



ONCOLOGYEDUCATION.CA
Improving patient care through education.

LATEST ONCOLOGY UPDATES

Title: Pazopanib in Locally Advanced or Metastatic Renal Cell Carcinoma: Results of a Randomized Phase III Trial

Background:

- Targeted therapy with VEGF inhibitors is the standard of care for good and intermediate risk metastatic clear cell first-line RCC.
- Pazopanib is another oral angiogenesis inhibitor that targets VEGF, PDGF and c-Kit.

Study design:

- Randomized, double-blind, placebo-controlled, phase III study in metastatic clear cell RCC
- 2:1 randomization.
- Patients:
 - Initially, second-line post-cytokine therapy
 - Amended – first-line as well.
- Stratified:
 - ECOG 0 vs. 1
 - Prior nephrectomy
 - Prior systemic therapy
- Pazopanib 800 mg p.o. qd 1 hour pre- or 2 hours post-meal.
- If progression and on placebo, patient are able to receive drug on open-label study.
- Primary endpoint = PFS.
- Secondary endpoint = overall survival, RECIST RR, HRQOL.
- Assessment – radiologically q6 weeks.

Statistics:

- Initially, 90% power to detect 80% improvement in PFS (HR=0.56) and 50% improvement in OS (HR=0.67).
- Amendment – 80% power to detect 80% improvement in PFS (HR=0.67) in each subgroup.
- One-sided $\alpha = 0.025$.
- N=400.

Study results:

- N=435 (n=233 first-line; n=202 second-line).
- From April 2006 – April 2007.
- Demographics:



	Pazopanib	Placebo
N=	290	145
MSKCC Risk:		
• Favorable	39%	39%
• Intermediate	55%	53%
• Poor	3%	3%
Prior Nephrectomy	89%	88%
First-line	53%	54%
Second-line	47%	46%

- Efficacy:

	Pazopanib	Placebo	HR	P Value
N=	290	145		
Patients Progressed	148	98		
PFS	9.2	4.2	0.46 (0.34-0.62)	p<0.0001
First-line	11.1	2.8	0.40	p<0.0001
Second-line	7.4	4.2	0.54	p<0.001
RR (CR + PR)	30%	3%		
PR	30%	3%		
Stable Disease	38%	41%		

- All subgroups benefited:
 - MSKCC risk, ECOG, sex, age
- Grade 3/4 AEs
 - Hypertension 4%
 - Diarrhea 3%
 - Fatigue 2%
- Arterial thrombotic events and hemorrhage:
 - MI/ischemia 2%
 - CVA < 1%
 - TIA < 1%
 - Hemorrhage 13% (all grades vs. 5%)
- Death from AEs (4% Pazopanib vs. 3% placebo).
- HRQOL – no differences.

Conclusions:

- Pazopanib significantly improves PFS and RR in metastatic clear cell RCC in first-line setting and post-cytokine therapy.



ONCOLOGYEDUCATION.CA[®]
Improving patient care through education.

- Acceptable safety/tolerability with most common grade 3/4 AEs being hypertension and diarrhea.
- No real grade 3/4 proteinuria, thrombocytopenia, hypothyroidism, hand-foot syndrome, and mucositis that can be seen with Bevacizumab/Sunitinib/Sorafenib.

Study commentary:

- Pazopanib is another oral VEGF inhibitor that ↑ RR and PFS in metastatic clear cell RCC.
- Toxicity profile from this trial does appear to be better than Sunitinib.
- Current phase III trial of first-line Pazopanib vs. Sunitinib will answer the question about equivalency in terms of efficacy and tolerability.
- In Canada, we will likely await the results of that study before a major change in practice occurs.

Website link to source: www.jco.org (*J Clin Oncol* 2010;28:1061-1068)