1	and	greater than or equal to 75	100%
less than 1	or	less than 75	<ul style="list-style-type: none"><li>Hold until ANC greater than or equal to 1 and/or PLT greater than or equal to 75</li><li>If recovery within 10 days restart same dose level; if not, reduce dose by 1 dose level</li></ul>

Discontinue if tumor progression or if patient with Grade 3-4 toxicities fail to recover to Grade 0-2 within three weeks.

### 2. Non-Hematologic Toxicity:

Grade of everolimus related adverse events	Dose Adjustments
Grade 0-2	<ul style="list-style-type: none"><li>100%</li><li>Grade 2 adverse events that are persistent and intolerable can result in dose delays or dose reductions to the next lower dose level</li></ul>
Grade 3-4	<ul style="list-style-type: none"><li>Hold therapy until recovery to grade 0-2</li><li>If recovery within 3 weeks, dose reduce by one dose level for subsequent treatment.</li></ul>

### 3. Everolimus induced pneumonitis:

Grade of everolimus related pneumonitis	Dose Adjustments
Grade 1 (Asymptomatic, radiographic changes only)	<ul style="list-style-type: none"> <li>• Establish absence of symptoms</li> <li>• Continue treatment with close observation for development of symptoms and repeat chest CT/CXR</li> <li>• Exceptions to be considered e.g. underlying ILD</li> </ul>
Grade 2 (Symptomatic; not interfering with the activities of daily living)	<ul style="list-style-type: none"> <li>• Rule out infection or co-existing infection</li> <li>• Consider short course of prednisone 20 mg/day for 10-14 days</li> <li>• Treatment break for 4-14 days</li> <li>• If improved to grade less than or equal to 1 within 2 weeks restart treatment</li> <li>• If it is a second occurrence , treat as above and restart at reduced dose of 5 mg daily</li> </ul>
Grade 3 (Symptomatic; interfering with the activities of daily living; oxygen indicated)	<ul style="list-style-type: none"> <li>• Interrupt mTor inhibitor</li> <li>• Rule out opportunistic infections</li> <li>• High-dose prednisone (less than 1 mg/kg/day) if impending respiratory failure</li> <li>• Lower prednisone dose may be adequate for less severe cases</li> <li>• Continuation of therapy with dose reduction in selected case if clinical benefit , otherwise treatment termination</li> </ul>
Grade 4	<ul style="list-style-type: none"> <li>• All of the above</li> <li>• Ventilator therapy</li> <li>• Termination of treatment</li> </ul>

#### PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BCCA Febrile Neutropenia Guidelines.
2. **Hypersensitivity:** For reactions with everolimus refer to BCCA [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. 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 the GI Systemic Therapy physician at your regional cancer centre or Dr. Bal Johal at (604) 930-2098 or 1-800-523-2885 with any problems or questions regarding this treatment program.**

Date activated: **1 Jun 2011**

Date revised:

**References:**

1. Yao, J et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364;6:514-23.