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SAFETY AND ACTIVITY OF TEMSIROLIMUS AND BEVACIZUMAB IN PATIENTS WITH ADVANCED RENAL CELL CARCINOMA PREVIOUSLY TREATED WITH TYROSINE KINASE INHIBITORS: A PHASE 2 CONSORTIUM STUDY

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Abstract

Purpose—Bevacizumab or Temozolomide regimens have clinical activity in the first line treatment of advanced renal cell carcinoma (RCC). This phase I/II trial was conducted to determine the safety of combining both agents and its efficacy in RCC patients who progressed on at least one prior anti-VEGF receptor tyrosine kinase inhibitor (RTKI) agent.

Methods—In the phase I portion, eligible patients were treated with Temozolomide (25 mg IV weekly) and escalating doses of IV Bevacizumab (level 1=5mg/kg; level 2=10 mg/kg) every other week. The primary endpoint for the phase II portion (RTKI resistant patients) was the 6-month progression free rate. Secondary endpoints were response rate, toxicity evaluation, PFS and OS.

Results—MTD was not reached at the maximum dose administered in 12 phase I patients. Forty evaluable patients were treated with the phase II recommended dose (Temozolomide 25 mg IV weekly and Bevacizumab 10 mg/kg IV every two weeks). The 6-month progression free rate was 40% (16/40 pts). Median PFS was 5.9 (4-7.8) months, and median OS was 20.6 (11.5-23.7) months. Partial response/stable/progressive disease were seen in 23%/63%/14% of patients. Most

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: "Informed consent was obtained from all individual participants included in the study."

common grade 3-4 AEs included fatigue (17.8%), hypertriglyceridemia (11.1%), stomatitis (8.9%), proteinuria (8.9%), abdominal pain (6.7%), and anemia (6.7%). Baseline levels of serum sFLT-1 and VEGF-A were inversely correlated with PFS and OS, respectively.

Conclusions—Temsirolimus and Bevacizumab is a feasible combination in patients with advanced RCC previously exposed to oral anti-VEGF agents. The safety and efficacy results warrant further confirmatory studies in this patient population.

Keywords

Renal cell carcinoma; mTOR; VEGF; biomarkers; phase I/II studies

INTRODUCTION

Targeted therapies have improved disease control rates and outcomes for patients with advanced conventional (clear cell) renal cell carcinoma (RCC) [1]. Current first line systemic therapies against advanced RCC target either the vascular endothelial growth factor (VEGF) or the mammalian target of rapamycin (mTOR) pathways [2-4]. Anti-VEGF therapies improve progression free survival in patients with advanced, treatment naïve RCC [1]. However, up to 26% of patients have primary refractory disease [5], and the majority of patients who initially benefit from such drugs eventually develop treatment resistance and progress within 12 months [6,4,7]. Available second line therapies for patients who progress to anti-VEGF therapies include the mTOR inhibitor everolimus [8] and the newer generation, VEGF receptor tyrosine kinase inhibitor (RTKI) Axitinib [9]. Other strategies include inhibition alternative angiogenesis pathways, such as bFGF receptor or c-met inhibitors [10,11], or targeted immunotherapy approaches [12-14].

Sustained angiogenesis in the presence of anti-VEGF agents is mediated in part by overexpression of (VEGF independent) hypoxia driven angiogenic pathways, a process dependent on the mTOR pathway. [15,16]. In the setting of treatment resistance, mTOR inhibition may down regulate hypoxia induced activation of alternative pathways and may restore tumor sensitivity to anti-VEGF therapies. To test this concept, a phase I/II trial was performed, where the safety (phase I) and activity (phase II) of the mTOR inhibitor Temsirolimus and the anti-VEGF monoclonal antibody Bevacizumab were evaluated. The clinical activity of the combination was assessed in RCC patients who progressed on prior RTKIs (Phase II portion), and outcomes were correlated with clinical-laboratory factors and angiogenesis biomarkers.

PATIENTS AND METHODS

Patients

Institutional review board approval was obtained from all participating centers. All patients provided written informed consent. Inclusion criteria: > 18 years of age; metastatic or unresectable RCC (with a component of clear cell type); up to 2 prior systemic therapies for RCC (phase 1 and 2 portions of the trial; for phase 2 patients: at least one of the two prior therapies should have been a VEGF RTKI); measurable disease per RECIST (v.1.0[17]); Eastern Cooperative Group (ECOG) performance status of 0-2; Adequate organ function:

ANC > 1500/mm³; platelets > 100,000/mm³; Hbg > 9.0 g/dl; creatinine < 1.5 upper limit of normal (ULN); urine protein/creatinine ratio < 1 (or urinalysis with < 1+ protein); INR < 1.5 (unless patient is on full dose warfarin, when INR should be within therapeutic range); Triglycerides < 1.5 ULN; cholesterol < 350 mg/dl; direct bilirubin < 1.5 x ULN; AST/ALK phosphatase < 2.5 x ULN (< 5 if liver metastases present); Exclusion criteria were prior therapy with Bevacizumab or mTOR inhibitors; active bleeding, bleeding diathesis or coagulopathy; active second malignancy; untreated CNS metastases; significant cardiovascular disease, cerebrovascular accident (within 6 months), peripheral vascular disease with claudication on < 1 block, uncontrolled hypertension, or other uncontrolled medical or psychiatric condition; pregnant or breastfeeding women were not eligible, and men or women (or sexual partners) of childbearing potential had to use adequate contraception; history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 28 days prior to registration; major surgical procedure within 28 days (brain surgery within 3 months) or bore biopsy within 7 days prior to registration.

Treatment Plan

Phase I study—Eligible patients were treated on a 28-day cycle. In the phase I portion of the study, Temsirolimus was administered at a fixed dose of 25 mg IV over 30 minutes on days 1, 8, 15, and 22, while Bevacizumab was administered at escalating doses (Level 1: 5 mg/kg; level 2: 10 mg/kg on a standard 3+3 dose escalation design) IV on days 1 and 15. DLT was defined during cycle 1, as grade 4 ANC for more than 5 days, or grade 4 anemia or thrombocytopenia of any duration; serum creatinine > 2 times baseline or 2 times upper limit of normal if baseline levels within normal range; grade 3 hypertriglyceridemia resistant to appropriate lipid lowering drug therapy; or any other > grade 3 nonhematologic toxicity per NCI CTCAE v.3-, except grade 3 fatigue and grade 3 hypertension that is well controlled with oral medication. Grade 3 nausea, vomiting or diarrhea persistent despite maximal supportive treatment was also considered dose limiting. Maximum tolerated dose (MTD) was defined as the highest safely tolerated dose having at least 2 patients who experience DLT (unless it is the maximum dose level). The recommended phase 2 recommended dose was defined as the MTD, or the highest dose level tested, if MTD was not reached. Patients in the phase I study were enrolled between 6/06/2005 and 7/19/2006.

Dose modifications were allowed for Temsirolimus after cycle 1, based on toxicities. A maximum of 2 dose reductions of Temsirolimus was allowed per patient. If one agent was discontinued due to toxicity, patients could continue on study and receive the other agent. Treatment was continued, provided that toxicities were tolerable, or until the following criteria applied: Disease progression, concurrent illness that prevents further administration of treatment, unacceptable adverse events, patient's decision to discontinue study treatment or goes to alternate treatment, or investigator's judgment.

Phase II study—As MTD was not reached in the phase I portion, the highest dose level (dose level 2: Temsirolimus 25 mg IV weekly and Bevacizumab 10 mg/kg IV every two weeks) was declared the recommended phase II dose. Drug administration, dose modification guidelines and discontinuation criteria were similar to that for phase I patients.

Patients in the phase 2 portion of the study were enrolled between 02/09/2007 and 02/09/2010.

Response and Toxicity Evaluation—Toxicity was evaluated at each visit (day 1 of each cycle) and graded according to the National Cancer Institute CTCAE v. 3. Response evaluation was performed by imaging studies (CT or MRI scans) every 2 cycles (8 weeks). Assessment of response was performed at individual sites, according to the Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.0 [17].

Biomarker studies—Phase II patients had blood correlative biomarkers at baseline (serum VEGF, sFLT-1, plasma angiogenic activity) and after cycle 1 (sFLT-1 and plasma angiogenic activity). Serum VEGF and sFLT-1 levels were determined by ELISA (R&D Systems), following manufacturer's directions. Plasma angiogenic activity is a cell based bioassay that measures the ability of patients' plasma to induce (or inhibit) in vitro endothelial cell (HUVEC) proliferation using a colorimetric assay, as previously described by us [18,19]. This is a functional assay, which measures the overall ability of the plasma to change endothelial proliferation, and may reflect changes in the balance between pro- and anti-angiogenic factors in the patient's plasma as a result of the treatment. Comparisons are made between the plasma angiogenic activity at baseline and after cycle 1, to establish potential correlations between functional changes in the plasma activity and clinical outcomes.

Statistical Methods—This was an open-label phase I/II clinical trial of Temsirolimus and Bevacizumab for stage IV renal cell carcinoma. In the phase I portion, a standard cohort of 3+3 design was utilized to determine the maximum tolerated dose (MTD) of the combination, where temsirolimus was given at a fixed dose, while bevacizumab was administered at escalating doses as above. The primary objective of the phase II portion was to assess the proportion of RTKI resistant patients who were progression-free at 6 months after registration. A single-arm modified Fleming's two-stage design [20] was applied, which permitted early stopping of the trial if there was strong evidence that the study regimen was inactive. The modified Fleming's design required 40 evaluable patients to test the null hypothesis that the true success rate in this patient population is at most 20% and has at least 90% power to determine that the regimen is promising if the true success rate is at least 40%.

The proportion of patients who were progression-free at 6 months was analyzed by a group-sequential binomial test with a 95% Duffy-Santner confidence interval [21]. For toxicity evaluation, the maximum grade for each type of toxicity was recorded for each patient, and frequency tables were reviewed to determine toxicity patterns. Kaplan-Meier curve was used to summarize overall survival (OS) and progression-free survival (PFS) and other time-to-event endpoints. Contingency tables with Chi-square tests were used for exploring the association between clinical factors and scatter plots and dot plots were used for exploring the association between biomarker and clinical outcomes. Multiplicity from these exploratory analyses was not adjusted and therefore, all the statistical significance (by using p-value < 0.05) must be interpreted in a hypothesis generating manner.

RESULTS

Patient Characteristics

A total of 60 subjects were enrolled. In the phase I portion, 2 subjects (of 14) were deemed unevaluable for dose escalation. Of the 12 evaluable patients in the phase I study, 6 were treated at dose level 1 and 6 at dose level 2. In the phase II portion, 5/46 patients were deemed ineligible (Papillary histology=1 pt; no prior RTKI therapy = 3 pts; no measurable disease= 1 pt) and one patient cancelled (never treated, due to worsening performance status due to development of brain metastases). Table 1 shows baseline demographics and disease characteristics of eligible patients (N=52). All patients had metastatic disease, with 46% (24/52) having 3 or more sites of metastases. Of the patients in the phase I study, 4/12 were treatment naïve, and none of them had received prior oral anti-VEGF RTKI therapy. All eligible patients enrolled in the phase II study had been exposed to at least one prior anti-VEGF RTKI, with the majority of patients receiving Sunitinib, compared to Sorafenib. Four patients received both agents.

Safety

AEs were recorded by highest NCI-CTCAE v.3 grade in each patient. No treatment related grade 4 or 5 AEs were observed in the phase I portion of the trial (Table 2). The MTD for the drug combination was not reached at the highest dose level tested in the phase I portion of the trial. Two DLTs were observed among the 12 subjects evaluable for dose escalation. In dose level 1 one of six patients had a DLT, which consisted of grade 3 hypertriglyceridemia. This was considered DLT in spite of it being controlled with lipid lowering agents, because the protocol at that time considered this a DLT regardless of the use of lipid lowering agents (the protocol was later amended). In dose level 2, one out of six patients developed a DLT, which consisted of grade 3 mucositis/stomatitis. The most common grade 3 treatment related adverse events in the phase I patients were hypertriglyceridemia, anorexia and nausea. One patient each had grade 3 upper gastrointestinal hemorrhage, peritoneal hemorrhage or pneumonitis.

The most common (> 10% of subjects) adverse events (definitely, probable or possible attributed to study agents) for all (phase I and II) evaluable patients who received treatment (N=52) are shown in Table 2. The two most common grade 3 and 4 toxicities were hypertriglyceridemia (14%), fatigue and mucositis (10% each). Two patients (4%) developed intestinal perforation (grade 3) and two patients (4%) developed grade 3 bleeding. Thirty-one (of 52 evaluable) subjects required dose modification for Temsirolimus whereas six patients required holding or discontinuation of Bevacizumab due to toxicity. Patients who discontinued one agent could continue receiving the other study agent. A total of 9 patients (3 patients in the phase I portion, and 6 patients in the phase II portion) were removed from the study due to toxicity.

Clinical Activity

Phase I—A total of 12 patients in the phase I study were evaluable for efficacy analysis. Partial response was observed in 7/12 (58%) subjects, with 3/6 and 4/6 patients having a partial response in dose levels 1 and 2, respectively (Table 3). Four out of 12 patients were

progression free at 6 months (33.3%), and median PFS was 4.8 and 7.1 months in patients treated at dose level 1 and 2, respectively. Median overall survival was 24.4 (95% CI: 4.6 - NR) and 17.0 (95% CI: 4.4 - 54.8) months, in dose levels 1 and 2, respectively.

Phase II—A planned interim analysis was performed (for primary endpoint) after the first 21 evaluable patients (stage I) were enrolled. Results of the interim analysis (6/21 patients progression free at 6 months) led to continuation of the study to complete the stage II (up to 40 evaluable subjects). For the primary endpoint, a total of 16/40 (40%, 95% CI: 25-55) of patients were progression free at 6 months (Table 2). Median time to progression was 7.6 (95% CI: 4.0-9.1) months, and median PFS was 5.9 (95% CI: 4.0-7.8) months (Fig. 1 A). Median OS for phase II patients was 20.6 (95% CI: 11.5-23.7) months (Fig. 1.B). Partial response, stable disease and progressive disease were observed in 20%, 65%, and 15% of patients, respectively (table 3). A waterfall plot of best responses in phase I and II patients is shown in Figure 2.

Correlative Studies—Associations between clinical factors, adverse events or biomarkers and clinical outcomes were examined in phase II study patients.

Clinical Factors—Baseline performance status and number of metastatic sites were significantly associated with PFS, while prior nephrectomy, performance status and IMDC (Heng) criteria [22] criteria were significantly associated with OS (Table 4). No associations were observed between age, gender, number of prior systemic therapies with PFS or OS.

Treatment induced thrombocytopenia, fatigue and hypertriglyceridemia were significantly associated with improved PFS. Patients who developed hypertension and hypertyglyceridemia (grade 2 and above) had improved OS. No statistically significant associations were observed between neutropenia, mucositis, hypercholesterolemia and outcomes.

Biomarker studies—Thirty (out of 40) phase II patients had adequate samples for analysis. Serum VEGF, sFLT-1 and plasma angiogenic activity were measured at baseline, and sFLT-1 and plasma angiogenic activity were measured after completion of cycle 1, and correlations with clinical outcomes were performed. Higher baseline serum sFLT-1 levels were significantly associated with poor PFS ($p=0.0332$; Fig S-1.A), while higher VEGF-A levels were associated with poor OS ($p=0.0487$; Fig S-1.B). A trend towards improved OS was observed in patients with lower plasma angiogenic activity ($p=0.0572$; Fig. S-1.C). No associations were found between changes of sFLT-1 or plasma angiogenic activity over time (from baseline to after cycle 1) and PFS or OS.

DISCUSSION

The objectives of the current study were to determine the safety of combining temsirolimus and bevacizumab in patients with advanced RCC, and to test the hypothesis that mTOR blockade restores sensitivity to VEGF inhibition in patients previously treated with anti-VEGF TKIs. Our results show that when given at full doses (Bevacizumab at 10 mg/kg every two weeks and Temsirolimus, 25 mg IV weekly), the combination is relatively well

tolerated, with the most common grade 3 and 4 toxicities being hypertriglyceridemia (14%), fatigue (10%), mucositis (10%) and anemia (8%). The observed adverse event profile is consistent with the known toxicity profiles of both agents, and is comparable to previously reported trials combining bevacizumab and the mTOR inhibitors everolimus or temsirolimus [23-25]. In the published first line trials, this combination was found to have increased toxicity compared to Interferon and Bevacizumab [23,24]. As the current report is a single arm, non-randomized study in a selected patient population, no toxicity comparisons can be made with published randomized phase III studies in the first line setting with larger number of patients.

Temsirolimus and Bevacizumab were found to be active in patients who progressed after one or two prior RTKIs (phase II study), with a 6 month progression free rate of 40%, median PFS of 5.9 months, and median overall survival of 20.6 months. Our results are comparable to a prior report of the combination of everolimus and bevacizumab in a similar setting [25]. In addition, our results compare favorably with the activity of everolimus, which is associated with a median PFS of 4.9 months and OS of 14.8 months [8], as well as axitinib, associated with a median PFS of 6.5 months and OS of 15.2 months in patients previously treated with sunitinib [26]. Our results, however, should be interpreted with caution, due to the limited number of patients tested in a non-randomized manner. The concept of mTOR inhibition (with everolimus) and bevacizumab in patients progressing after first line therapy is currently being investigated in the randomized setting (NCT01198158).

In patients not previously exposed to RTKIs (phase I study), the combination was associated with limited clinical benefit. Even though a high proportion of patients achieved partial responses, the median PFS in this patient population (7.1 months) was inferior to what is achieved with currently available first line agents [27,3]. This, and recently reported negative randomized trials comparing this combination to sunitinib or Bevacizumab/ Interferon- α [24,23], indicate that there is no role for this combination in the first line therapy of clear cell renal cell carcinoma.

Correlative studies performed in RTKI resistant patients suggest that those who develop treatment induced thrombocytopenia, hypertension, fatigue and hypertriglyceridemia derived clinical benefit (improved PFS or OS), consistent with prior reports on the association of adverse events with clinical benefit in patients with RCC [28]. We found an inverse association between baseline serum sFLT-1, suggested to represent a biomarker of resistance to anti-VEGF therapies [29], and progression free survival, as well as baseline VEGF levels and overall survival. In addition, we found a trend towards improved OS in patients with lower plasma angiogenic activity [30,18,19]. These hypothesis generating results suggest that patients with a lower baseline systemic angiogenic state (reflected by lower serum VEGF levels, lower plasma angiogenic activity) may derive benefit from this combination. No firm conclusion can be made, however, on whether these factors are predictive or prognostic, due to the small number of patients. Further validation of these and other novel biomarkers in large randomized trials is necessary.

In summary, the combination of bevacizumab and temsirolimus is feasible and well tolerated. Our safety and activity results suggest that this combination may benefit patients who have failed prior anti-VEGF RTKIs and warrant further confirmation of this concept in the randomized setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) overall survival (OS) in RTKI refractory patients (N=40).

Figure 2.

Waterfall plot of maximal change in sum of target lesions. The plot includes 51 evaluable patients. *One patient (phase I portion, dose level 2) who had no post baseline measurement is excluded.

TABLE 1

Patient characteristics

	Phase I		Phase II				Total	
	Dose Level 1 (N=6)		Dose Level 2 (N=6)		(N=40)		(N=52)	
Characteristic	N	%	N	%	N	%	N	%
Age, years								
Median Range	65.0 (50.0-75.0)		66.0 (61.0-77.0)		62.0 (38.0-82.0)		63.0 (38.0-82.0)	
Sex								
Male	5	83.3	5	83.3	31	77.5	41	78.8
Female	1	16.7	1	16.7	9	22.5	11	21.2
ECOG Performance Status								
0	3	50	4	66.7	21	52.5	28	53.8
1	3	50	2	33.3	16	40	21	40.4
2	0	0	0	0	3	7.5	3	5.8
Prior Nephrectomy								
Yes	5	83.3	5	83.3	37	92.5	47	90.4
No	1	16.7	1	16.7	3	7.5	5	9.6
Number Metastatic Sites								
1	1	16.7	1	16.7	17	42.5	19	36.5
2	1	16.7	2	33.3	6	15	9	17.3
3+	4	66.7	3	50	17	42.5	24	46.2
Sites of Metastases								
Nodal	3	50	3	50	18	45	24	46.1
Bone	1	16.7	2	33.3	9	22.5	12	30
Lung	4	66.7	4	66.7	24	60	32	61.5
Liver	0	0	3	50	12	30	15	37.5
Abdominal	3	50	2	33.3	11 27.5		16	40
Brain	0	0	0	0	2	5	2	3.8
Subcutaneous	1	16.7	0	0	1	2.5	2	3.8
Other Distant	2	33.3	3	50	9	22.5	14	35
Prior Systemic Therapy								
Immunotherapy	6	100	1	16.7	2	4.1	9	17.3
Chemotherapy	0	0	0	0	3	6	3	5.8
Vegf Trap	0	0	0	0	1	2	1	1.8
Anti αvβ3 antibody	0	0	1	16.7	0	0	1	1.8
Sorafenib	0	0	0	0	4	10	4	10
Sunitinib	0	0	0	0	32	80	32	80
Sorafenib & Sunitinib	0	0	0	0	4	10	4	10
International mRCC Database Consortium (Heng) Criteria								
Favourable	3	50	3	50	6	15	12	23.1
Intermediate	2	33.3	3	50	31	77.5	36	69.2

Characteristic	Phase I				Phase II		Total	
	Dose Level 1 (N=6)		Dose Level 2 (N=6)		(N=40)		(N=52)	
	N	%	N	%	N	%	N	%
Poor	1	16.7	0	0	3	7.5	4	7.7

TABLE 2

Treatment Related Toxicity (> 10% of patients; n=52)

CTC Grade	PI/DL-1				PI/DL-2				Phase II				Total			
	All	3	4	All	All	3	4	All	All	3	4	All	All	3	4	All
	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	(%)
Hematologic																
Anemia	3	1		5			3	29	3	37	(71)	4	(8)			
Neutropenia	2			3				3		8	(15)					
Thrombocytopenia	3			4			1	14	1	21	(40)	1	(2)			
Non-hematologic																
Epistaxis	2			3				17	2	22	(42)	2	(4)			
ALT elevation				1				6		7	(13)					
AST elevation	1			1				8		10	(19)					
Hypercholesterolemia	2			6				25	1	33	(63)	1	(2)			
Hyperglycemia								9	1	9	(17)	1	(2)			
Hypertiglyceridemia	2	1		3	2			28	3	33	(63)	6	(12)	1	(2)	
Hypocalcemia	1			3				5		9	(17)					
Hypophosphatemia	2			1				7		10	(19)					
Alkaline phosphatase elevation				1				7	1	8	(15)	1	(2)			
Headache	2			1				4	1	7	(13)	1	(2)			
Pneumonitis				2	1			4		6	(12)	1	(2)			
Creatinine elevation	3			3				14		20	(38)					
Proteinuria	3	1		2				20	2	25	(48)	3	(6)	1	(2)	
Hypertension	2			1	1			11	1	14	(27)	2	(4)			
Fatigue	2			5				27	5	34	(65)	5	(10)			
Weight loss				1	1			8		9	(17)	1	(2)			
Rash	3			5				14		22	(42)					
Hand-foot syndrome								6	1	6	(12)	1	(2)			
Anorexia	2			6	2			11		19	(37)	2	(4)			
Diarrhea	3			5				13	2	21	(40)	2	(4)			

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CTC Grade	Phase II										Total	
	PI/DL-1		PI/DL-2		All		4		3		4	
	All	N	All	N	All	N	All	N	All	N	All	N
Nausea	2	1	3	1	8	13	25	2	4			
Mucositis oral	2		5	1	28	35	67	5	10			
Vomiting	1		4	1	3	8	15	1	2			

TABLE 3

Treatment Efficacy

	Phase I				Phase II	
	Dose Level 1 (N=6)		Dose Level 2 (N=6)		(N=40)	
	No.	%	No.	%	No.	%
Best Response						
Partial *	3	50	4	66.7	8	20.0
Stable *	2	33.3	1	16.7	26	65.0
Progression **	1	16.6	0	0	6	15.0
Not evaluable	0	0	1	16.7	0	0.0
Progression Free rate at 6 Months	33.3 %		33.3 %		40.0 %	
95% CI					25 - 55 ¹	
Median PFS ² , months	4.8		7.1		5.9	
95% CI	2.7 - 15.4		3.3 - 16.4		4 - 7.8	
Median Overall survival ² , months	24.4		17.0		20.6	
95% CI	4.6 - NR		4.4 - 54.8		13 - 27	
Time To Treatment Failure ² , months	5.2		5.0		5.0	
95% CI	3.6 - 15.8		1.3 - 14.7		3.7 - 6.9	
Patients with Measurable Tumor Shrinkage ³ (%)	6 (100)		5 (83.3)		32 (80)	

Abbreviation: NR, Not reached

* Best response per RECIST criteria

** Includes subjects with clinical progression

¹ 95% Duffy-Santner confidence interval² Kaplan-Meier method³ Represented in Waterfall Plot

TABLE 4

Effects of clinical and laboratory factors on progression-free and overall survival

Factor	Progression Free Survival		Overall Survival	
	Hazard Ratio (95% CI)	P-value *	Hazard Ratio (95% CI)	P-value *
Baseline Characteristics				
Age	1.007 (0.973 - 1.041)	0.6934	0.966 (0.932 - 1.002)	0.0638
Prior Nephrectomy (Yes vs. No)	1.656 (0.622 - 4.409)	0.3130	0.339 (0.127 - 0.906)	0.0310
Performance Score (1 vs. 0)	1.097 (0.613 - 1.962)	0.7559	2.180 (1.125 - 4.227)	0.0210
IMDC Criteria (Favorable & Intermediate vs. Poor)	0.559 (0.198 - 1.578)	0.2721	0.291 (0.101 - 0.843)	0.0229
Adverse Event **				
Thrombocytopenia	0.487 (0.264 - 0.897)	0.0211	0.535 (0.279 - 1.025)	0.0592
Fatigue	0.379 (0.198 - 0.724)	0.0033	0.570 (0.287 - 1.132)	0.1082
Hypertension	0.708 (0.394 - 1.272)	0.2481	0.324 (0.157 - 0.668)	0.0023
Triglyceridemia (Grade 2+)	0.445 (0.237 - 0.838)	0.0122	0.473 (0.228 - 0.979)	0.0436
Cholesterol (Grade 2+)	0.695 (0.311 - 1.555)	0.3760	0.408 (0.144 - 1.154)	0.0910
Biomarker				
Baseline VEGF	1.000 (0.999 - 1.001)	0.5617	1.001 (1.000 - 1.003)	0.0487
Baseline FLT	1.002 (1.000 - 1.003)	0.0332	1.000 (0.998 - 1.001)	0.6618
Baseline angiogenic activity	1.559 (0.482 - 5.047)	0.4587	3.312 (0.964 - 11.38)	0.0572

HR: Hazard ratio, CI: Confidence interval

* Wald P-Value (P-value derived from likelihood ratio test)

** Grade 1 or higher unless otherwise specified (All Attributions)