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ECOG-ACRIN (E4805) Randomized Phase II Study to Determine the Effect of 2 Different Doses of Aflibercept in Patients with Metastatic Renal Cell Carcinoma

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Abstract

Background—Aflibercept is a recombinantly-produced fusion protein that has potent anti-VEGF activity. We tested whether aflibercept has clinical activity in clear cell renal cell carcinoma (ccRCC). The recommended Phase 2 dose was 4 mg/kg but several patients treated at 1 mg/kg demonstrated prolonged progression-free survival (PFS). We therefore tested both doses in a parallel group randomized trial.

Methods—Eligible patients (pts) had histologically confirmed advanced or metastatic ccRCC and previous treatments including prior exposure to a VEGF RTKI. Patients received aflibercept (either 1 mg/kg or 4 mg/kg) day 1 of a 14-day cycle until progression. Patients randomized to 1 mg/kg could crossover to 4 mg/kg at progression. The primary endpoint was proportion alive and progression-free at 8 weeks. A Simon 2-stage design was used for each arm with 33 and 24 eligible pts/arm enrolled in stages 1 and 2.

Results—94 pts were enrolled, 59 and 35 to 4 mg and 1 mg doses, respectively. 72% had 1 prior tx most commonly sunitinib. 16 eligible pts crossed over at progression to the 4 mg dose. Most common adverse events were hypertension, proteinuria, and fatigue. Only 4 pts reported Grade 4

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or higher toxicity. With 36/59 (61%) pts PFS at 8 wks, the 4-mg/kg dose met protocol specified efficacy criteria.

Conclusions—Aflibercept is active in previously treated ccRCC and may be worthy of further study.

Keywords

renal cell carcinoma; antiangiogenesis; VEGF blocker

Introduction

Renal cell carcinoma is the fourth most common genitourinary cancer with approximately 30,000 new cases diagnosed annually causing 12,000 deaths¹. Approximately 45% of patients, at the time of diagnosis, have disease localized to their kidney; 30% have distant metastases; and 25% have locally advanced disease². Surgical resection is the only potentially curative therapy. The five-year survival for stage I or II disease patients is 66%; 42% for stage III disease; and less than 5% for stage IV disease².

Angiogenesis, an orderly and tightly controlled process through which tumor is neovascularized, is required for metastasis and tumor progression. This process is controlled by multiple factors, one of which is the vascular endothelial growth factor (VEGF) – a protein that has a critical role in initiating and sustaining tumor angiogenesis. Clear cell renal cell carcinoma (ccRCC), the most common type of kidney cancer, harbor genetic and epigenetic alteration of the von Hippel- Lindau (VHL) gene and consequently the stabilization of the transcriptional factor hypoxia inducible factors (HIFs) with down-stream upregulation of VEGF². Over the past 10 years the use of VEGF/VEGF receptor targeting drugs has changed the treatment of ccRCC. However, despite the proven clinical benefit, eventually patients develop progressive disease due to drug resistance.

Aflibercept has been developed as a decoy receptor and blocking drug with greater binding affinity to VEGF as compared to bevacizumab³. Its ability also to bind other related proangiogenic factors such as VEGF-B and the placental growth factors, PlGF1 and PlGF2 makes this agent an appealing anti-angiogenesis drug for ccRCC. Aflibercept has been reported to have preclinical activity in several tumor models including renal cell carcinoma and has been approved for the treatment of colon carcinoma in combination with chemotherapy^{4–6}.

In the present study we evaluated the efficacy and safety of two doses of aflibercept in the treatment of patients with metastatic ccRCC who had progressive disease after tyrosine kinase inhibitor (TKI) therapy.

Methods

Study design and participants

Eligible patients were 18 years or older with histologically confirmed metastatic or unresectable ccRCC with measurable lesions per Response Evaluation Criteria In Solid

Tumors (RECIST) criteria. Patients also had evidence of progressive disease following a prior VEGF receptor TKI treatment received for at least 12 weeks; an Eastern Cooperative Oncology Group (ECOG) performance status between 0–2; adequate organ function as measured by appropriate blood chemistries; and recovered from any toxic effects of prior radiotherapy or surgical procedures within 4 weeks prior to randomization. No prior cellular therapy, vaccine, hormonal, or chemotherapy was allowed. HIV-positive patients receiving ART were also excluded due to pharmacokinetic interactions with aflibercept; patients with history of metastatic CNS, pulmonary embolism, DVT, or other thromboembolic events were excluded. Patients were randomized into two treatment arms (A and B) to determine the effect of two different doses of aflibercept. Randomization was stratified by MSKCC⁷ risk category and prior cytokine therapy.

Patients randomized to Arm A received 4mg/kg of aflibercept, on Day 1 of every 14-day cycle, intravenously over 1 hour into a peripheral vein or central venous catheter using an infusion pump. Patients in Arm B received 1mg/kg using the same schedule and infusion method (Figure 1). Tumor status was assessed every 8 weeks (every 4 cycles) after starting treatment. Tumor progression was defined using RECIST criteria. At the time of progression, the dose of patients in Arm B was escalated to 4mg/kg. A patient continued receiving protocol treatment until he/she developed progressive disease or unacceptable toxicity and all patients, including those who discontinued protocol therapy early, were followed for response until progression and for survival for 3 years from the date of randomization. Aflibercept was supplied by Aventis Pharmaceuticals and Regeneron, and distributed by Cancer Trials Evaluation Program (CTEP) of the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI). The ClinicalTrials.gov identifier for this study is NCT00357760.

Statistical analysis

The primary endpoint was defined as the proportion of patients alive and progression-free at 8 weeks. Progression-free survival was defined as time from randomization to the earlier of documentation of progression or death. Patients alive and progression-free at the time of analysis were to be censored at the date of last disease assessment without evidence of progression. Extensive data on progression-free survival among patients who have previously been treated with TKI was not available at the time the study was designed. In this study, a progression-free proportion of 50% at 8 weeks was not of interest, while a proportion at 8 weeks of 67% signified that aflibercept was worthy of further study. Assuming an exponential distribution, this corresponds to an improvement in median progression-free survival from 8 weeks to 14 weeks.

A two-stage design was used within each arm. In the first stage, 33 eligible patients were accrued. If 16 or fewer patients were progression-free at 8 weeks, then the arm was to be closed. If at least 17 patients were progression-free at 8 weeks, then an additional 24 eligible patients would be accrued. If at least 34 of 57 eligible patients were progression-free at 8 weeks, the dose would be considered worthy of further study. Using this design, the probability on each arm of declaring a dose unworthy of further study was 91% (statistical power) if the true 8-week progression free rate was 50% and 10% (Type I error) if the true 8-

week progression-free rate was 67%. To assure 33 and 24 eligible patients in the two stages of accrual, 35 and 25 patients, respectively, were to be randomized per stage and dose level for a total maximum of 60 patients per treatment arm.

Secondary endpoints were objective response rate, toxicity, response duration, and overall survival. A true objective response rate of 10% was of interest, whereas a true rate of 1% was not. Given 57 eligible patients per arm, the response rate would be considered interesting if 3 or more patients achieved an objective response. All patients receiving treatment, regardless of eligibility, were included in the assessment of toxicity. This study used Common Terminology Criteria for Adverse Events (CTCAE) Version 3 definition and only events with CTCAE attribution of possibly, probably, or definitely are reported. Response duration was defined as the time, in weeks, from onset of treatment response to disease progression. Patients without documented progression were censored at the date of last follow-up.

The efficacy analysis population included all eligible and treated patients. All treated patients, regardless of eligibility, were included in the toxicity analysis. The Kaplan-Meier (KM) method⁸ was used to describe overall and progression-free survival. Descriptive statistics was used to summarize patient characteristics at baseline. Two-sided 90% exact binomial CIs were computed for the assessment of toxicity and response rate.

Results

The total patient accrual was 94. The study was activated on 12/21/2007 and suspended on 03/27/2012 having reached its stage 1 accrual goal. The study was then reactivated on 06/20/2012 and only Arm A reopened to accrual – Arm B remained suspended and subsequently closed for failing to meet protocol specified efficacy criteria for continuation to stage 2. A total of 35 patients were accrued to Arm B by the end of stage 1; 3 of these 35 patients were ineligible for efficacy analysis of PFS. The number of patients alive and progression-free at 8 weeks was 16 (50%) and thus Arm B did not meet the criteria for continuing to stage 2 accrual. Fifty-nine (59) patients were accrued to Arm A by the end of stage 2 and the study was terminated on 12/06/2013. Figure 2 shows this trial's CONSORT diagram.

Patient Characteristics

Table 1 shows demographic and prognostic characteristics of patients in both treatment arms. The median age was 60 and 62 years respectively for patients in Arm A and B. More than 90% of patients in both treatment arms had an ECOG performance status of 0 or 1. The randomization process was effective in ensuring that patients in the treatment arms were comparable with respect to demographic and prognostic factors using appropriate statistical tests.

Toxicity

Table 2 provides a summary of treatment-related toxicities of all grades. The denominator included patients who received protocol therapy irrespective of eligibility status. The most common treatment-related toxicities in Arm A were fatigue (63%), hypertension (54%),

proteinuria (47%) and anorexia (39%). The proportion (90% CI) of severe (Grade of 3 or higher) toxicity in Arms A and B was 61.4% (49.7, 72.2) and 52.9% (37.7, 67.8) respectively. One patient in treatment Arm B experienced a grade 5 event described as intracranial hemorrhage. There were 10 grade 5 events (6 in treatment Arm A and 4 in Arm B) but were considered unrelated to treatment – 6 were due to disease progression and 4 each due to renal failure, dyspnea, infection, and upper respiratory tract related toxicity.

Efficacy

As estimated from Kaplan Meier survival estimates, the proportion of patients alive and progression-free at 8 weeks (90% CI) was 70% (59, 79%) in treatment Arm A and 52% (37, 66%) in Arm B. The proportion alive and progression free estimate of 70% for Arm A was higher than the proportion of interest value of 67% specified in the protocol. Likewise, the number of patients alive and progression free at 8 weeks was 39 which was higher than the protocol pre-specified number of 34 patients suggesting worthiness for further study. The PFS curve is shown in Figure 3. The estimated median PFS for treatment Arms A and B patients were 10.86 and 8.29 weeks respectively. The p-value of the log rank test comparing PFS between arms is 0.37; however this study was not powered to detect difference in PFS. A total of 52 (91%) events occurred among patients in treatment A and 31 (97%) in treatment B. Table 3 shows overall response by treatment arm among patients who were eligible and treated. The response rates with 90% CI for Arms A and B were 5.3% (1.4, 13.0) and 3.1% (0.2, 14.0), respectively. The pre-specified number of objective responses of interest (3 patients) was satisfied in Arm A, suggesting efficacy. Waterfall plots of maximum percent change from baseline in the sum of lesions longest diameter for both treatment arms are shown in Figure 4. A reference line at –30% represents the RECIST criteria cutoff corresponding to a partial response (PR) to treatment. A patient in Arm B was identified as having progressive disease despite having about 70% reduction in lesion size because the patient developed multiple new lesions. Four (4) patients, from both treatment arms, experienced an objective response, the KM estimated median response duration (90% CI) among these four patients was 43.9 (31.4, 56.4) weeks. The median response duration among patients (n=23) with stable disease was 13.0 (8.1, 22.6) weeks. Sixteen (16) patients in treatment Arm B (1mg/kg) had their dosage escalated to 4mg/kg after disease progression. The median PFS (90% CI) before and after escalation were 8.6 (8.0, 14.0) weeks and 14.6 (7.6, 33.0) weeks respectively (Figure 5). An overall survival curve for eligible and treated patients is shown in Figure 6. The OS and PFS curves for all randomized patients (Supplementary Fig. 1 A and B) were estimated to confirm that survival experience did not considerably differ between all randomized and only eligible, treated patients.

Discussion

The results from this study confirm the hypothesis that continuous VEGF blockade following disease progression VEGF RTKIs may have clinical benefit in ccRCC patients. This study met the protocol specified criteria for significant improvement in progression-free survival among Arm A patients only (PFS of 0.67 and 34 patients alive and progression-free at 8 weeks). Also, the protocol specified criterion for objective response was met among Arm A patients only (3 patients with response). Overall, the treatment was well tolerated,

though there was a greater percentage of patients who experienced treatment-related, grade 3 or higher, toxicities in Arms A as compared to Arm B.

The treatment landscape for ccRCC is rapidly evolving⁹. The recent approval of two new multi-kinase inhibitors in the second line setting such as cabozantinib and lenvatinib suggests that sequential inhibition of additional tyrosine kinases besides VEGF RTKs may induce clinical benefit^{10,11}. The treatment options for ccRCC are also significantly expanding due to the approval and clinical development of PD1/PD-L1 inhibitors¹². Continuous VEGF inhibition remains an important tool to induce prolonged clinical response in ccRCC patients. The original approval of axitinib has validated retrospective studies suggesting that sequencing of TKIs can still induce disease control despite progression following frontline therapies with anti-VEGF therapies¹³. The VEGF ligand blocker bevacizumab has been approved in combination with interferon α for the treatment of renal cell carcinoma in the first line setting based on the results of two Phase III randomized studies^{14,15}. Different combination strategies with bevacizumab have been also tested but these have been hampered by toxicities, and did not show greater efficacy as compared to single agent bevacizumab¹⁶. The assessment of the role of bevacizumab in the second and third line setting in RCC patients has been relatively limited. One report showed an ORR of 9% and a median PFS of 4.4 months in previously treated ccRCC patients¹⁷. In our study, the median PFS, ORR and toxicity profile observed in patients randomized to the either the 4 mg aflibercept arm or in those who crossed over to that dose appear similar to the historical data attributed to bevacizumab in the same setting. Thus, the results from our clinical trial are consistent with a dose-dependent benefit of aflibercept that was evident also in the crossed-over patients. Similar dose-dependent effect was observed also in the original single-agent study with bevacizumab in RCC¹⁸.

As the armamentarium for treating ccRCC is growing it becomes challenging to position new drugs in the current treatment algorithm. Aflibercept has shown preclinical more potent and broader activity than bevacizumab⁴. Identifying patients who may most benefit from the pharmacodynamics of aflibercept may represent a clinically relevant question. As HIF-2 α antagonists are becoming available, a potential combination with an effective VEGF blocker such as aflibercept appears a rational strategy for ccRCC^{19,20}.

Conclusions

This study confirms the potential benefit of VEGF blockade in previously treated patients with metastatic ccRCC. Aflibercept shows evidence of activity in previously treated ccRCC and may be worthy of further study in rational combination strategies where continuous VEGF blockade may be beneficial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Clinical Practice Points

- The treatment of metastatic ccRCC is rapidly evolving but therapies targeting the VEGF axis remain the main treatment of this disease.
- The use of the VEGF blocker aflibercept in pretreated ccRCC patients was safe and showed clinical benefit.
- Rational combination strategies with aflibercept may be beneficial in ccRCC patients.

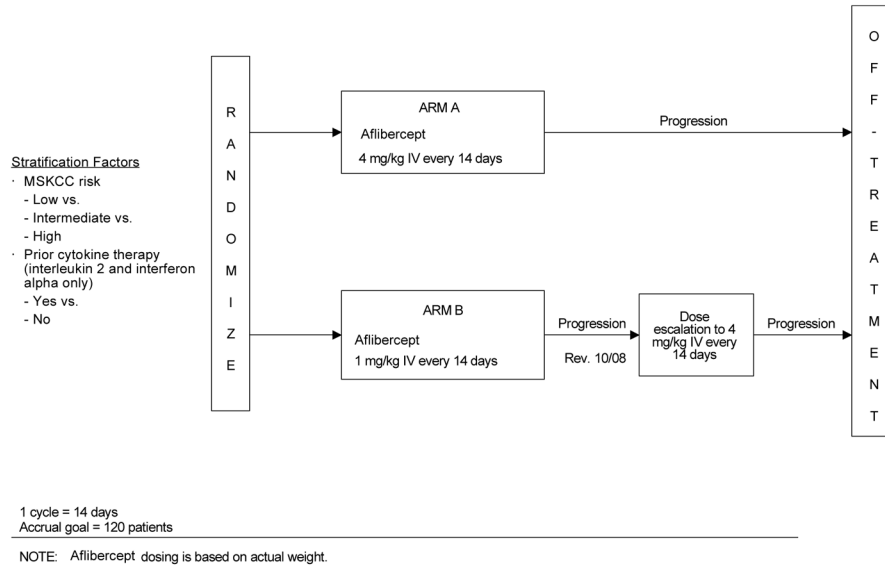


Figure 1.
Study Schema

NOTE: Afibercept dosing is based on actual weight.

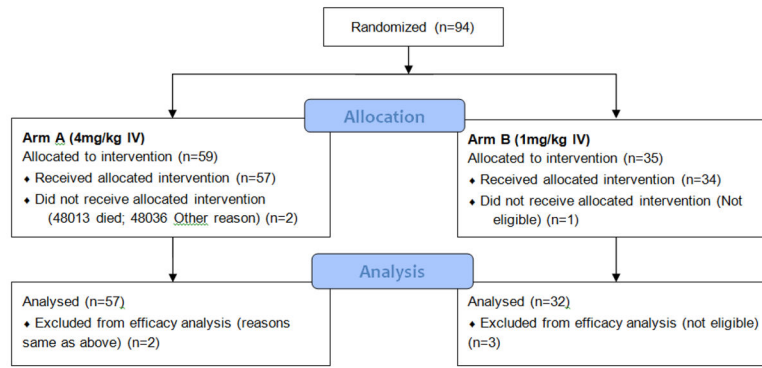
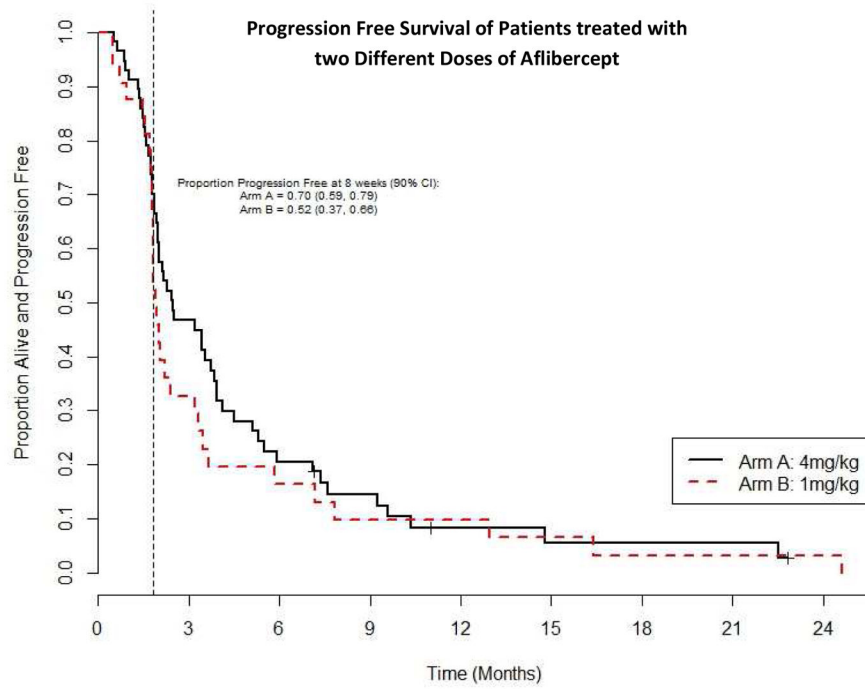


Figure 2. CONSORT diagram (with patient flow)



	Arm A	Arm B
Proportion Progression-free at 8 weeks (90% CI)	0.70 (0.59, 0.79)	0.52 (0.37, 0.66)
Median PFS Estimate in weeks (90% CI)	10.86 (8.57, 15.43)	8.29 (7.86, 9.57)
Number of		
Subjects	57	32
Events (at any time)	52	31

Figure 3. Progression-Free Survival for Eligible and Treated Patients

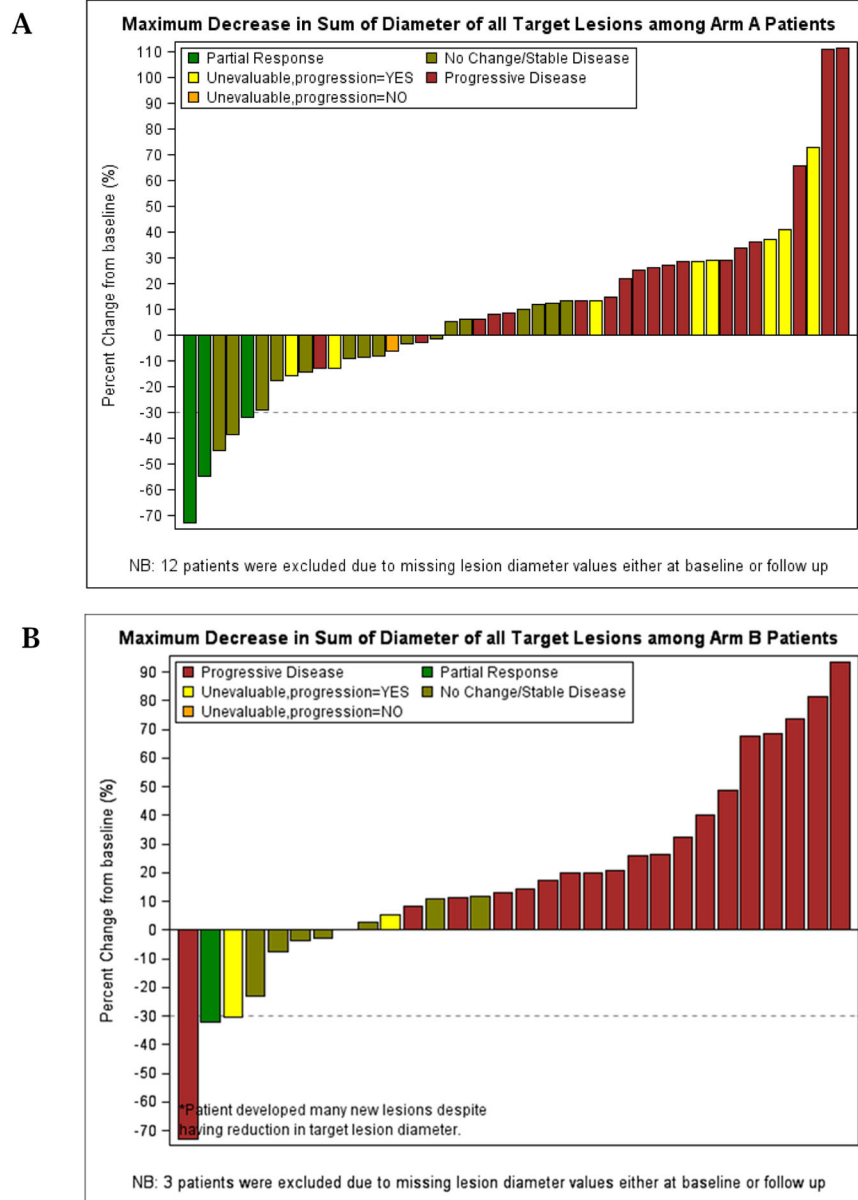


Figure 4. Waterfall Plots of Maximum Decrease in Sum of Lesions' Longest Diameter by Treatment Arm

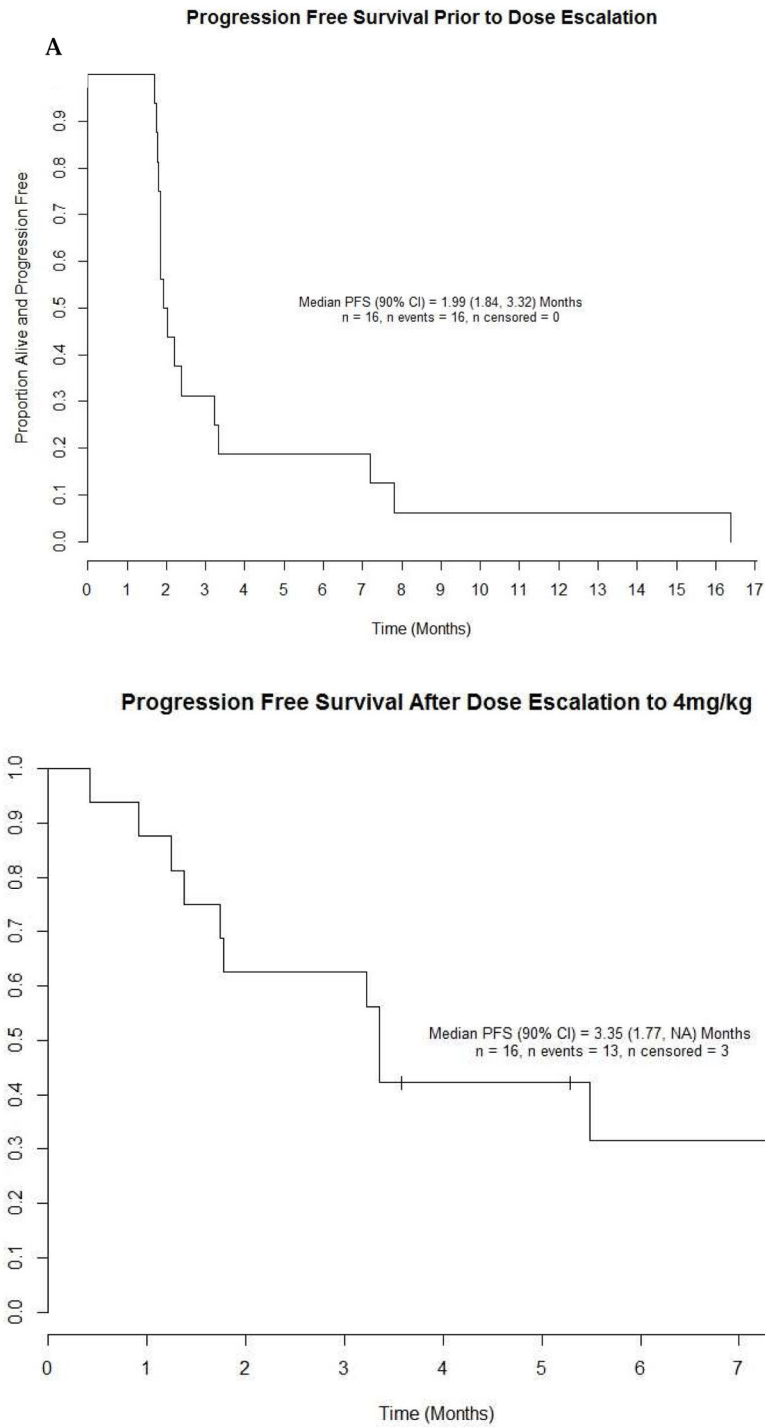
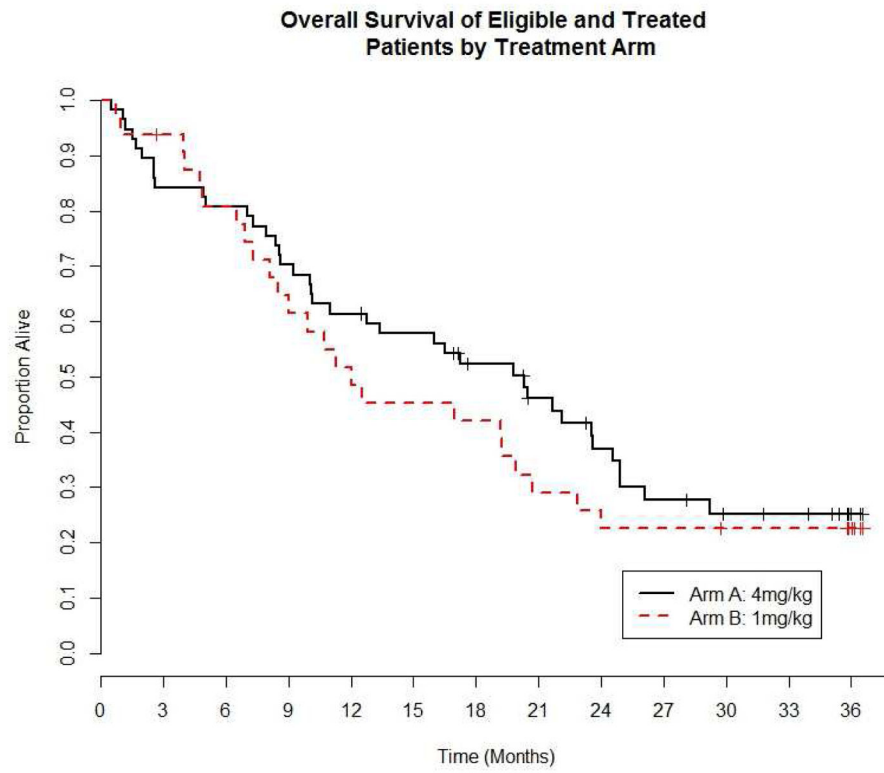


Figure 5. Progression-Free Survival before and after Dose Escalation (1mg/kg to 4mg/kg)



	Arm A	Arm B
Median overall survival in weeks (90% CI)	88.3 (47.9, 102.6)	52.3 (37.0, 83.6)
Number of		
Subjects	57	32
Events	39	24
Censored observations	18	8

Figure 6.
Overall Survival of Eligible and Treated Patients

Table 1

Patient Demographics at Baseline

Variable	Treatment Arm N(%)	
	Arm A (n=57)	Arm B (n=32)
Age		
Median	60	62
(Min, Max)	(35,80)	(33,73)
Mean \pm SD	59.7 \pm 10.4	60.2 \pm 9.0
Sex		
Male	43 (75.4)	22 (68.7)
Female	14 (24.6)	10 (31.3)
Race		
White	54 (94.7)	31 (96.9)
Black	3 (5.3)	1 (3.1)
ECOG Performance Status		
0	28 (49.1)	15 (46.9)
1	26 (45.6)	15 (46.9)
2	3 (5.3)	2 (6.2)
Renal Histology Type		
Clear Cell Carcinoma	53 (93.0)	31 (96.9)
Mixed	4 (7.0)	1 (3.1)
Pre-Registration Evaluation		
Progressive Disease	57 (100)	32 (100)
Prior Disease Treatment		
Surgery	16 (28.1)	10 (31.3)
Nephrectomy	52 (91.2)	26 (81.3)
Radiation therapy	15 (26.3)	10 (31.3)
Immunotherapy	6 (10.5)	3 (9.4)
Sunitinib	47 (82.5)	30 (93.8)
Sorafenib	14 (24.6)	6 (18.8)
Interleukin 2 (IL2)	5 (8.8)	3 (9.4)
Pazopanib	8 (14.0)	-
Interferon	1 (1.8)	-
Axitinib	3 (5.3)	-
Other TKI Anti-VEGF	3 (5.3)	-
Other Prior Therapy	8 (14.0)	7 (21.9)
Metastatic Sites		
Bone	22 (38.6)	9 (28.1)

Variable	Treatment Arm N(%)	
	Arm A (n=57)	Arm B (n=32)
Liver	16 (28.1)	7 (21.9)
Lung	49 (86.0)	19 (59.4)
Brain	-	-
Pleura	8 (14.0)	3 (9.4)
Subcutaneous	5 (8.8)	1 (3.1)
Lymph Nodes	36 (63.2)	20 (62.5)
Other	16 (28.1)	15 (46.9)

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Table 2
Treatment-related Toxicities (occurring in 10% of patients) by Treatment Arm

Toxicity Type	Treatment Arm									
	A-4 mg/kg (n = 57)					B-1 mg/kg (n = 34)				
	1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)		
Alkaline phosphatase	7	-	-	-	15	-	-	-	-	
ALT, SGPT	11	-	-	-	3	-	-	-	-	
Anorexia	37	2	-	-	47	-	-	-	-	
CNS, hemorrhage	-	-	-	-	-	-	-	-	3	
Constipation	19	-	-	-	29	-	-	-	-	
Cough	14	-	-	-	18	-	-	-	-	
Creatinine	14	-	-	-	18	-	-	-	-	
Diarrhea	19	-	-	-	24	-	-	-	-	
Dyspnea	12	5	-	-	32	3	-	-	-	
Edema limb	7	-	-	-	15	-	-	-	-	
Fatigue	60	4	-	-	56	21	-	-	-	
Head/headache	30	4	-	-	24	-	-	-	-	
Hemoglobin	19	4	-	-	26	9	-	-	-	
Hyperglycemia	5	-	-	-	15	-	-	-	-	
Hyperkalemia	4	-	-	-	12	-	-	-	-	
Hypertension	19	35	-	-	21	15	-	-	-	
Hypoalbuminemia	11	-	-	-	3	3	-	-	-	
Hyponatremia	12	4	-	-	21	-	-	-	-	
Joint, pain	19	-	-	-	24	-	-	-	-	
Muco/stomatitis (symptom) oral cavity	9	-	-	-	18	-	-	-	-	
Muco/stomatitis by exam, oral cavity	-	-	-	-	12	-	-	-	-	
Nausea	19	-	-	-	50	-	-	-	-	
Neuropathy-sensory	4	-	-	-	12	-	-	-	-	
Nose, hemorrhage	5	-	-	-	18	-	-	-	-	
Proteinuria	32	16	-	-	53	6	-	-	-	

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Toxicity Type	Treatment Arm											
	A-4 mg/kg (n = 57)					B-1 mg/kg (n = 34)						
	Grade		Grade			Grade		Grade				
	1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)
Voice changes/dysarthria	21	-	-	-	-	29	-	-	-	-	-	-
Vomiting	2	-	-	-	18	-	-	-	-	-	-	-
Weight loss	12	-	-	-	12	-	-	-	-	-	-	-
WORST DEGREE	32	56	5	-	44	50	-	-	44	50	-	3

Table 3

Best Overall Response

Best Overall Response	Treatment Arm	
	Arm A (4 mg/kg) n (%)	Arm B (1 mg/kg) n (%)
Overall Response (OR)	3 (5.3)	1 (3.1)
Complete response (CR)	-	-
Partial response (PR)	3 (5.3)	1 (3.1)
No change/Stable	16 (28.1)	7 (21.9)
Progression (PD)	26 (45.6)	19 (59.4)
Unevaluable	12 (21.0)	5 (15.6)
Total	57	32

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