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# Outcomes of patients with metastatic renal cell carcinoma (mRCC) treated with pazopanib after progression on other targeted therapies: A single institution experience

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## Background

In the past few years, considerable progress has been made in the management of patients with mRCC. There are now seven (five in the first-line setting) FDA-approved treatments for mRCC, however, most patients experience disease progression within a year or less. Retrospective studies and prospective phase II and III trials have demonstrated benefit of sequential administration of targeted therapy after disease progression with other targeted therapies given earlier. Everolimus and axitinib are the only agents with level 1 evidence in the salvage setting. Everolimus is associated with a 1% PR rate and 4-mo median PFS. Axitinib is associated with a 19% PR rate and a 6.7-mo median PFS in the second-line setting.

Pazopanib is a multi-tyrosine kinase inhibitor that selectively inhibits VEGFR1-3, PDGFR, c-Kit, and Flt-3. Results of a phase III clinical trial of pazopanib in patients with mRCC (233 patients treatment naive (54%) and 202 cytokine pretreated patients (46%) revealed that progression-free survival was significantly prolonged with pazopanib compared with placebo in the overall study population (median, PFS 9.2 v 4.2 months; hazard ratio [HR], 0.46; 95% CI, 0.34 to 0.62; P < .0001). The objective response rate was 30% with pazopanib compared with 3% with placebo (P < .001). The median duration of response was longer than 1 year. Most adverse events were grade 1 or 2. Common adverse events included diarrhea, hypertension, hair color changes, nausea, anorexia, and vomiting.

Pazopanib has been FDA approved for the treatment of mRCC, and data suggests it is efficacious in treatment-naive or cytokine pretreated patients. Current treatment algorithms now designate pazopanib as first-line therapy. However, there is limited data on the use of pazopanib as salvage therapy after failure of other targeted therapies.

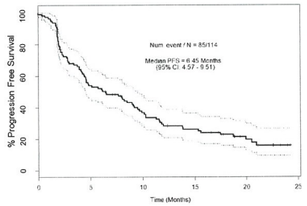
## Patients and Methods

We retrospectively reviewed 114 consecutive pts with mRCC who received salvage pazopanib between 11/09-11/11. Kaplan-Meier method was used to estimate survival outcomes. PFS was calculated from start of pazopanib until progressive disease (PD) or death. Univariable and multivariable Cox proportional hazards models were fitted to evaluate associations of PFS with covariables. Toxicity was graded by NCI CTCAE v3.0.

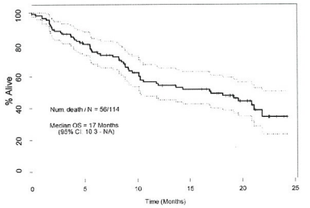
| **Demographics %, (n=)** | |
|---|---|
| Median Age, yrs | 63 (range 22-80) |
| Male | 67% (76) |
| Clear Cell | 83% (94) |
| Median number of prior targeted agents | 2 (range 1-6) |
| Median time on previous treatments | 23.3 months (range 1 – 58 mos ) |
| **Prognostic Features %, (n=)** | |
| KPS <80 | 31% (35) |
| Low Hemoglobin | 84% (96) |
| Corrected Calcium >10 mg/dL | 11% (12) |
| **Previous Therapies, % (n=)** | |
| Chemotherapy | 25.4% (29) |
| Cytokine Therapy | 15.8% (18) |
| Bevacizumab | 22.8% (26) |
| Sorafenib | 38.6% (44) |
| Sunitinib | 78.9% (90) |
| Temsirolimus | 19.3% (22) |
| Everolimus | 58.8% (67) |
| Other Targeted Agents | 18% (20) |
| **Previous Therapies, Mean Duration in Days (range)** | |
| Chemotherapy | 120.5 (7 - 1456) |
| Cytokine Therapy | 137.5 (27 - 943) |
| Bevacizumab | 234 (103 - 853) |
| Sorafenib | 201 (14 - 1673) |
| Sunitinib | 273 (31 - 1380) |
| Temsirolimus | 152 (56 - 611) |
| Everolimus | 106 (11 - 712) |
| Other Targeted Agents | 184 (31- 869) |

## Results

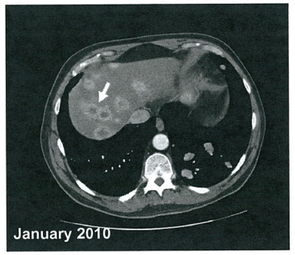
- 85 events (PD or death) occurred. Median Time to Follow-up was 19.4 months (95% CI: 18.7-20.8). 51% of subjects were dead at the time of analysis.
- Median PFS was 6.4 mos (95% CI: 4.5-9.5).
- Median OS was 17 mos (95% CI: 10.3-NA).
- By multivariate analysis: PFS was associated with male gender (HR=0.433, 95%CI: 0.269-0.696; p=0.0006), hypertension exacerbation (HR=0.378; CI: 0.175-0.813; p=0.0128), pancreatic metastases (HR=0.41, 95% CI: 0.194-0.869; p=0.02), number of metastatic sites (HR=1.252; 95%CI: 1.04-1.503; p=0.016), and PS 2+ vs.0-1 (HR=2.067; CI: 1.243-3.437; p=0.0052).
- 13 pts received 2nd line pazopanib after 1st line sunitinib with a median TTF of 3.5 mos (range 1.8-10), 38% remained on treatment at last follow-up. 25 pts received 3rd line pazopanib after 1st line sunitinib and 2nd line everolimus with a median TTF of 3.7 mos (range 1.2-11), 44% remained on treatment at last follow-up.
- 58% discontinued pazopanib due to PD, 12% died of PD on treatment, and 11% discontinued pazopanib due to adverse events (AEs). There were no treatment related deaths.
- Common AEs included: fatigue (44%), diarrhea (29%), nausea/vomiting (15%), anorexia (14%), hypertension exacerbation (11%), hypothyroidism (11%), hand-foot skin reaction (9%), and increase LFTs (4%). 86% of AEs were grade 1/2.

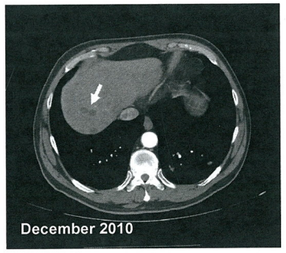



Progression Free Survival

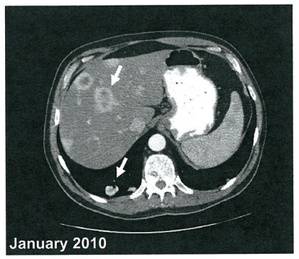


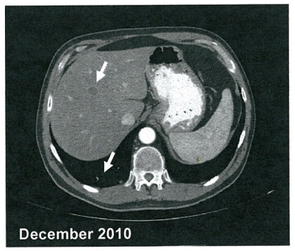

Overall Survival




Response to pazopanib in a patient with mRCC who had progressive disease through multiple previous targeted therapies (sunitinib, everolimus, and gemcitabine/capecitabine/bevacizumab)




## Conclusions

- In this retrospective study, pazopanib demonstrated clinically relevant activity in mRCC following PD with other targeted therapies, including TKIs inhibiting similar pathways.
- Adverse events were mostly mild-to-moderate and manageable.
- Our findings support the use of pazopanib in the salvage setting after failure of other targeted agents.
- Prospective evaluation is required to define the most optimal sequence of therapies in the salvage setting.

## References

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