Published in final edited form as:

Eur J Cancer. 2013 October ; 49(15): . doi:10.1016/j.ejca.2013.06.003.

Outcomes of patients with metastatic clear-cell renal cell carcinoma treated with pazopanib after progression during treatment with other targeted therapies

M. R. Matrana¹, C. Duran², A. Shetty³, L. Xiao⁴, B. J. Atkinson⁵, P. Corn⁶, L. C. Pagliaro⁶, R. E. Millikan⁷, C. Charnsangavej², E. Jonasch⁶, and N. M. Tannir⁶

¹Hematology and Medical Oncology Fellowship Program, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

²Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

³Internal Medicine Residency Program, The University of Texas Medical School at Houston, Houston, Texas, USA

⁴Division of Quantitative Sciences, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

⁵Clinical Pharmacy Programs, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

⁶Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

⁷Essentia Health Cancer Center, Duluth, Minnesota, USA

Abstract

Aim—The multi-tyrosine kinase inhibitor pazopanib prolongs progression-free survival (PFS) versus placebo in treatment-naïve and cytokine-refractory metastatic renal cell carcinoma (mRCC). Outcomes and safety data with pazopanib after targeted therapy (TT) are limited.

Methods—We retrospectively evaluated records of 112 consecutive mRCC patients with progressive disease (PD) after TT who received pazopanib from November 2009 through November 2011. Tumor response was assessed by a blinded radiologist using RECIST. PFS and overall survival (OS) were estimated by Kaplan-Meier methods.

Results—We report data on 93 patients with metastatic clear-cell RCC. Median number of prior TTs was 2 (range, 1–5). There were 68 events (PD or death). Among 85 evaluable patients, 13 (15%) had a partial response. Median PFS was 6.5 months (95% CI: 4.5–9.7); median OS was 18.1 months (95% CI: 10.26–NA). Common adverse events (AEs) included fatigue (44%), elevated transaminases (35%), diarrhea (30%), hypothyroidism (18%), nausea/vomiting (17%), anorexia (14%), and hypertension exacerbation (14%); 91% of AEs were grade 1/2. Eleven patients (12%) discontinued therapy due to AEs. There were no treatment-related deaths.

Correspondence to: Nizar M. Tannir, MD, FACP, Department of Genitourinary Medical Oncology, Unit 1374, The University of Texas MD Anderson Cancer Center, 1155 Pressler Street, Houston, TX 77030, USA. Tel.: +1-713-563-7265; Fax: +1-713-745-0422; ntannir@mdanderson.org.

Conflict of Interest Statement

Drs. Nizar Tannir and Eric Jonasch have research funding and have participated in an Advisory Board Meeting with GlaxoSmithKline.

Concluding Statement—Pazopanib demonstrated efficacy in patients with metastatic clear-cell RCC after PD on other TT. Toxicity overall was mild or moderate and manageable.

Keywords

renal cell carcinoma; angiogenesis; pazopanib; tyrosine kinase inhibitor; targeted therapy; mammalian target of rapamycin

INTRODUCTION

Approximately 30% of patients with renal cell carcinoma (RCC) have advanced disease at their initial diagnosis, and 20–30% develop metastases after surgery for earlier-stage disease ^(1, 2). Although select patients with limited metastatic disease may be cured with metastasectomy, the vast majority with metastatic disease are incurable and require systemic therapy for palliation and prolonged survival ⁽³⁾. Until recently, cytokine therapy with interleukin-2 or interferon-alfa was the mainstay of systemic treatment in patients with metastatic RCC (mRCC). Recently, the anti-vascular endothelial growth factor (VEGF) agents and mammalian target of rapamycin (mTOR) inhibitors have supplanted cytokines as the mainstay therapy and have led to prolongation of progression-free survival (PFS) and, in some patients, overall survival (OS) ⁽⁴⁾. Currently, there are four Food and Drug Administration–approved tyrosine-kinase inhibitors (TKIs) in the United States: sorafenib, sunitinib, pazopanib, and axitinib; approval of tivozanib is anticipated in the near future ⁽⁵⁾. Several other novel agents are in preclinical development and clinical trials ⁽⁶⁾. Sorafenib, sunitinib, and pazopanib have all gained marketing authorization from the European Medicines Agency (EMA), and axitinib has been granted orphan drug status by the EMA.

Pazopanib is an oral angiogenesis inhibitor of VEGF receptors 1, 2, and 3, platelet-derived growth factor receptors alpha and beta, and c-Kit (CD117); it was approved for treatment of mRCC in the U.S. in November 2009 and in Europe in June 2010. The safety and efficacy of pazopanib were evaluated in a randomized double-blind, placebo-controlled phase III trial in both treatment-naïve and cytokine-pretreated patients ⁽⁷⁾. Pazopanib demonstrated superior efficacy outcomes compared to placebo, with an improved median PFS of 9.2 months for all patients, 11 months for treatment-naïve patients, and 7.4 months for cytokine-pretreated patients, versus 4.2, 2.8, and 2.8 months, respectively, for patients treated with placebo. The overall response rate (ORR) with pazopanib was 30% versus 3% with placebo. Pazopanib is currently a National Comprehensive Cancer Network Class I treatment recommendation in the first-line setting and after cytokine therapy.

The efficacy and safety of pazopanib after treatment with other TTs are currently unknown. The goal of this retrospective study was to provide such data for pazopanib in patients with mRCC after treatment with other TTs.

PATIENTS AND METHODS

We included in this retrospective analysis consecutive patients with mRCC treated from November 1, 2009, through November 1, 2011, in the Genitourinary Medical Oncology Clinic at The University of Texas, MD Anderson Cancer Center (MDACC) who received pazopanib after they experienced progressive disease (PD) with other TT (sorafenib, sunitinib, bevacizumab, temsirolimus, and/or everolimus). Inclusion criteria included mRCC, prior systemic therapy with at least one TT, and adequate follow-up, defined as at least one clinic visit at MD Anderson every 3 months while receiving pazopanib. Patients who received prior chemotherapy or cytokines besides TTs were also included.

The study was approved by the MD Anderson Institutional Review Board. Clinical data were collected from the institution's electronic medical records system. Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events version 4.0. Radiographic response to pazopanib was assessed on blinded independent radiology review (C. Duran) using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. PFS was defined as the time elapsed between the initiation of pazopanib therapy and tumor progression or death from any cause. OS was defined as the time from initiation of pazopanib therapy to death from any cause.

Kaplan-Meier methods were used to estimate survival outcomes. Univariable and multivariable Cox proportional hazards models were fitted to evaluate the association of PFS with clinical factors. Variables with P values < 0.15 in the univariable analysis were included in the multivariable analysis. The backward selection procedure was used for model selection. Variables with P values < 0.05 were considered statistically significantly different.

RESULTS

Patients' Characteristics

One hundred twelve consecutive patients with mRCC previously treated with TT met our study's initial inclusion criteria. Of those, 93 patients had clear-cell type mRCC and constituted the patient cohort in our analysis. Table 1 lists their characteristics. The patients' median age was 65 years, and 69% were men. All patients had PD after treatment with at least one TT. The median number of prior TTs was 2 (range, 1–5). Including all prior TTs, cytokines, cytotoxics, and experimental agents, 18 patients (20%) received pazopanib as second-line therapy; 30 patients (32%), as third-line; 16 patients (17%), as fourth- and fifth-line, and 13 patients (14%) each as the sixth-, seventh-, and eighth-line therapy. The median treatment duration for all therapies prior to pazopanib was 23.6 months (range, 1–68 months) (Table 2).

Eighty-nine percent of patients had prior nephrectomy; 31 patients (33%) had Karnofsky Performance Status scores (KPS) < 80 ; and 14% had favorable-risk, 52%, intermediate-risk, and 34%, poor-risk disease per Memorial Sloan-Kettering Cancer Center criteria ⁽⁸⁾. The median number of metastatic sites was 3 (range, 1–8) (Table 1).

Efficacy and Safety

Sixty-eight events (i.e., PD or death) occurred while patients were receiving pazopanib therapy. Eighty-five patients had evaluable imaging by RECIST criteria, and 13 of these patients (15%) had a partial response (PR) (Figure 1). The median follow-up time for all patients who were alive at the time of analysis was 17.6 months (range, 0.4–24.2 months). The median PFS for all patients was 6.5 months [95% confidence interval (CI): 4.5–9.7 months] (Figure 2).

By multivariable analysis, PFS was significantly associated with male sex [hazard ratio (HR)=0.53; 95% CI: 0.32–0.89; $P=0.016$], pancreatic metastases (HR=0.38; 95% CI: 0.17–0.86; $P=0.019$), number of metastatic sites (HR= 1.25; 95% CI: 1.03–1.52; $P=0.025$), KPS ≥ 60 (HR=1.93; 95% CI: 1.07–3.48; $P=0.029$), elevated serum lactate dehydrogenase (LDH) concentration (HR=1.78; 95% CI: 1.06–2.98; $P=0.029$), and neutrophil count $>$ upper limit of normal (HR=2.92; 95% CI: 1.11–6.56; $P=0.029$).

The median OS was 18.1 months (95% CI: 10.26–NA months). By multivariable analysis, OS was significantly associated with previous nephrectomy (HR=0.26; 95% CI: 0.11–0.61; $P=0.002$), liver metastases (HR=2.14; 95% CI: 1.08–4.21; $P=0.028$), previous treatment

with bevacizumab (HR=2.72; 95% CI: 1.32–6.24; $P=0.007$), low hemoglobin concentration (HR=2.91; 95% CI: 1.35–6.24; $P=0.006$), brain metastasis (HR=3.02; 95% CI: 1.376–6.63; $P=0.006$), neutrophil count > upper limit of normal (HR=4.45; 95% CI: 1.47–13.45; $P=0.008$), and KPS 60 (HR=4.93; 95% CI: 2.60–9.36; $P=0.0001$). Twenty-one percent of patients were still receiving pazopanib at the time of our analysis, 58% had discontinued pazopanib because of PD, and 9% had died of PD during pazopanib treatment. There were no treatment-related deaths.

Eleven patients (12%) discontinued pazopanib because of adverse events (AEs) (3 due to cardiac AEs, 3 due to fatigue, 2 due to hypertension exacerbation, 1 due to anorexia and vomiting, 1 due to increased LFTs, and 1 due to hypernatremia). Common AEs (all grades) are summarized in Table 3; 91% of the AEs were grade 1/2. Fifty-eight (62%) of the 93 patients were being treated for hypertension at the time pazopanib was started. Only 7 (8%) patients developed new-onset hypertension during treatment with pazopanib, with five requiring initiation of antihypertensive medications and the other two using lifestyle modifications to address their hypertension. Twenty-six (28%) patients were being treated for hypothyroidism when pazopanib was started, and 14 (15%) additional patients required initiation of thyroid hormone supplementation during pazopanib therapy. No grade 4 toxicity was reported.

Of the 93 patients, 17 received second-line pazopanib after first-line sunitinib, with a median PFS of 3.5 months (range, 1–15.5 months); 35% of these 17 patients were still receiving pazopanib at last follow-up. Sixteen patients received third-line pazopanib after first-line sunitinib and second-line everolimus, with a median PFS of 4.7 months (range, 2–12 months); 31% of these 16 patients were still receiving pazopanib at last follow-up.

DISCUSSION

Studies have established the efficacy of pazopanib in improving PFS in treatment-naïve and cytokine-pretreated patients with mRCC⁽⁸⁾. Our data suggest that pazopanib is also efficacious in the salvage setting after failure of other targeted agents, even in a heavily pretreated population, including patients treated previously with other TKIs. A median PFS of 6.5 months and an ORR of 15% are clinically meaningful for heavily pretreated patients with clear-cell mRCC.

In comparison, everolimus and axitinib are the only agents with published level 1 evidence in the salvage setting. Everolimus was studied in the RECORD-1 trial⁽⁹⁾. Patients with mRCC whose disease had progressed on sunitinib, sorafenib, or both were randomized to receive everolimus or placebo. The PR rate with everolimus was 1%, and the median PFS was 4.9 months (95% CI: 3.7–5.5), versus 1.9 months (95% CI 1.8–1.9) with placebo⁽⁹⁾. In the AXIS trial⁽¹⁰⁾, axitinib yielded a 19% PR rate, and the median PFS for patients who received axitinib after first-line therapy with sunitinib, bevacizumab plus interferon-alfa, temsirolimus, or cytokines was 6.7 months, versus 4.7 months for patients who received second-line sorafenib (HR=0.665; 95% CI: 0.544–0.812; $P<0.0001$)⁽¹⁰⁾. In the INTORSECT study⁽¹¹⁾, temsirolimus was compared with sorafenib in patients with mRCC after sunitinib failure. Temsirolimus was associated with a median PFS of 4.28 months, versus 3.91 months with sorafenib. Both agents had an 8% PR rate in this second-line setting.

In our study, pazopanib, in the second- through eighth-line settings in unselected patients, produced a 15% PR rate and a median PFS of 6.5 months. Numerous other studies have shown benefit from sequential VEGF-targeted TKI therapy after progression with another

TKI⁽¹¹⁾. Supplementary Table S1, available at *Annals of Oncology* online summarizes these investigations^(9–11, 13–25).

Pazopanib was reasonably well tolerated in our heavily pretreated patients, with 91% of AEs being mild to moderate (grade 1 or 2), and only 12% of patients discontinuing therapy for toxicity. Although not observed in our study, it was previously noted that improved oncologic outcomes are associated with hypertension exacerbation in patients receiving anti-VEGF TKIs (12–15). Only 7 (8%) of our patients developed new-onset hypertension, and 13 (14%) of patients had an exacerbation of preexisting hypertension. These unusually small numbers of patients with new-onset hypertension and exacerbated preexisting hypertension may be partly due to incomplete data on hypertension in our records. Likewise, the lack of association between hypertension and outcomes in our study may be accounted for by this gap.

Our data did reveal an association between decreased PFS and relatively greater number of metastatic sites, poor performance status, increased neutrophils, and increased serum LDH, all of which are known to confer poor prognosis⁽¹⁶⁾. The association we found between prolonged PFS and pancreatic metastases is interesting. Although the pancreas is a relatively uncommon site of RCC metastases, 14% of our patients had pancreatic metastases on imaging. Pancreatic metastases of mRCC are recognized as a favorable prognostic factor and a signature of indolence in mRCC: the association between such metastases and improved outcomes with antiangiogenic therapy was noted previously in a retrospective review of 40 patients with mRCC by Albouy et al.⁽¹⁷⁾ and in other smaller studies⁽¹⁸⁾. Therefore, it is likely that the prolonged PFS noted in our patients with pancreatic metastases reflects both the more indolent nature of those metastases and the positive response of these lesions to TKIs.

An intriguing observation from our study was that men with mRCC treated with pazopanib in the salvage setting had a longer PFS than women did. The reason for this is unknown, but further studies should be undertaken to investigate this potential variability.

We are aware of the inherent limitations of a retrospective study in this setting and acknowledge that our conclusions are restricted by the imperfect and at times incomplete data available in our medical records. We further recognize the intrinsic selection biases that exist in all retrospective studies and have attempted to limit these as much as possible.

In summary, our findings support the use of pazopanib in the salvage setting after failure of other TTs, including other VEGF-targeted TKIs. The most optimal sequence of TTs has yet to be determined. Furthermore, whether patients derive survival benefit from salvage therapy beyond the second-line setting as compared with best supportive care can be addressed only in a large prospective randomized trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Special thanks to Karen Phillips, ELS(D), for reviewing and editing the manuscript.

FUNDING

This work was supported in part by the National Institutes of Health through MD Anderson's Cancer Center Support Grant [5 P30 CA016672]. Dr. Matrana is supported by NIH [T32CA009666-15].

REFERENCES

1. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol.* 1999; 17:2530–2540. [PubMed: 10561319]
2. Mekhail TM, Abou-Jawde RM, Boucher G, et al. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. *J Clin Oncol.* 2005; 23:832–841. [PubMed: 15681528]
3. Alt AL, Boorjian SA, Lohse CM, Costello BA, Leibovich BC, Blute ML. Survival after complete surgical resection of multiple metastases from renal cell carcinoma. *Cancer.* 2011; 117:2873–2882. [PubMed: 21692048]
4. Buchler T, Pavlik T, Bortolicek Z, et al. Objective response and time to progression on sequential treatment with sunitinib and sorafenib in metastatic renal cell carcinoma. *Med Oncol.* 2012; 29:3321–3324. [PubMed: 22752573]
5. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with advanced renal cell carcinoma: results from a phase III randomized, open-label, multicenter trial. *J Clin Oncol.* 2012; (Suppl) Abstract 4501.
6. Matrana MR, Atkinson B, Jonasch E, Tannir NM. Emerging targeted therapies in metastatic renal cell carcinoma. *Curr Clin Pharmacol.* 2011; 6:189–198. [PubMed: 21827388]
7. 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. [PubMed: 20100962]
8. Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2004; 22:454–463. [PubMed: 14752067]
9. 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; 372:449–456. [PubMed: 18653228]
10. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet.* 2011; 378:1931–1939. [PubMed: 22056247]
11. Escudier, B.; Hutson, T.; Esteban, E., et al. Temsirolimus vs sorafenib as second line therapy in metastatic renal cell carcinoma: results from the INTORSECT trial. Presented at the 37th European Society for Medical Oncology Congress; September 28 –October 2, 2012; Vienna, Austria. Abstract LBA22-PR.
12. Dienstmann R, Brana I, Rodon J, Tabernero J. Toxicity as a biomarker of efficacy of molecular targeted therapies: focus on EGFR and VEGF inhibiting anticancer drugs. *Oncologist.* 2011; 16:1729–1740. [PubMed: 22135123]
13. Robinson ES, Khankin EV, Karumanchi SA, Humphreys BD. Hypertension induced by vascular endothelial growth factor signaling pathway inhibition: mechanisms and potential use as a biomarker. *Semin Nephrol.* 2010; 30:591–601. [PubMed: 21146124]
14. Rini BI, Cohen DP, Lu DR, et al. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst.* 2011; 103:763–773. [PubMed: 21527770]
15. Rini, BI.; Cohen, DP.; Lu, D., et al. Hypertension (HTN) as a biomarker of efficacy in patients (pts) with metastatic renal cell carcinoma (mRCC) treated with sunitinib. Presented at ASCO Genitourinary Cancers Symposium; 2010. Abstract 312.
16. Manola J, Royston P, Elson P, et al. for the International Kidney Cancer Working Group. Prognostic model for survival in patients with metastatic renal cell carcinoma: results from the International Kidney Cancer Working Group. *Clin Cancer Res.* 2011; 17:5443–5450. [PubMed: 21828239]
17. Albouy B, Billemont B, Massard C, Gross-Goupil M, Rixe O, Escudier B. Pancreatic metastasis from renal cell carcinoma: Presentation, recurrence, survival, and response to antiangiogenic therapy. *J Clin Oncol.* 2009; 27(Suppl) Abstract e16137.

18. D'Ambra M, Ricci C, Casadei R, Minni F. Pancreatic metastasis from renal cell carcinoma. *Urologia*. 2011; 78(Suppl 18):5–8. [PubMed: 22139800]
19. Tannir NM, Wong YN, Kollmannsberger CK, et al. Phase 2 trial of linifanib (ABT-869) in patients with advanced renal cell cancer after sunitinib failure. *Eur J Cancer*. 2011; 47:2706–2714. [PubMed: 22078932]
20. Di Lorenzo G, Carteni G, Autorino R, et al. Phase II study of sorafenib in patients with sunitinib-refractory metastatic renal cell cancer. *J Clin Oncol*. 2009; 27:4469–4474. [PubMed: 19652053]
21. Garcia JA, Hutson TE, Elson P, et al. Sorafenib in patients with metastatic renal cell carcinoma refractory to either sunitinib or bevacizumab. *Cancer*. 2010; 116:5383–5390. [PubMed: 20806321]
22. Zimmermann K, Schmittel A, Steiner U, et al. Sunitinib treatment for patients with advanced clear-cell renal-cell carcinoma after progression on sorafenib. *Oncology*. 2009; 76:350–354. [PubMed: 19321976]
23. Sepulveda J, Maroto P, Andres R, et al. Sorafenib as a second-line and sequential therapy for patients with metastatic renal cell carcinoma (mRCC): analysis for safety and activity on sunitinib progressive pts. *J Clin Oncol*. 2008; 26 (May 20 Suppl): Abstract 16100.
24. Porta C, Procopio G, Carteni G, et al. Sequential use of sorafenib and sunitinib in advanced renal-cell carcinoma (RCC): an Italian multicentre retrospective analysis of 189 patient cases. *BJU Int*. 2011; 108(8 Pt 2):E250–E257. [PubMed: 21599821]
25. Herrmann E, Marschner N, Grimm MO, et al. Sequential therapies with sorafenib and sunitinib in advanced or metastatic renal cell carcinoma. *World J Urol*. 2011; 29:361–366. [PubMed: 21461939]
26. Sablin MP, Negrier S, Ravaud A, et al. Sequential sorafenib and sunitinib for renal cell carcinoma. *J Urol*. 2009; 182:29–34. [PubMed: 19447417]
27. Dudek AZ, Zolnieriek J, Dham A, Lindgren BR, Szczylik C. Sequential therapy with sorafenib and sunitinib in renal cell carcinoma. *Cancer*. 2009; 115:61–67. [PubMed: 19051290]
28. Choueiri TK, Brick AJ, McDermott D, et al. Treatment and dosing patterns for angiogenesis inhibitor (AIS) therapies in patients with metastatic renal cell carcinoma (MRCC). *Ann Oncol*. 2008; 19(Suppl 8):viii191–viii192. Abstract 593P.
29. Eichelberg C, Heuer R, Chun FK, et al. Sequential use of the tyrosine kinase inhibitors sorafenib and sunitinib in metastatic renal cell carcinoma: a retrospective outcome analysis. *Eur Urol*. 2008; 54:1373–1378. [PubMed: 18692304]
30. Di Lorenzo G, Buonerba C, Federico P, et al. Third-line sorafenib after sequential therapy with sunitinib and mTOR inhibitors in metastatic renal cell carcinoma. *Eur Urol*. 2010; 58:906–911. [PubMed: 20884115]
31. Park K, Lee JL, Park I, et al. Comparative efficacy of vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) and mammalian target of rapamycin (mTOR) inhibitor as second-line therapy in patients with metastatic renal cell carcinoma after the failure of first-line VEGF TKI. *Med Oncol*. 2012; 29:3291–3297. [PubMed: 22460837]

Figure 1. Waterfall plot showing tumor response to pazopanib by RECIST. Bars represent individual evaluable patients. Red, progressive disease; blue, stable disease; and green partial response.

A

Figure 2.
Kaplan-Meier curves for progression-free survival (A) and overall survival (B).

Table 1

Patients' Characteristics (N=93)

Characteristic	Number (%) ^a
Median age (range), years	65 (45–83)
Sex	
Male	64 (69)
Female	29 (31)
Ethnic origin	
White	74 (80)
Hispanic	10 (11)
Black	5 (5)
Asian	3 (3)
Other	1 (1)
Karnofsky Performance Status (KPS) score	
90–100	17 (18)
70–80	45 (48)
50–60	24 (26)
30–40	7 (8)
Prior nephrectomy	83 (89)
Prognostic feature	
KPS score < 80	31 (33)
Time from diagnosis to treatment < 1 year	51 (55)
Low hemoglobin	78 (84)
Corrected calcium > 10 mg/dl	10 (11)
Neutrophil count > ULN	7 (8)
Neutrophil-to-lymphocyte ratio > 3	55 (59)
Platelet count > ULN	6 (6)
MSKCC risk subgroup	
Favorable (0 MSKCC risk factors)	12 (14)
Intermediate (1 MSKCC risk factor)	48 (52)
Poor (2 or 3 MSKCC risk factors)	33 (34)
Sites of metastases	
Lung	77 (83)
Lymph node	54 (58)
Bone	42 (45)
Adrenal gland	26 (28)
Liver	25 (27)
Contralateral kidney	16 (17)
Brain	15 (16)
Pancreas	15 (16)
Other ^b	26 (28)

Line of Therapy (Pazopanib), including previous chemotherapy, cytokines, etc.

Characteristic	Number (%) ^a
2 nd Line	
3 rd Line	18 (20%)
4 th Line	30 (32%)
5 th Line	16 (17%)
6 th , 7 th , and 8 th Line	16 (17%)
	13 (14%)

^aUnless otherwise indicated.

^bIncludes chest wall, muscle, pleura, renal fossa, spine, eye.

mRCC, metastatic renal cell carcinoma; ULN, upper limit of normal range; MSKCC, Memorial Sloan-Kettering Cancer Center.

Table 2**Prior Therapies**

Prior therapy^a	No. of patients (%)	Median (range) treatment duration, months^b
Sunitinib	77 (83)	9.4 (1–46)
Everolimus	55 (59)	3.7 (0.4–24)
Sorafenib	39 (42)	7.3 (0.5–56)
Bevacizumab	21 (23)	7.8 (3.4–28)
Temsirolimus	20 (22)	5 (1.8–20)
Other targeted agents ^c	15 (16)	6 (1–28)
Chemotherapy ^d	21 (23)	4 (0.2–23)
Cytokine therapy (IL-2, INF- α)	18 (16)	5.1 (1–31)

^a Median number of prior targeted agents, 2 (range, 1–5).

^b Median duration of all prior therapies, 23.6 months (range, 1–68 months)

^c Included axitinib, erlotinib, linifanib, and cediranib.

^d Chemotherapy regimens included capecitabine + gemcitabine, combinations of capecitabine or gemcitabine with targeted agents or cytokines, and decitabine.

IL-2, interleukin 2; INF- α , interferon alfa.

Table 3

Adverse events occurring in 5% of patients during pazopanib therapy

Adverse event	Number (%) of events ^a		
	Grade 1	Grade 2	Grade 3
Fatigue	18 (19)	14 (15)	9 (10)
Increased liver function tests	30 (32)	3 (3.2)	—
Diarrhea	19 (20)	7 (7.5)	2 (2.2)
Hypothyroidism	3 (3.2)	14 (15)	—
Nausea/vomiting	12 (13)	2 (2.2)	2 (2.2)
Anorexia	5 (5.4)	8 (8.6)	—
Hypertension exacerbation	6 (6.5)	6 (6.5)	1 (1.1)
Hand-foot reaction	3 (3.2)	3 (3.2)	1 (1.1)
New-onset hypertension	2 (2.2)	5 (5.4)	—
Hair and skin changes	3 (3.2)	3 (3.2)	—
Dysgeusia	3 (3.2)	2 (2.2)	1 (1.1)
Abdominal pain	1 (1.1)	2 (2.2)	1 (1.1)

^a No grade 4 toxicity occurred.