

BCCA Protocol Summary for Therapy for Advanced Renal Cancer Using Everolimus

Protocol Code

UGUEVER

Tumour Group

Genitourinary

Contact Physician

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ELIGIBILITY:

- Advanced renal cell carcinoma after failure of first-line tyrosine-kinase inhibitor therapy (sunitinib, sorafenib, pazopanib)
- Compassionate Access Program (CAP)/Undesignated Indication approval granted by BCCA

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, glucose, calcium, phosphorus, AST, 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	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:

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	<ul style="list-style-type: none"> 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

Dose levels:

Standard	10 mg
Dose level – 1	5 mg

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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • All of the above • Ventilator therapy • Termination of treatment

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

Date activated: **1 February 2011**

Date revised: **1 Mar 2011 (Updated pneumonitis grading)**

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.