BC Cancer Protocol Summary for Palliative Therapy for Renal Cell Carcinoma Using PAZOpanib

Protocol Code	*GUPAZO*
Tumour Group	*Genitourinary*
Contact Physician	*Dr. C. Kollmannsberger*

ELIGIBILITY:

Patients must have:

- Advanced renal cell carcinoma,
- Any histology and IMDC risk group, and
- No prior systemic therapy (first-line therapy) or after failure of first-line immunotherapy

Patients should have:

- ECOG performance status less than or equal to 2

NOTE: refer to renal cell carcinoma funding algorithm for more details

EXCLUSIONS:

Patients must not have:

- Pregnancy
- Moderate or severe hepatic impairment (baseline plasma bilirubin greater than 1.5 x ULN and ALT elevations of greater than 2 x ULN)
- Significant cardiovascular disease and/or LVEF less than 45%
- Uncontrolled hypertension

TESTS:

- Baseline: CBC and differential, platelets, sodium, potassium, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, ALT, urine analysis, TSH
- Every 2 weeks for Cycle 1 and 2: CBC and differential, platelets, creatinine, ALT, bilirubin
- Before Cycle 3 and each subsequent cycle: CBC and differential, platelets, creatinine, ALT, bilirubin; TSH every other cycle or if clinically indicated
- MUGA scan or echocardiogram if clinically indicated or if history of cardiac problems

PREMEDICATIONS:

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

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
PAZOpanib	800 mg	PO once daily

1 cycle = 4 weeks

Dose reduction:

Dose level – 1: 400 mg
Dose level – 2: 200 mg

DOSE MODIFICATIONS:

1. Hematological

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose (all drugs)
Greater than or equal to 1.0	and	Greater than or equal to 75	100%
Less than 1.0	or	Less than 75	Delay

2. Non-Hematological toxicity:

CTC-Grade	Dose
1-2	100%
3-4	Delay until less than or equal to grade 1 Dose reduce by 1 dose level

3. Dosage in hepatic impairment:

Bilirubin total (µmol/L)		ALT (IU/L)	Dose
Less or equal than 1.5 X ULN	and	Less or equal than 2 X ULN	100 %
More than 1.5 X ULN	and	More than 2 -3 X ULN	Hold until ALT less or equal than 2.5 X ULN; If benefit outweighs risk, restart at reduced dose no more than 400 mg PO once daily and measure serum liver tests weekly x 8 weeks
More than 1.5 X ULN	and	More than 3 X ULN	Delay

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
2. **Hepatic dysfunction**: PAZOpanib is mainly metabolized and excreted through the liver. PAZOpanib appears safe in patients with mild hepatic impairment (bilirubin less than or equal to 1.5 x upper limit of normal). **Therapy with PAZOpanib may result in hepatobiliary abnormalities (increase of serum transaminase levels and bilirubin). Severe and fatal hepatotoxicity has been reported**. It is important to monitor serum liver tests (ALT, bilirubin) prior to initiation of PAZOpanib, increase frequency of monitoring during weeks 2, 4, 6, 8 and prior to each cycle or as clinically indicated.
3. **Renal dysfunction:** Only a very small percentage of PAZOpanib and its metabolites are excreted by the kidney. PAZOpanib appears safe in patients with mild renal impairment (creatinine clearance greater than or equal to 30 mL/min). No data exist for PAZOpanib in patients with severe renal impairment or in patients undergoing peritoneal dialysis or hemodialysis.
4. PAZOpanib is predominantly metabolized and excreted through cytochrome P450 3A4 in the liver. Potential drug interactions with cytochrome P450 3A4 interacting agents must be considered (see also: http://medicine.iupui.edu/flockhart/table.htm).
5. **Hypertension**: Patients with hypertension should exercise caution while on PAZOpanib. Blood pressure should be well controlled prior to initiating treatment. Treatment with PAZOpanib should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persists despite anti-hypertensive therapy and PAZOpanib dose reduction. It is recommended that for at least the first 2 cycles of treatment, patients monitor their blood pressure daily (home measurements, GP's office, etc.) and keep a journal of their blood pressure measurements that can be submitted to the physician.

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. Sternberg CN, Davis ID, Mardiak J et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28: 1061-1068.