BC Cancer Protocol Summary for Therapy for Advanced Renal Cancer Using Everolimus

Protocol Code	*GUEVER*
Tumour Group	*Genitourinary*
Contact Physician	*C. Kollmannsberger*

ELIGIBILITY:

- Advanced renal cell carcinoma after failure of first-line tyrosine-kinase inhibitor therapy (SUNItinib, SORAfenib, PAZOpanib) or after failure of first-line immunotherapy
- Any histology and IMDC risk group
- Patients are eligible to receive nivolumab or everolimus, but not sequential use of these agents.

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, sodium, potassium, creatinine, BUN, glucose, calcium, phosphorus, 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
- **If clinically indicated:** any abnormal baseline tests

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

2. **Everolimus Related Toxicity**: Dose modification required for everolimus.

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 • Short course of prednisone 20 mg/day for 10-14 days • Treatment break for 4-14 days • If improved to grade ≤ 1 within 2 weeks restart treatment • If it is a second occurrence , treat as above and restart at reduced dose of 5 mg daily
Grade 3 (Symptomatic; interfering with the activities of daily living; oxygen indicated)	• Interrupt mTor inhibitor • Rule out opportunistic infections • High-dose prednisone (>1 mg/kg/day) if impending respiratory failure • Lower prednisone dose may be adequate for less severe cases • Continuation of therapy with dose reduction in selected case if clinical benefit , otherwise treatment termination
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

*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. 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. **Lung dysfunction**: Caution is advised for patients with significant lung dysfunction due to the risk for pneumonitis (mTOR inhibitor class effect)
6. **Stomatitis Prophylaxis:** Dexamethasone mouthwash 0.1 mg/mL (alcohol-free) can significantly reduce the incidence of stomatitis caused by everolimus

- 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.

Call Dr. Kollmannsberger or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Amato RJ, Jac J, Giessinger S, et al. A phase 2 study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metastatic clear cell renal cell cancer. Cancer 2009;115(11):2438-46.
2. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372:449-56.