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Comprehensive genomic profiling of metastatic tumors in a phase II biomarker study of everolimus in advanced renal cell carcinoma

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Abstract

Purpose—Genomic events leading to activation of mechanistic target of rapamycin (mTOR) are common in renal cell carcinoma (RCC). Everolimus is an allosteric mTOR inhibitor with efficacy in metastatic RCC (mRCC). We characterized the genomic profile of RCC tumors from metastatic sites and assessed whether particular alterations correlate with clinical response to everolimus.

Patients and Methods—An open-label, single-arm phase II biomarker study of everolimus 10 mg daily was conducted in mRCC patients. Needle biopsy or metastasectomy was performed on metastatic tumors prior to everolimus initiation. Next-generation sequencing (NGS) was performed using a targeted hybrid capture panel detecting alterations within exons and key introns of 300 cancer-associated genes. Disease assessments were obtained every 8 weeks using standard radiographic modalities and evaluated by RECIST criteria.

Results—Objective response was seen in 1/24 (4.2%) patients. Two (8.3%) patients had stable disease lasting >6 months. Median (90% CI) overall and progression-free survival were 20.1 (8.6, NA) and 3.8 (2.4, 5.4) months, respectively. NGS was successful on 18 pre-treatment specimens and 3 on-treatment specimens. Alterations in the PI3K-AKT-MTOR pathway were identified in 8/18 (44%) pre-treatment samples. An *MTOR* E2419D mutation was identified in the patient who experienced partial response. Alterations in *VHL*, *PBRM1*, *SETD2*, *KDM5C*, and *ATM* were common in the RCC metastases prior to initiation of everolimus.

Conclusion—Nearly half of heavily pre-treated RCC metastases may harbor mutations in components of the PI3K-AKT-MTOR pathway. Commonly mutated genes in primary RCC were also altered at a high frequency in RCC metastases.

Keywords

metastatic kidney cancer; mTOR; genomic profiling; next-generation sequencing; targeted therapy

Introduction

Renal cell carcinoma (RCC) is the most common type of adult kidney cancer and has increased in incidence over the past several decades.[1] The treatment armamentarium against RCC has expanded greatly over the past decade with approvals of multiple targeted therapies against the vascular endothelial growth factor (VEGF) and mechanistic target of rapamycin (mTOR) pathways as well as immune checkpoint inhibition targeting programmed cell death protein 1 (PD-1).[2] Therapeutic targeting of mTOR is particularly appealing as components of the PI3K-AKT-MTOR signaling pathway are altered in approximately 28% of RCC samples.[3]

Everolimus is an allosteric mTOR inhibitor with proven clinical activity against metastatic RCC. A randomized, double-blind, placebo-controlled trial of everolimus in metastatic RCC (mRCC) patients with prior progression on VEGF-targeted therapy showed improved progression-free survival (PFS) of 4.9 vs 1.9 months, leading to approval by the United States Food and Drug Administration.[4] However, despite improvements in PFS and overall survival (OS) with allosteric mTOR inhibitors in randomized trials, clinical benefit is

limited, with most patients displaying stable disease and fewer than 10% of patients experiencing partial response.[5, 6]

Several studies have attempted to identify biomarkers that may predict the subset of patients who may respond well to mTOR inhibition. In particular, genomic alterations along the PI3K-AKT-MTOR pathway have been an area of focus as mutations in *MTOR*, *TSC1*, and *TSC2* have been found in case reports and small case series to be associated with improved response to mTOR inhibition in RCC and other tumor types.[7, 8, 9, 10, 11, 12] However, the largest series in RCC patients found that while somatic mutations in mTOR pathway genes were more common in responders to mTOR inhibitors than non-responders, a large proportion of responding patients had no alterations in mTOR pathway genes and several patients with mTOR pathway mutations were non-responders to mTOR inhibitor therapy. [12] Other studies in RCC have examined the correlation between common RCC mutations in *PBRM1*, *BAP1*, *SETD2*, and *KDM5C* and response to everolimus in the first-line setting. [13] These studies investigated genomic alterations predominantly in primary tumor samples. Given the documented intratumoral heterogeneity of RCC, metastatic tumors may harbor a very different genomic profile not previously seen in studies using nephrectomy specimens.

We report here the results of comprehensive genomic profiling via a targeted next-generation sequencing (NGS) panel of cancer-associated genes performed on the metastatic tumors of patients enrolled in a phase II trial of everolimus for advanced RCC. We aimed to characterize the genomic profile of mRCC lesions and evaluate whether alterations in critical genes in the PI3K-AKT-MTOR pathway or other common alterations in RCC may be associated with clinical benefit from everolimus.

Patients and Methods

Patients and Study Design

An open-label, single-arm phase II trial of everolimus with pre-treatment biopsy of a metastatic lesion or metastasectomy was conducted in patients with advanced RCC (NCT00827359). Key eligibility criteria included ECOG performance status (PS) 1; no prior treatment with mTOR inhibitors; age 18 years or older; and adequate kidney, liver, and bone marrow function. Patients were also required to have a safely accessible site of metastatic disease for biopsy and at least one additional site of measurable disease. A subset of patients was asked to undergo an on-treatment biopsy of the same metastatic lesion between days 7 to 14 after initiation of everolimus. The on-treatment biopsy was not a requirement for participation in the trial. All patients received everolimus 10 mg by mouth daily for each 28-day cycle and continued treatment until disease progression, intolerable toxicity, or withdrawal of consent. The trial accrued patients at three major academic cancer centers – Beth Israel Deaconess Medical Center (Boston, MA), Dana-Farber Cancer Institute (Boston, MA), and Duke University Cancer Center (Durham, NC) – and was approved by their respective institutional review boards.

The original primary objective of the trial was to prospectively validate the expression of phospho-Akt and phospho-S6 as predictive biomarkers of response to everolimus by

measure of PFS. However, phospho-Akt and phospho-S6 immunohistochemistry was unsuccessful due to the lack of adequate tissue samples and was not pursued further. One secondary endpoint was to develop a genomic predictor of response to everolimus based on microarray analysis of pretreatment biopsy samples. The secondary endpoint was subsequently modified to use comprehensive genomic profiling of metastatic tumors via a targeted NGS panel to evaluate whether PI3K-AKT-MTOR pathway alterations in mRCC tumors may predict for response to everolimus.

Twenty-five patients enrolled in the study between April 2009 and November 2012. One patient became ineligible due to the inability to obtain a pre-treatment biopsy. A total of 27 tissue samples were successfully obtained from 24 patients, with 3 sets of paired tissues obtained pre-treatment and on-treatment. Targeted NGS was successful in 21 samples from 19 patients, including 2 pairs of pre-treatment and on-treatment tissues and one on-treatment sample from a patient whose pre-treatment sequencing was unsuccessful. Of the 18 patients who had sequencing from pre-treatment tissue available, 4 discontinued treatment due to unacceptable toxicity. Therefore, the analyses of genomic predictors of response to everolimus include 14 patients who had pre-treatment NGS of metastatic tumor and for whom response data were available.

Tumor Assessments

Objective tumor response was determined every 8 weeks (+/- 1 week) on study by either computed tomography or magnetic resonance imaging according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Patients who left the study had evaluations performed at the time of everolimus discontinuation and prior to initiation of other therapies. All patients, including those who discontinued therapy early, were followed for response until progression and for survival for 2 years from the date of registration. Following off-study visit, the study team updated survival data every 6 months for up to 3 years. Best overall response was determined by the maximal tumor shrinkage recorded from patient registration until disease progression or recurrence. Partial response was confirmed by repeat assessments performed no less than four weeks later. The final analyses data cutoff date was January 11, 2018.

Next-Generation Sequencing

Targeted NGS was performed via an institutional hybrid capture panel.[14, 15] DNA was extracted from archival formalin-fixed paraffin-embedded tumor samples containing at least 20% tumor nuclei and analyzed by massively parallel sequencing with a solution-phase Agilent SureSelect hybrid capture kit and Illumina HiSeq 2500 sequencer. The panel detects mutations, insertions, deletions, copy number changes, and rearrangements within exons of 300 cancer-associated genes and 113 key introns of 35 cancer-associated genes (Supplemental Table 1). Genes involved in the PI3K-AKT-MTOR pathway captured by the NGS panel include: *PIK3C2B*, *PIK3CA*, *PIK3CG*, *PIK3R1*, *PTEN*, *TSC1*, *TSC2*, *MTOR*, *RHEB*, *RPTOR*, *NPRL2*, *NPRL3*, *NF1*, *NF2*, *FLCN*, *RICTOR*, *DEPDC5*, and *STK11*. Genes commonly altered in RCC captured by the panel include: *VHL*, *PBRM1*, *SETD2*, *KDM5C*, *BAP1*, *TP53*, *ATM*, and *ARID1A*.

Statistical Analysis

PFS was defined as the time from date of registration onto the study to time of disease progression or death from any cause. Patients who were alive and progression-free were censored at the date of last disease assessment without evidence of progression. OS was defined as the time from study registration to death from any cause. Patients who were alive were censored at the date of last contact. Overall response was defined as the proportion of patients achieving complete or partial response to treatment per RECIST criteria.

Measures of frequencies and proportion were used to describe categorical variables; and measures of dispersion for continuous variables. Kaplan-Meier method, with 90% log-log confidence interval (CI), was used to describe time-to-event endpoints (PFS and OS). Log-rank test was used to assess difference in these endpoints by levels of categorical variables. Cox proportional hazards model was used for univariate and multivariate modelling of the impact of predictors on time-to-event endpoints.

Results

Patient Characteristics

Baseline patient characteristics are summarized in Table 1. The study closed early due to low accrual after enrolling 25 patients. One (1) of the enrolled patients was ineligible per trial criteria, did not receive protocol therapy, and was therefore excluded from analyses. Thus, there were a total of 24 eligible patients enrolled. Median length of follow-up [90% confidence interval (CI)] for OS and PFS were 42.5 [38.3, 56.2] and 14.1 [6.9, NA] months, respectively. Median age in years at registration was 64.0. The trial enrolled 16 men and 8 women. Histologically, 18 (75%) specimens were clear cell RCC, 4 (16.7%) were papillary RCC, and 2 (8.3%) had missing histology information. Patients received a median of 2 prior lines of therapies (range 1 to 7), including anti-angiogenic therapy (100%) and immunotherapy (25%). Prior anti-angiogenic therapies included sunitinib, sorafenib, bevacizumab, pazopanib, axitinib, cabozantinib, and investigational agents such as foretinib and tivozanib. Prior immunotherapies included interleukin-2, interferon alfa, and nivolumab. Twenty-two (22) of 24 patients had prior nephrectomy, and the majority (63%) of patients had ECOG PS score of 0. Eighteen (75%) patients had Memorial Sloan-Kettering Cancer Center (MSKCC) risk score of 2, and all patients were classified into the favorable or intermediate risk group per International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria. The site of most frequent metastases was lung (67%) followed by intra-abdominal lymph nodes (46%).

Treatment Response and Toxicity

The median (range) number of everolimus cycles started and completed was 4 (1 – 22) and 4 (0 – 21), respectively. The median (90% CI) OS and PFS were 20.1 (8.6, NA) and 3.8 (2.4, 5.4) months, respectively (Figure 1). Median (90% CI) duration of stable disease was 3.9 (2.1, 48.4) months. There was no statistically significant difference (at the 5% level) in baseline demographic variables between patients with successful NGS on pre-treatment biopsy (n = 18) and those without (n = 6). Overall response rate (90% exact CI) was 4.2 (0.2, 18.3) % (Table 2). Best overall response by RECIST criteria included a partial response in 1

patient, stable disease in 17 patients, and progressive disease in 3 patients. Two of 24 (8.3%) patients had stable disease lasting greater than 6 months.

Sixteen (16) patients (67%) had toxicity-related events. Table 3 shows treatment-related toxicities of any grade defined using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. There were no treatment-related grade 4 or 5 toxicities. Five (5) treatment-related grade 3 toxicities were reported, each occurring in different CTCAE categories: anorexia, diarrhea, fatigue, stomatitis, and renal failure. The most frequent grade 2 toxicity was limb edema. The most frequent grade 1 toxicities include rash (n=16), hypertriglyceridemia (n=14), and stomatitis (n=12). Approximately 67% of patients discontinued treatment due to disease progression, and 21% (n = 5) due to unacceptable toxicity (Supplemental Table 2).

PI3K-AKT-MTOR Pathway Alterations

A summary of the key genomic findings is shown in Figure 2. NGS was successful on 18 pre-treatment specimens and 3 on-treatment specimens with a mean coverage of 265 (range 74 – 405) reads across all targeted exons. Mutations in the PI3K-AKT-MTOR pathway were identified in 8 out of the 18 patients (44%) who had successful NGS from pre-treatment metastatic tissue specimens. PI3K-AKT-MTOR pathway mutations included *MTOR* S2215Y, *MTOR* E2419D, *PIK3CA* D152H, *PIK3CA* H1047R, *PIK3C2B* R221C, *PIK3C2B* R672Q, *PTEN* A34Lfs*20, *NPRL3* V549M, *DEPDC5* S1123F, and *FLCN* I172T (Supplemental Table 3). Two pre-treatment samples carried multiple alterations in PI3K-AKT-MTOR pathway genes. There was no difference in PFS between patients with and without mutation in the PI3K-AKT-MTOR pathway (Supplemental Figure 1). Similarly, there was no difference (Wilcoxon Rank Sum test p=0.610) in the percentage change in tumor diameter between patients with and without mutation in the PI3K-AKT-MTOR pathway (Figure 3). Best overall response for patients with PI3K-AKT-MTOR pathway mutations included 6 cases of stable disease, one case of partial response, and one case that was unevaluable. The patient who experienced partial response on everolimus had a PFS of 7 months and harbored an *MTOR* E2419D mutation. One of the patients with PI3K-AKT-MTOR pathway mutations (*FLCN* I172T) discontinued treatment due to toxicity. None of the patients with PI3K-AKT-MTOR pathway mutations in the pre-treatment metastatic lesions underwent an on-treatment biopsy, and there were no PI3K-AKT-MTOR pathway mutations identified in the 3 post-treatment biopsy specimens.

Common Gene Alterations in RCC

Genes known to be commonly mutated in primary clear cell RCC were also found to be significantly altered in our pre-treatment metastatic lesions, including *VHL* (10 patients; 56%), *PBRM1* (10; 56%), *SETD2* (6; 33%), *KDM5C* (4; 22%), *ATM* (3; 17%), *ARID1A* (2; 11%), *BAP1* (1; 6%), and *TP53* (1; 6%) (Supplemental Table 3). There was a high concordance between mutations in *VHL* and *PBRM1*, with 8 pre-treatment metastatic lesions harboring mutations in both genes. Mutations in *SETD2* occurred alongside mutations in *PBRM1* in 5 of 6 cases. All 4 cases with mutations in *KDM5C* also carried mutations in *VHL*.

Metastatic Genomic Profiles On-Treatment

One patient who had paired pre-treatment and on-treatment sequencing information harbored mutations in *VHL*, *KDM5C*, and *BAP1* that were maintained in both specimens. Interestingly, the pre-treatment specimen also had a *TP53* mutation that was lost in the on-treatment sample. The second case with paired sequencing information showed similar results pre- and on-treatment: *NPRL3* and *PIK3C2B* alterations were identified both samples and in a similar proportion of reads. One patient who had sequencing performed on-treatment only and did not have pre-treatment sequencing had alterations in *PBRM1*, *BAP1*, *ARID1A*, and *TP53*.

Discussion

While comprehensive genomic profiling has significantly enhanced understanding of the molecular drivers and vulnerabilities of human cancers, the vast majority of such studies in RCC have been performed on primary tumor specimens and may not be fully representative of the molecular landscape of advanced disease given the well-documented intratumoral heterogeneity within RCC.[16, 17, 18] Nonetheless, large studies like those conducted by The Cancer Genome Atlas have shown a high frequency of PI3K-AKT-MTOR pathway mutations in primary RCC tumors, prompting interest in using genomic profiling to identify predictive biomarkers for mTOR inhibitors. One study utilizing mostly primary nephrectomy specimens found mTOR pathway mutations to be more common in patients who responded to mTOR inhibitors, but a significant number of responding patients did not harbor any alterations in the mTOR pathway.[12] Another study found that mutations in *PBRM1* and *BAP1* in primary nephrectomy specimens were associated with longer and shorter PFS, respectively, with first-line everolimus.[13] With the emergence of immune checkpoint inhibitors and newer anti-angiogenic therapies, mTOR inhibitors are now more commonly used in heavily pre-treated patients. Therefore, assessment of the genomic profile of metastatic tumors immediately prior to treatment initiation would more likely capture associations between molecular alterations and treatment response. Our study characterizes the genomic landscape of RCC metastases from patients who have been heavily treated with systemic therapies and asks whether molecular alterations in the mTOR pathway or other commonly mutated genes in RCC may correlate with response to everolimus.

We defined PI3K-AKT-MTOR pathway genes as those directly on pathway or well-characterized regulators of mTOR signaling that are captured by our targeted NGS panel. Nearly half of the patients in our study were found to have genomic alterations affecting the PI3K-AKT307 MTOR pathway, including 10 distinct alterations in 7 genes. Overall, there was no association between presence of a PI3K-AKT-MTOR pathway alteration and clinical outcome, particularly given the low response rate and small sample size of our study. The single patient who experienced a partial response to everolimus harbored an MTOR E2419D mutation in the pre-treatment metastatic specimen. The MTOR E2419K mutation is a well-characterized activating mutation in the mTOR kinase domain previously described in a case report of a patient with urothelial carcinoma who experienced a long-lasting complete response to everolimus and the VEGF inhibitor pazopanib.[11] While the glutamic acid to lysine substitution in *MTOR* E2419K results in constitutive activation of mTOR signaling, it

is not clear that the glutamic acid to aspartic acid change found in our study would confer a similar functional change. In fact, glutamic acid to aspartic acid changes are conservative mutations that typically preserve biochemical function. Further studies may be helpful to elucidate the functional relevance of the *MTOR* E2419D mutation.

The heavily pre-treated patients in our study are likely representative of real-world mRCC patients currently receiving mTOR inhibitors. Patients derived a modest clinical benefit from everolimus similar to the reported efficacy from larger randomized studies. The RECORD-1 trial demonstrated a clinical benefit of everolimus over placebo in patients with mRCC. Patients treated with everolimus experienced a median PFS of 4.9 months, but the ORR was only 1.8%.[6] Subsequently, the METEOR and CheckMate 025 trials showed cabozantinib and nivolumab, respectively, to be superior to everolimus, with the mTOR inhibitor providing a similar PFS of 3.8 to 4.4 months and ORR of 5% in both studies.[19, 20] Our study showed a comparable PFS of 3.8 months and ORR of 4.2% with single-agent everolimus.

Discontinuation of treatment due to unacceptable toxicity occurred in 5 (21%) patients in our study, a rate that is slightly higher than the 9 to 13% reported in the large randomized trials. However, no grade 4 or 5 toxicities occurred in our study. Furthermore, the grade 3 toxicities in our trial included well-defined adverse events related to mTOR inhibitors, including anorexia, diarrhea, fatigue, stomatitis, and renal failure. No unexpected adverse events were observed in our study. No specific genomic alteration appeared to be enriched in the patients who discontinued everolimus due to toxicity.

We acknowledge several limitations. First, the small number of patients enrolled in the clinical trial limited the number of cases of successful NGS performed on metastatic specimens. Second, follow-up on-treatment biopsies were not mandatory and thus, we did not have many pre- and on-treatment paired specimens for analysis. Third, genomic profiling was not performed on the primary nephrectomy specimens of patients enrolled in the current study, and we are therefore unable to compare the molecular profile of RCC metastases with primary tumors over time. Finally, we did not analyze normal tissue and therefore cannot determine whether any of the alterations seen in the metastatic specimens were somatic vs germline.

Several factors may account for the low response rate to everolimus despite the relatively high prevalence of PI3K-AKT-MTOR pathway alterations in our study. First, it is possible that only a fraction of the genomic alterations in this pathway confers functional hyperactivation of mTOR signaling, and are bona fide oncogenic drivers. Second, in cancers driven by PI3K-AKT-MTOR pathway alterations, everolimus monotherapy may be ineffective due to its limited activity in inhibiting only the mTORC1 complex, and only some downstream effectors (e.g. S6K) and not others (e.g. 4EB-P1). Third, multiple inducible feedback loops exist within the PI3K-AKT-MTOR pathway and may allow cells to bypass allosteric mTOR inhibition.[21] Finally, it is possible that newer ATP-competitive inhibitors of the mTOR kinase domain that fully inhibit both the mTORC1 and mTORC2 complexes may be more effective than allosteric mTOR inhibition by everolimus. Such mTOR kinase inhibitors are currently in clinical development.

Although an association between PI3K-AKT-MTOR pathway alterations and response to mTOR inhibitors was not seen in this study, a previous study by some of the authors here that examined much larger numbers of responding patients indicated that mutations in *MTOR*, *TSC1*, or *TSC2* were more common in patients who derived clinical benefit from allosteric mTOR inhibitors than in those who progressed.[12] Nonetheless, many patients with *MTOR*, *TSC1*, or *TSC2* mutations did not respond to mTOR inhibition, and many patients who responded to mTOR inhibition did not have *MTOR*, *TSC1*, or *TSC2* mutations in their tumors. The present study is of smaller size and did not include many responders, so the statistical power is inadequate to associate pathway alterations with therapeutic response. Based on the available data, we do not presently advocate routine genotyping of RCC biopsies to drive clinical decision-making. However, if such information is available and a PI3K-AKT-MTOR pathway alteration is identified, it may be reasonable to consider mTOR inhibitor monotherapy or the combination of everolimus plus lenvatinib over other potential treatment options using appropriate clinical judgment.

Conclusion

In conclusion, we present one of the first reports of comprehensive genomic profiling of RCC metastases and show that genomic alterations involving the PI3K-AKT-MTOR pathway and other commonly altered RCC genes are very common in this heavily pre-treated patient population. We hope that our results will help to guide future studies on kidney cancer biology and therapeutic targeting of the PI3K-AKT-MTOR pathway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Practice Points

- Genomic alterations and hyperactivation of the PI3K-AKT-MTOR pathway are common features of RCC.
- The allosteric mTOR inhibitor everolimus has shown limited efficacy in patients with mRCC, with small subsets of patients experiencing significant responses in their tumors.
- While several prior studies have attempted to identify genetic alterations in RCC that may be predictive of response to mTOR inhibitors, our study is the first to examine exclusively metastatic tumors rather than primary nephrectomy specimens.
- Alterations in the PI3K-AKT-MTOR pathway are indeed common in RCC metastases, occurring in 44% of pre-treatment samples in our study.
- Response to everolimus occurred in 1 of 24 (4.2%) patients. Two (8.3%) patients had stable disease lasting >6 months. The lone responding patient had a metastatic tumor with an *MTOR* E2419D mutation of unclear significance. There was no significant association between the presence of PI3K-AKT-MTOR pathway gene alterations and PFS.
- Further studies on specific PI3K-AKT-MTOR pathway alterations or gene or protein expression level analyses in metastatic specimens may identify more robust predictive biomarkers for mTOR inhibitor therapy in patients with mRCC.

Figure 1.
Kaplan-Meier curves for overall survival and progression-free survival in the overall patient population.

Figure 2.

Summary of genomic alterations and best overall response to everolimus. The plot describes all patients with their respective genomic alterations, best response, and histology.

Change in Tumor SPD, between Baseline and Best Reponse, by mTOR Pathway Alteration Status

Figure 3.

Waterfall plot of sum of the product of lesion diameter (SPD) according to PI3K-AKT-MTOR pathway alteration status. The single case of partial response occurred in a patient with tumor metastasis showing an MTOR E2419D mutation.

Table 1

Baseline demographics and clinical characteristics of patients enrolled in a phase II study of everolimus in patients with advanced RCC.

Characteristic	N = 24 (%)
Age	
Median	64.0
(Min, Max)	(52.0, 80.0)
Mean $\pm$ SD	66.1 $\pm$ 8.7
Gender	
Male	16 (66.7)
Female	8 (33.3)
Race	
Asian	1 (4.2)
White	23 (95.8)
Race & Ethnicity	
White, Non-Hispanic	22 (91.6)
White, Unknown	1 (4.2)
Asian, Non-Hispanic	1 (4.2)
ECOG Performance Status	
0	15 (62.5)
1	9 (37.5)
Prior Lines of Therapy, Median (Range)	2 (1–7)
Anti-angiogenic therapy	24 (100)
Immunotherapy	6 (25)
Histology	
Clear Cell	18 (75.0)
Papillary	4 (16.7)
Missing	2 (8.3)
Metastatic RCC Risk Classifications	
MSKCC	
Favorable (0 risk factors)	4 (16.7)
Intermediate (1–2 risk factors)	14 (58.3)
High (3 risk factors)	6 (25.0)
IMDC	
Favorable (0 risk factors)	5 (20.8)
Intermediate (1–2 risk factors)	19 (79.2)
Poor (3 risk factors)	-

Characteristic	N = 24 (%)
Prior Nephrectomy	
Yes	
Radical	21 (95.5)
Partial	1 (4.5)
Missing	2
Metastatic Sites	
Bone	4(16.7)
Liver	8 (33.3)
Lung	16 (66.7)
Brain	-
Renal	6 (25.0)
Pancreas	3 (12.5)
Lymph nodes, Intra-abdominal	11 (45.8)
Lymph nodes, Pulmonary	7 (29.2)
Adrenal Glands	5 (20.8)
Other	15 (62.5)

Table 2

Summary of best overall treatment response in the overall patient population.

Best Overall Response	n (%) [90% CI]
Overall Response (OR)	1 (4.2) [0.2, 18.3]
Complete response (CR)	-
Partial response (PR)	1 (4.2) [0.2, 18.3]
Stable Disease (SD)	17 (70.8) [52.1, 85.4]
Progressive Disease(PD)	3 (12.5) [3.5, 29.2]
Unevaluable	3(12.5) [3.5, 29.2]
Total	24

Table 3

Treatment-related adverse events according to CTCAE v3.0. No treatment-related grade 4 or 5 toxicities occurred. Five treatment-related grade 3 toxicities were reported.

Toxicity Description CTCAE v3.0	Grade (n = 16)		
	1	2	3
Abdomen- pain	2	-	-
Anorexia	-	2	1
Cheilitis	1	-	-
Cough	1	-	-
Dehydration	-	3	-
Diarrhea w/o prior colostomy	4	1	1
Dry skin	1	-	-
Edema, limb	1	5	-
Fatigue	3	2	1
Hand-foot reaction	1	-	-
Hemoglobin	-	2	-
Hypercholesterolemia	5	3	-
Hypertriglyceridemia	14	4	-
Hypotension	-	1	-
Muco/stomatitis (symptom) oral cavity	12	3	1
Muco/stomatitis by exam- oral cavity	2	-	-
Neck- pain	-	1	-
Pneumonitis/pulmonary infiltrates	1	2	-
Proteinuria	1	3	-
Pruritus/itching	1	-	-
Pulmonary/Upper Respiratory-other	-	1	-
Rash/desquamation	-	1	-
Rash: acne/acneiform	16	3	-
Renal failure	-	-	1
Taste disturbance	1	-	-