Original Study

Phase 2 Study of Bevacizumab and Temsirolimus After VEGFR TKI in Metastatic Renal Cell Carcinoma

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Abstract

Combining bevacizumab and temsirolimus in metastatic renal cell carcinoma patients previously treated with vascular endothelial growth factor receptor tyrosine kinase inhibitor is possible, but with dose reductions and treatment discontinuations. This combination resulted in modest activity. Temsirolimus and bevacizumab combination is not recommended for use outside of a clinical trial.

Background: Inhibiting VEGF and mammalian target of rapamycin (mTOR) pathways are standard treatment approaches for patients with metastatic renal cell carcinoma (mRCC). Here we report the activity and safety of the VEGF ligand inhibitor bevacizumab and the mTOR inhibitor temsirolimus combination in patients with clear cell (CC) and non-clear cell (NCC) mRCC whose disease had failed to respond to prior VEGF blockade. **Patients and Methods:** In this phase 2 investigator-initiated multicenter study, patients received bevacizumab and temsirolimus. The primary end point was 4-month progression-free survival (PFS) rate. Secondary end points included overall response rate, median overall survival (OS), toxicity, and correlative studies of biomarkers downstream of mTOR. **Results:** Forty patients received at least 1 dose of therapy. Thirty-three (82.5%) had favorable/intermediate risk disease according to International Metastatic Renal Cell Carcinoma Database Consortium criteria, 13 (32.5%) with nccRCC histology. Nineteen (48.7%) had primary vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI)-refractory disease. The 4-month PFS rate was 65%. Overall median PFS and OS were 5.6 and 12.2 months. Median PFS and OS were 6.5 and 9.6 months in patients with primary VEGFR TKI-refractory disease, and 5.6 months and 13.1 months in patients with nccRCC. Dose reductions were needed in 80% of patients. Most frequent toxicities included fatigue, hypertension, dyslipidemia, and proteinuria. Dose discontinuation due to adverse events occurred in 27.5% of patients. Baseline tumor immunohistochemistry for phospho-S6 protein was not associated with clinical benefit. **Conclusion:** Combining bevacizumab and temsirolimus in patients previously treated with VEGFR TKI was possible but with dose reductions and treatment discontinuations. This combination resulted in modest activity, including in patients with primary VEGF-refractory disease and NCC histology.

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Introduction

Over the last decade, several therapies targeting molecular pathways have been approved by the US Food and Drug Administration for the treatment of patients with metastatic renal cell carcinoma (mRCC).[1-12] Drugs such as sorafenib, sunitinib, pazopanib, axitinib, and bevacizumab target vascular endothelial growth factor (VEGF) by inhibiting either the VEGF tyrosine kinase receptor (VEGFR) or by binding VEGF directly. Temsirolimus and everolimus inhibit the mammalian target of rapamycin (mTOR) pathway. Resistance to these therapies typically occurs sooner than a year while receiving treatment. With the recent survival benefit observed with either the PD-1 blocking agent nivolumab or the tyrosine kinase inhibitor (TKI) cabozantinib compared to everolimus, the appropriate place for mTOR inhibitor monotherapy with everolimus in the current algorithm of treating patients with mRCC is under question.[13,14]

Soon after VEGF pathway and mTOR inhibitor single agents were developed, combination therapy was pursued to investigate potential synergistic effects.[15-18] In treatment-naive patients, the combination of a VEGF pathway and mTOR inhibitor was associated with toxicity and no apparent antitumor synergy. Some postulated that not only was the benefit of combining VEGFR TKI and mTOR inhibitors over VEGFR TKI alone affected by dose reductions required for toxicity but also that the dose reductions may negatively affect the benefit expected from first-line VEGFR TKI therapy. However, while the VEGF binding agent bevacizumab does not produce impressive tumor regression, its combination with interferon proved to be tolerable and improved progression-free-survival over interferon alone.[19] Nevertheless, only a few studies have explored combining temsirolimus and bevacizumab in patients with disease that has already progressed while receiving 1 or more VEGF pathway inhibitors.[20-22]

We aimed to address the role of bevacizumab and temsirolimus in patients with VEGFR TKI-primary refractory disease[23] and those with non–clear cell (NCC) RCC histology. In addition, we explored phospho-S6 (p-S6), a downstream measure of mTOR pathway activation, as a potential biomarker of temsirolimus-based therapy.[24]

Methods

Patients

Eligible patients were 18 years of age or older with advanced or metastatic RCC with measurable disease. Both histologically confirmed clear cell (CC) or nccRCC subtypes were allowed. Patients must have experienced disease progression or intolerable toxicity with a VEGFR TKI. Patients may have had only 2 prior VEGFR TKI therapies. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate organ and marrow function. Key exclusion criteria included prior bevacizumab or prior mTOR inhibitor.

Study Design

This was an investigator-initiated, multicenter, single-arm, phase 2 trial. Sites included Beth Israel Deaconess Medical Center, Dana-Farber Cancer Institute, Massachusetts General Hospital, and Vanderbilt University. The institutional review board at each site approved the protocol before patient enrollment. Bevacizumab was administered intravenously at a dose of 10 mg/kg every 2 weeks and temsirolimus, was administered intravenously at a dose of 25 mg weekly for a 28-day cycle. There were no dose reductions for bevacizumab allowed. If adverse effects occurred that required holding bevacizumab, the same dose would be used if treatment were resumed. If adverse effects occurred that required holding temsirolimus, the same dose or a reduced dose (15 mg intravenously weekly) could be used upon resumption of therapy. Treatment was continued until the development of unacceptable toxicity or disease progression.

Clinical End Point and Assessment

The primary end point was progression-free survival (PFS) rate, defined as the proportion of patients alive and without evidence of tumor progression or appearance of new metastatic disease after 4 months (16 weeks) of treatment. Disease assessment occurred every 8 weeks until disease progression. Secondary end points included objective response rate (partial response or better); clinical benefit rate, defined as stable disease or objective response for at least 4 cycles (16 weeks); median PFS; and overall survival (OS). The Response Evaluation Criteria in Solid Tumors, version 1.1, was used to assess objective response and progression. Investigators used the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, to assess adverse effects.

Immunohistochemical (IHC) Analysis of p-S6

IHC analysis of p-S6 was performed on formalin-fixed, paraffin-embedded (FFPE) samples. Four-micron-thick slides were prepared and immunostained using a rabbit monoclonal anti–p-S6 antibody (Ser235/236) (D57.2.2E, Cell Signaling Technology) and the Dako EnVision System, according to the manufacturer's instructions. The assay was validated using FFPE LNCaP cells, either untreated or treated with LY294002 (Cell Signaling Technology) as positive and negative controls, respectively. The percentage of tumor cells that stained positive for p-S6 within the cytoplasm and the staining intensity were evaluated by a single pathologist. Quantification of p-S6 expression was performed using an H score calculated by the formula [3 × percentage of strongly staining cytoplasm + 2 × percentage of moderately staining cytoplasm + percentage of weakly staining cytoplasm], resulting in a range of 0 to 300.

Statistical Analysis

This was a single arm, single stage design evaluating the 4-month PFS rate in 40 eligible patients. If 25 or more patients were alive and progression-free at 4 months, this regimen would be considered for further study. If the true 4-month PFS rate was 50% (historical control rate), the probability of concluding the treatment was effective was ≤ 0.10 (Type I error). If the true rate was 70% (alternative rate), this probability was >0.90 (power). The binomial 4-month PFS rate was calculated with a 90% confidence interval. In secondary analyses, time-to-event distributions were estimated by the Kaplan-Meier method and subgroups compared using the log-rank test. Comparison of response rates between subgroups was assessed using Fisher's exact test.

Post hoc analysis focused on patients with primary VEGFR TKI-refractory disease ($n = 19$) and nccRCC histology ($n = 13$). Disease was considered to be primary refractory if the best response on prior

Table 1 Patient Demographics and Disease Characteristics (n = 40)

Characteristic	Value
Age (years), median (range)	50 (32-80)
Sex	
Male	33 (82.5)
Female	7 (17.5)
Race	
White	36 (90%)
Black	1 (2.5%)
Other	3 (7.5%)
Histology	
Clear cell	27 (67.5%)
Non–Clear Cell	13 (32.5%)
Unclassified	5 (12.5%)
Papillary	6 (15%)
Chromophobe	1 (2.5%)
Poorly differentiated	1 (2.5%)
Time since initial diagnosis (years), median (range)	1.6 (0.2-17.4)
Most Common Site of Metastasis	
Lung	27
Lymph node (intraabdominal; pulmonary)	10; 13
Liver	14
Bone	12
Kidney	10
Pancreas	2
Adrenal	6
Brain	3
No. of Organs Involved	
1	10 (25%)
2	10 (25%)
≥3	20 (50%)
ECOG Status	
0	13 (32.5%)
1	27 (67.5%)
IMDC Risk Category	
Favorable	5 (12.5%)
Intermediate	28 (70%)
Poor	7 (17.5%)
MSKCC Risk Category	
Favorable	5 (12.5%)
Intermediate	31 (77.5%)
Poor	4 (10%)
Prior nephrectomy	34 (85%)
Prior interleukin 2 therapy	7 (17.5%)
Prior VEGFR TKI Inhibitor	
1 TKI	37 (92.50%)
2 TKI	3 (7.5%)
Response to Previous VEGFR TKI	
SD or PR at first evaluation	20 (50%)
PD at First Evaluation (Primary Refractory)	
Present	19 (47.5%)
Unevaluable	1 (2.5%)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC = Memorial Sloan Kettering Cancer Center; PD = progressive disease; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

VEGFR TKI therapy was progressive disease or if duration of prior VEGFR TKI therapy was < 3 months with progression at the end of therapy. Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk criteria were collected as prognostic factors to be evaluated.

Results

Patient Characteristics

From April 2009 to May 2013, a total of 40 patients were eligible and began therapy on trial (Table 1). Patients had an ECOG status of 0 or 1 (n = 13 and n = 27, respectively). Twenty-seven patients had predominantly ccRCC. Thirteen patients had nccRCC histology; 6 patients had papillary RCC histology; 5 had unclassified nccRCC; 1 had chromophobe RCC; and 1 had "poorly differentiated" RCC, which was included as nccRCC. The majority of patients had disease of intermediate risk by MSKCC risk criteria (n = 31, 78%) or IMDC risk criteria (n = 28, 70%). Half the patients had 3 or more organs involved with metastasis. The majority of patients had received prior sunitinib therapy (75%), and the majority of patients had received only 1 prior therapy with TKIs (92.5%, n = 37). Nineteen subjects (48.7%) had primary VEGFR TKI-refractory disease.

Treatment Received and Efficacy

The median survival follow-up from registration was 56 months. The median of cycles started was 5.0 (range, 1-39). The objective response rate was 17.5% (90% CI, 8.5-30.4). Seven patients (18%) had partial response as their best response, 24 patients (60%) had stable disease, and 8 patients (20%) had progressive disease (Table 2). No patient experienced a complete response. The PFS at 4 months was 65% (90% CI, 50.8-77.5). The median PFS was 5.6 months (90% CI, 4.2-8.1; Figure 1). The 1- and 2-year PFS probabilities were 25% and 5.6% (90% CI, 14.4-37.1 and 1.4-14.1, respectively). The median OS was 12.2 months (90% CI, 7.7-21.9; Figure 2). The 1- and 2-year OS probabilities were 50% and 29.5% (90% CI, 36.5-62.1 and 18.2-41.6, respectively). Over half of the patients treated exhibited some degree of tumor shrinkage (64%; Figure 3).

Subgroup analysis showed that there was no statistical difference in median PFS between patients with primary VEGFR TKI-refractory disease (6.5 months, 90% CI, 3.0-10.3) versus primary VEGFR TKI-responsive disease (5.3 months, 90% CI, 3.6-5.9; log-rank $P = .85$) (Supplemental Figure 1). Patients with primary TKI-refractory disease had PFS rates at 1 year of 31.6% (95% CI, 15.5-49.1) versus 26.3% (95% CI, 11.7-43.5) for those with

Table 2 Summary of Key Efficacy End Points

End Point	Variable	Value	95% CI
PFS 4-month probability		65% (26)	50.8-77.5
Best response	PR	7 (17%)	NA
	SD	24 (60%)	
	PD	8 (20%)	
	Unevaluable	1 (2.5%)	
PFS by IMDC	Median (months)	5.6	4.2-8.1
	1-year probability	25%	14.4-37.1
	2-year probability	5.6%	1.4-14.1
Clinical benefit (at 4 cycles)		25 (62.5%)	
OS	Median	12.2	7.7-21.9
	1-year probability	50%	36.5-62.1
	2-year probability	29.5%	18.2-41.6
ORR by subgroup	**ORR by Prior Response to TKI**		NA
	Primary VEGFR TKI-Responsive (n = 20)		
	PR	4 (20%)	
	SD	13 (65%)	
	PD	3 (15%)	
	Primary VEGFR TKI-Refractory (n = 19)		
	PR	2 (10.5%)	
	SD	11 (57.9%)	
	PD	5 (26.3%)	
	Unevaluable	1 (5.3%)	
ORR by histology	**Clear Cell RCC (n = 27)**		NA
	PR	6 (22.2%)	
	SD	14 (51.9)	
	PD	6 (22.2%)	
	Unevaluable	1 (3.7%)	
	Non–Clear Cell RCC (n = 13)		
	PR	1 (7.7%)	
	SD	10 (76.9%)	
	PD	2 (15.4%)	
PFS by subgroup	**PFS by Prior Response to TKI**		
	Primary VEGFR TKI-Responsive (n = 20)		
	Median (months)	5.3	3.6-5.9
	1-year probability	26.3%	11.7-43.5
	2-year probability	5.3%	0.6-18.1
	Primary VEGFR TKI-Refractory (n = 19)		
	Median (months)	6.5	3.0-10.3
	1-year probability	31.6%	15.5-49.1
	2-year probability	6.3%	0.8-20.9
PFS by histology	**Clear Cell (n = 27)**		
	Median (months)	5.6	3.3-10.3
	1-year probability	23.1	11.2-37.5
	2-year probability	3.9	0.5-13.7
	Non–Clear Cell (n = 13)		
	Median (months)	5.6	3.4-13.7
	1-year probability	30.8%	12.2-51.7
	2-year probability	10.3%	1.2-30.9
OS by subgroup	**OS by Prior Response to TKI**		
	Primary VEGFR TKI- Responsive (n = 20)		
	Median (months)	12.1	5.4-31.1
	1-year probability	50.0%	30.8-66.5
	2-year probability	40.0%	22.4-57.1
	Primary VEGFR TKI- Refractory (n = 19)		
	Median (months)	9.6	6.6-20.0
	1-year probability	47.4%	28.0-64.5
	2-year probability	13.2%	3.4-29.6
OS by histology	**Clear Cell (n = 27)**		
	Median (months)	10.9	7.5-22.8
	1-year probability	48.2	31.8-62.7
	2-year probability	29.6	16.3-44.2
	Non–Clear Cell (n = 13)		
	Median (months)	13.1	5.0-24.6
	1-year probability	53.8%	29.4-73.1
	2-year probability	28.8%	10.4-50.6

Abbreviations: CI = confidence interval; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; NA = not applicable; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RCC = renal cell carcinoma; SD = stable disease; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

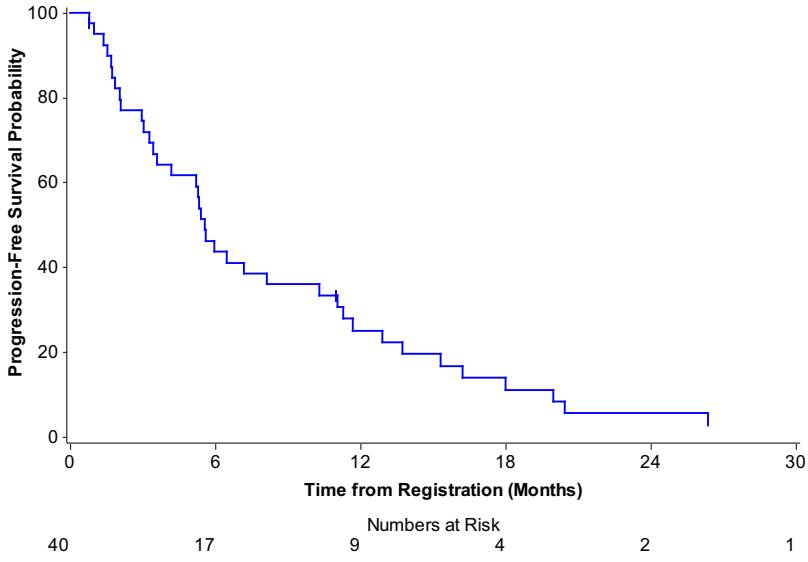
primary VEGFR TKI-responsive disease. Median OS was 9.6 months (95% CI, 6.6-20.0) and 12.1 months (95% CI, 5.4-31.1) for primary TKI-refractory and primary TKI-responsive RCC (Supplemental Figure 2).

Similarly, there was no statistical difference in median PFS between patients with nccRCC (5.6 months, 90% CI, 3.4-13.7) and ccRCC disease (5.6 months, 90% CI, 3.3-10.3; log-rank $P = .54$) (Supplemental Figure 3). One-year PFS probability was 30.8% (95% CI, 12.2-51.7) for nccRCC versus 23.1% (95% CI, 11.2-37.5) for ccRCC. Median OS was also not significantly different between patients with nccRCC and ccRCC disease (13.1 months vs. 10.9 months, log-rank $P = .72$) (Supplemental Figures 4).

Toxicity

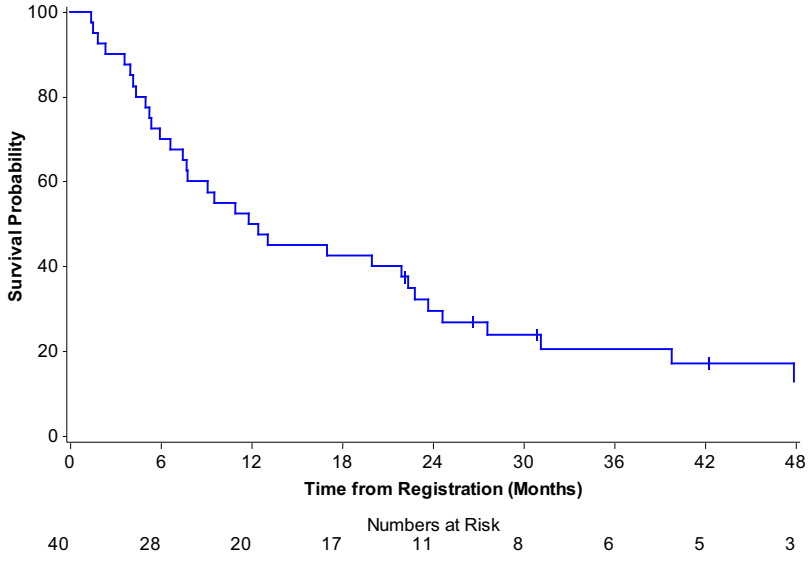
Eighty percent of patients required dose modification of either temsirolimus (77.5%) or bevacizumab (60%). Unacceptable toxicity was the reason for stopping therapy in 27.5% of patients. A total of 95% of patients experienced toxicity (any grade), while 70% of patients had grade 3 or higher toxicity (Supplemental Table 1). Most frequent severe toxicities included fatigue (n = 4), hypertension (n = 5), hypertriglyceridemia (n = 6), and proteinuria (n = 4). Serious adverse events included deep vein thrombosis (n = 1),

Figure 1 Progression-Free Survival



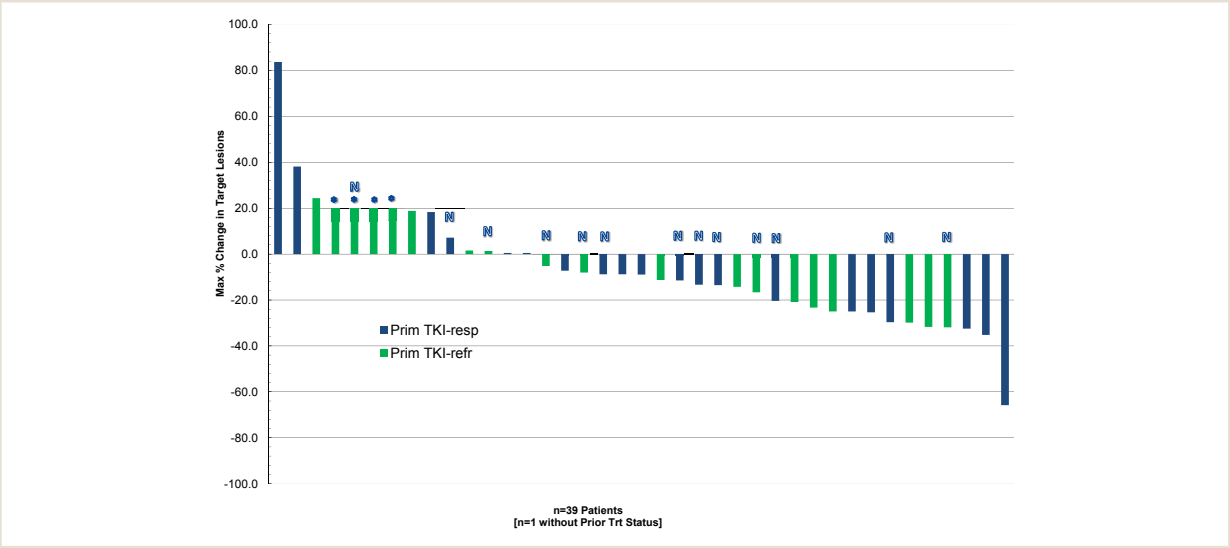
N Patients/Events	40/38
Median (90% CI) [mos]	5.6 (4.2-8.1)
1-Year Prob (90% CI) [%]	25.0 (14.4-37.1)
2-Year Prob (90% CI) [%]	5.6 (1.4-14.1)

Figure 2 Overall Survival



N Patients/Events	40/34
Median (90% CI) [mos]	12.2 (7.7-21.9)
1-Year Prob (90% CI) [%]	50.0 (36.5-62.1)
2-Year Prob (90% CI) [%]	29.5 (18.2-41.6)

Figure 3 Waterfall Plot Showing Percentage Change in Sum Long-Diameter Target Lesions Receiving Treatment



One patient without prior treatment duration reported was excluded but had partial response with maximum change in target lesion of 38.7% reduction. "N" denotes non–clear cell histology. Four patient who went off study because of progressive disease by clinical picture before first scan all had VEGFR TKI-refractory disease, are marked with asterisks, and are listed as PD at 20% change as placeholder.

esophageal fistula (n = 1), bowel perforation (n = 1), cerebrovas cular accident (n = 1), and ventricular arrhythmia/cardiac arrest (n = 1).

p-S6 Expression

Correlative studies from a phase 2 temsirolimus trial suggested that p-S6 expression is a potential predictive biomarker for response to temsirolimus.[24] We thus assessed whether p-S6 expression was associated with benefit or response to temsirolimus-based combination therapy. Of the 40 patients who were treated, 26 (65%) had pretreatment FFPE tumor tissue available for IHC analysis of p-S6 (Figure 4). Patients were classified by their tumor's H score tertile status into low (≤ 35), intermediate (> 35-115), and high (≥ 115) groups. Subsets of low, intermediate, or high p-S6 H scores were evaluated for possible association with clinical benefit. Clinical benefit status was evaluated in 69% (18 of 26) of patients tested for p-S6 (Table 3). The rate of clinical benefit was 75% (6 of 8 patients), 44.4% (4 of 9 patients), and 88.9% (8 of 9 patients) in the low, intermediate, and high p-S6 H score groups, respectively (Table 3). In this underpowered analysis, no significant association between clinical benefit and p-S6 H score groups was observed (Fisher's exact test, $P = .19$) (Supplemental Table 2, Table 3 and Supplemental Figure 5).

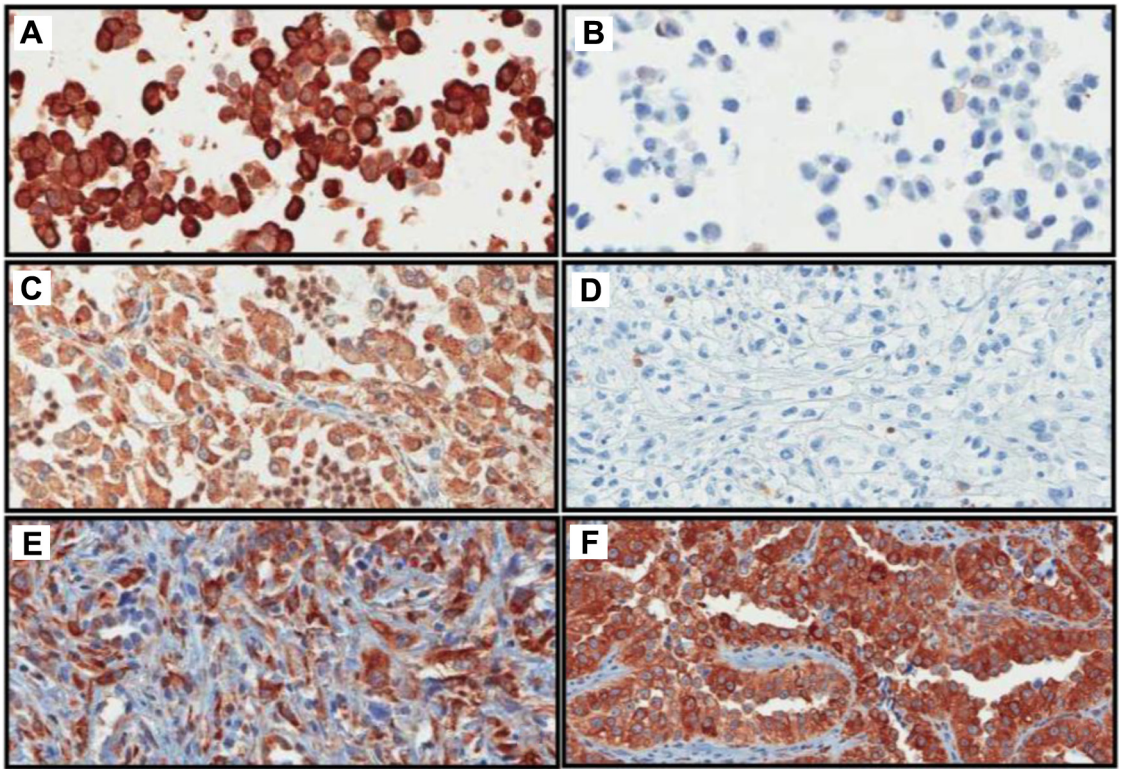
Discussion

RCC is unique in that it is a highly VEGF-dependent cancer. The biallelic inactivation of the Von Hippel-Lindau (VHL) tumor suppressor occurs in the vast majority of ccRCC through either loss of heterozygosity, deletion, or hypermethylation. VHL inactivation results in accumulation of hypoxia-inducible factor and overexpression of genes, including those for VEGF. While VEGFR inhibitor therapy can lead to tumor shrinkage, it also produces intratumoral hypoxia, which induces both additional VEGF production and mTOR pathway activation.[25] Because progressive RCC on a VEGFR TKI can be associated with increased intratumoral VEGF levels, this combination with the VEGF-depleting antibody bevacizumab is a rational second-line therapy.

Our trial was slow to accrue in the setting of competing trials and the emerging disappointing results with the combination of VEGFR TKI and mTOR in the first-line setting[15-18,26] (Table 4). The activity of this combination in our cohort was active despite dose reductions. However, this activity was modest and failed to meet its primary end point of a 4-month PFS rate of 70% in subjects with mRCC previously treated with VEGFR TKIs. With the exception a first-line combination of bevacizumab and everolimus in patients with nccRCC,[27] trials combining VEGF and mTOR inhibitors have predominantly enrolled patients with ccRCC. In a phase 2 trial enrolling only patients with nccRCC, antitumor effects were noted in patients with chromophobe or papillary tumor histologies.[27] In our study, the median PFS and OS for patients with nccRCC was not different than those with CC histology. We also focused on characterizing patients with primary VEGF pathway inhibitor–refractory RCC, a significant unmet need affecting as much as 15% to 20% of patients.[23] The PFS of 5.6 months in this patient population (no different than patients with a history of benefit with a VEGF pathway inhibitor) is of interest. This observation suggests that VEGF pathway or mTOR inhibitors may be of particular use in this primary VEGF pathway inhibitor–refractory population and may encourage testing for genomic alterations in the mTOR pathway, for which mTOR inhibitors may be preferred. Unfortunately, our selected biomarker, p-S6 IHC, was not associated with benefit with this combination.

A major limitation in this exploratory analysis is that 35% (14 of 40) of subjects did not have a tumor specimen for analysis. This precluded any conclusions, although in the patients studied, there

Figure 4 Representative Images of FFPE Samples Immunostained With Anti–p-S6 Antibody. (A) Positive Control: LNCaP Cells. (B) Negative Control: LNCaP Cells Treated With LY294002. (C) Positive Primary Clear Cell RCC. (D) Negative Primary Clear Cell RCC With Positive Tumor-infiltrating Immune Cells. (E) Positive Sarcomatoid RCC (Lung Metastasis). (F) Positive Papillary RCC (Omentum Metastasis)



Abbreviations: FFPE = formalin fixed, paraffin embedded; p-S6 = phospho-S6; RCC = renal cell carcinoma.

was no clear association between p-S6 IHC expression and clinical benefit. While the majority of patients with high p-S6 derived clinical benefit from treatment, lack of or low phosphorylation of S6 did not preclude benefit from combination therapy.

We found that the combination therapy toxicities can be manageable but require significant dose reductions and therapy discontinuation as a result of adverse events. This mirrors the experience with prior combinations of VEGF pathway and mTOR inhibitors.[20-22] It remains unknown whether starting at lower doses of drugs could have translated into superior tolerability or more sustained antitumor activity. In fact, the recently reported phase 2 combination of lenvatinib, a VEGFR TKI, and everolimus used significantly lower doses for each drug and reported significant clinical activity.[28] This antitumor activity may require validation in confirmatory clinical trial, although at the time of writing, the US Food and Drug Administration has granted a priority review designation to the combination of lenvatinib and everolimus as a treatment for patients with metastatic RCC after 1 prior VEGF-targeted therapy.

Table 3 H Score (Categorical 3 Level Tertiles) by Clinical Benefit Status[a]

Tertile	Clinical Benefit Status		
	No	Yes	Total
T1: Low (H score $\leq$35)	2 (25.0%)	6 (75.0%)	8
T2: Intermediate (35 < H score < 115)	5 (55.6%)	6 (44.4%)	9
T3: High (H score $\geq$115)	1 (11.1%)	8 (88.9%)	9
Total	8	18	26
Frequency missing = 14			

[a]Data are presented as score upper tertiles and frequency row percentages.

With the advent of immune checkpoint inhibitors, numerous combinations are in development.[29] Ongoing combination trials with nivolumab include ipilimumab or VEGFR TKI. Alternatively, combining bevacizumab and immune checkpoint inhibitors may be less toxic and particularly reasonable, given the immunosuppressive properties of VEGF, and that pretreatment serum VEGF are associated with worse OS in RCC.[30-32] A phase 1 trial combining bevacizumab with the PD-L1 blocking atezolizumab showed that this combination is very safe and resulted in a high response rate,[33] which has lead to a pivotal phase 3 trial in untreated patients with advanced RCC (NCT02420821).

Finally, recent phase 3 studies have shown that both the PD-1 blocking nivolumab and the VEGFR + MET/AXL inhibitor cabozantinib both have superior efficacy to the mTOR inhibitor

Table 4 Comparison of Anti-VEGF and mTOR-Targeted Combination Trials

Characteristic	First, ≥2 Lines		First Line			First Line	Second–Third Line			
Trial[a]	Hainsworth 2010[15]		TORAVA (Negrier 2011[16])	INTORACT (Rini 2014[17])	RECORD-2 (Ravaud 2015[18])	Voss 2015[27]	Bitting 2014[20]	Harshman 2013[21]	Merchan 2015[22]	AVATOR (Mahoney 2015[29])
Treatment	Bev + Evero		Tem + Bev (phase 2)	Bev + Tem (phase 3)	Evero + Bev (phase 2)	Evero + Bev (phase 2)	Vat + Evero (phase 1b)	Bev + Evero (phase 2)	Bev + Tem (phase 2)	Bev + Tem (phase 2)
No. treated	50 first line; 30 ≥2L		88 in arm A	400 in arm A	182 in arm A	34	10 prior therapy[c] (23 total)	10 enrolled[b]	40 prior TKI therapy	40 prior TKI therapy
Histology	CC[d]		CC[e]	CC predominately	CC[e]	NCC[e]	CC + NCC[f]	CC	Component of CC	CC + NCC
Primary end point	8-week PFS		48-week PFS	PFS	—	6-month PFS	Toxicity and ORR	PFS	6-month PFS	4-month PFS
Response, n (%)	**1L**	**≥2L**	**1L**	**1L**	**1L**	**1L**	**≥2L**	**≥2L**	**≥2L**	**≥2L**
CR	1 (2%)	1 (3%)	2 (2%)	2 (<1%)			NR	0	0	0
PR	14 (28%)	6 (20%)	22 (25%)	106 (26.5%)				1 (10%)	8 (20%)	(17.5%)
SD	25 (50%)	19 (64%)	46% (52%)	218 (54.5%)				9 (90%)	26 (65%)	(60%)
PD	3 (6%)	3 (10%)	15 (17%)	41 (10.3)				0	6 (15%)	(20%)
Unevaluated	7 (14%)	1 (3%)	—	5 (1.3%)				—	—	—
ORR (%)	30	23		27		29	NR	10	20	17.5
Median PFS (months)	9.1	7.1	8.2	9.1	9.3	10.9	4.6	5.1	5.9	5.6
Median OS (months)	NA			25.8	27.1	16.7	6.3	21	20.6	12.2
Toxicity			Grade 3 or higher, 77%; SAE 44%					40% stopped as a result of toxicity		Grade 3 or higher, 70%
Biomarker correlatives						NGS of genomics	p-S6 assay (pharmacodynamic)		sFLT-1 VEGF	Pretreatment p-S6

Abbreviations: Bev = bevacizumab; CC = clear cell; CR = complete response; Evero = everolimus; mOS = median OS; mPFS = median progression-free survival; NCC = non–clear cell; NGS = next-generation sequencing; NR = not reported; mTOR = mammalian target of rapamycin; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; p-S6 = phospho-S6; RCC = renal cell carcinoma; SAE = serious adverse event; SD = stable disease; Tem = temsirolimus; Vat = vatalanib; VEGF = vascular endothelial growth factor.

[a]Fishman et al,[26] who studied tivozanib + temsirolimus, phase 1b, 7 untreated, 20 treated, was not included because outcomes were not broken down by prior therapy.

[b]Harshman et al[21] enrolled 10 of 30 planned; enrollment was slow as a result of toxicity.

[c]Efficacy analysis by RCC variant; there was a significant difference in the clinical outcomes between the subgroup with a major papillary component (12.9 mPFS, 16.7 mOS) and those without a major papillary component (1.9 mPFS, 9.5 mOS). Presented at Genitourinary Symposium, American Society of Clinical Oncology 2015.

[d]Hainsworth et al[15] studied bevacizumab + everolimus, CC or predominantly CC (≥75%).

[e]Negrier et al[16] reported 95% CC in the treatment arm. Ravaud et al[18] reported 94% ccRCC or 97.8% ccRCC; if sarcomatoid (6 patients, 3.3%), it was considered ccRCC (only 4 patients with papillary disease).

[f]Bitting et al[20] assessed vatalanib + everolimus in a phase 1b study of 23 RCC, 18 ccRCC; 5 NCC but 13 (56.5%) without prior VEGF therapy.

everolimus in patients with VEGF pathway–resistant RCC.[13,14] Either of these agents would be a preferred option to the bevacizumab plus temsirolimus combination in patients with ccRCC, even in the population of patients with disease that is primary refractory to VEGF pathway inhibitors. However, comparing the combination of bevacizumab and TORC1 inhibitors with VEGFR TKI alone in patients with nccRCC may be warranted in light of our findings and those of the ASPEN and ESPN trials.

Conclusion

Combining bevacizumab and temsirolimus in a VEGFR TKI-refractory mRCC population was possible but required significant dose reductions and discontinuations. This combination at full doses of each drug resulted in modest activity overall and would not be recommended for routine clinical use.

Clinical Practice Points

- The combination bevacizumab and temsirolimus in subjects with mRCC previously treated with VEGFR TKIs showed modest activity despite dose reductions and discontinuations.
- Subgroup analyses found that patients with nccRCC or primary VEGFR TKI-refractory disease did not have a remarkably different clinical outcome from ccRCC or primary VEGFR TKI-responsive disease, respectively.
- p-S6 IHC did not differentiate a group with better clinical outcomes.
- Without the development and validation of effective biomarkers, the temsirolimus and bevacizumab combination is not recommended for clinical use outside of a clinical trial.

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Disclosure

M.D.M. is an advisory board member for Pfizer, Novartis, Exilixis, and Eisai. M.B.A. is a consultant for BMS, Pfizer, Novartis, Genentech-Roche, Merck, Amgen, and Nektar. D.F.M. is a consultant for BMS, Pfizer, Novartis, Genentech-Roche, Merck, and Exilixis. T.K.C. is an advisory board member for Novartis, Roche, Merck, Pfizer, and Prometheus. The other authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental tables and figures accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clgc.2016.02.007.

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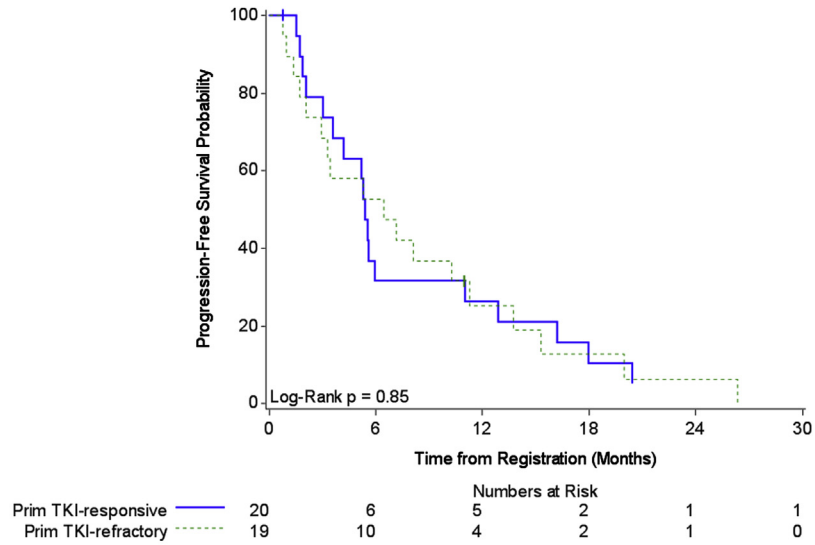
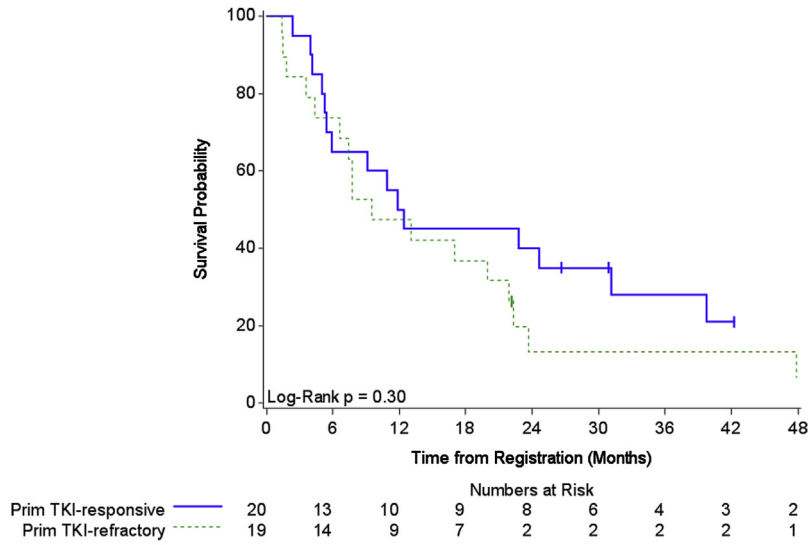
Supplemental Figure 1 Progression-Free Survival by Primary VEGFR TKI-Responsive/Refractory Subgroup



Primary VEGFR TKI-Responsive	
N Patients/Events	20/19
Median (90% CI) [mos]	5.3 (3.6-5.9)
1-Year Prob (90% CI) [%]	26.3 (11.7-43.5)
2-Year Prob (90% CI) [%]	5.3 (0.6-1.8)
Primary VEGFR TKI-Refractory	
N Patients/Events	19/18
Median (90% CI) [mos]	6.5 (3.0-10.3)
1-Year Prob (90% CI) [%]	31.6 (15.5-49.1)
2-Year Prob (90% CI) [%]	6.3 (0.8-20.9)

Abbreviations: TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

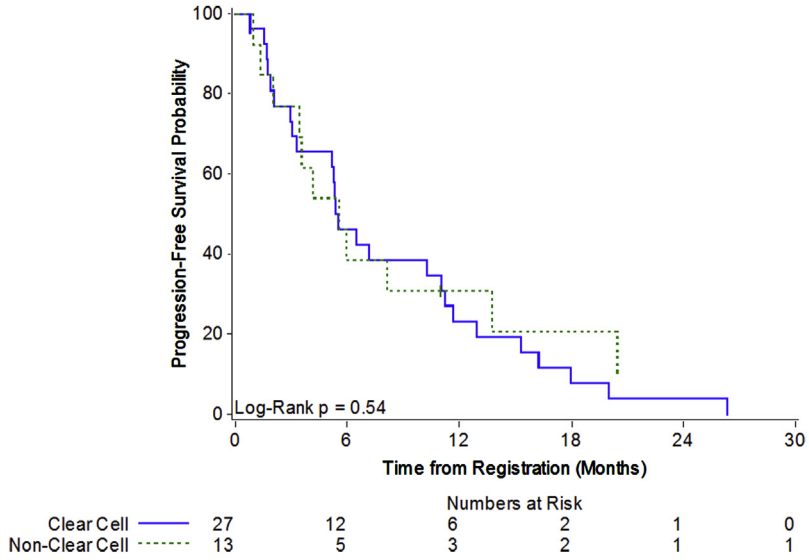
Supplemental Figure 2 Overall Survival by Primary VEGFR TKI-Responsive/Refractory Subgroup



Primary VEGFR TKI-Responsive	
N Patients/Events	20/16
Median (90% CI) [mos]	12.1(5.4-31.1)
1-Year Prob (90% CI) [%]	50.0 (30.8-66.5)
2-Year Prob (90% CI) [%]	40.0 (22.4-57.1)
Primary VEGFR TKI-Refractory	
N Patients/Events	19/17
Median (90% CI) [mos]	9.6 (6.6-20.0)
1-Year Prob (90% CI) [%]	47.4 (28.0-64.5)
2-Year Prob (90% CI) [%]	13.2 (3.4-29.6)

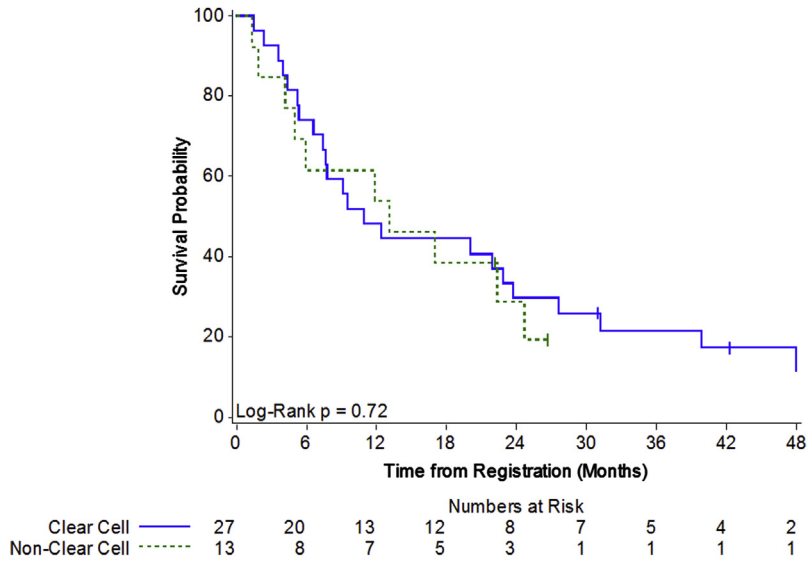
Abbreviations: TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

Supplemental Figure 3 Progression-Free Survival by Clear Cell or Non–Clear Cell Histology Subgroup



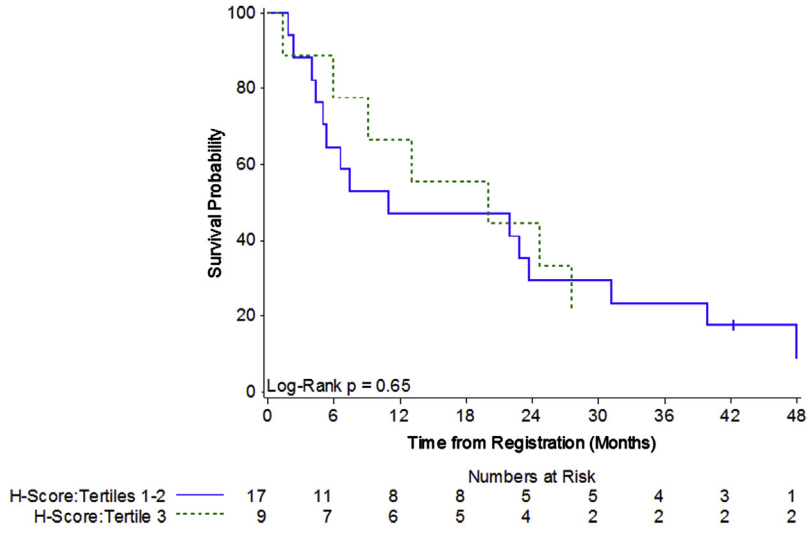
Clear Cell	
N Patients/Events	27/26
Median (90% CI) [mos]	5.6 (3.3-10.3)
1-Year Prob (90% CI) [%]	23.1 (11.2-37.5)
2-Year Prob (90% CI) [%]	3.9 (0.5-13.7)
Non-Clear Cell	
N Patients/Events	13/12
Median (90% CI) [mos]	5.6 (3.4-13.7)
1-Year Prob (90% CI) [%]	30.8 (12.2-51.7)
2-Year Prob (90% CI) [%]	10.3 (1.2-30.9)

Supplemental Figure 4 Overall Survival by Clear Cell or Non–Clear Cell Histology Subgroup



Clear Cell	
N Patients/Events	27/23
Median (90% CI) [mos]	10.9 (7.5-22.8)
1-Year Prob (90% CI) [%]	48.2 (31.8-63.7)
2-Year Prob (90% CI) [%]	29.6 (16.3-44.3)
Non-Clear Cell	
N Patients/Events	13/11
Median (90% CI) [mos]	13.1 (5.0-24.6)
1-Year Prob (90% CI) [%]	53.8 (29.4-73.1)
2-Year Prob (90% CI) [%]	28.8 (10.4-50.6)

Supplemental Figure 5 Overall Survival by High or Intermediate—Low Phospho-S6 Status



H-Score: Tertile 3	
N Patients/Events	9/8
Median (90% CI) [mos]	20.0 (5.9-27.6)
1-Year Prob (90% CI) [%]	66.7 (34.8-85.6)
2-Year Prob (90% CI) [%]	44.4 (17.8-68.3)
H-Score: Tertiles 1-2	
N Patients/Events	17/15
Median (90% CI) [mos]	10.9 (5.0-23.7)
1-Year Prob (90% CI) [%]	47.1 (26.7-65.1)
2-Year Prob (90% CI) [%]	29.4 (13.2-47.8)

Supplemental Table 1 Toxicity of Bevacizumab and Temsirolimus Combination

Toxicity	Maximum Grade	
	3 (Severe)	4 (Life-Threatening)
ALT	1	—
AST	2	—
Alkaline phosphatase	1	—
Anorexia	2	—
Dehydration	1	—
Dizziness	1	—
Dyspnea	2	—
Edema limb	1	—
Enteritis	1	—
Fatigue	4	—
Fever without neutropenia	1	—
Fistula, esophageal	—	1
Glomerular filtration rate	1	—
Haptoglobin	1	—
Head/headache	1	—
Hemoglobin	1	1
Hypercholesterolemia	2	—
Hyperglycemia	1	—
Hypertension	5	—
Hypertriglyceridemia	6	—
Hyponatremia	1	—
Hypophosphatemia	4	—
Hypotension	—	1
Infection with unknown ANC blood	1	—
Infection with unknown ANC skin (cellulitis)	1	—
Lower GI, hemorrhage NOS	1	—
Muco/stomatitis (symptom) oral cavity	2	—
Muco/stomatitis by exam, oral cavity	1	—
Nausea	3	—
Neck, pain	1	—
Neutrophils	1	—
Nose, hemorrhage	1	—
PTT	1	—
Pneumonitis/pulmonary infiltrates	2	—
Proteinuria	4	—
Pulmonary/upper respiratory—other	1	—
Rash/desquamation	1	—
Syncope	—	1
Syndromes—other	—	1
Thrombosis/thrombus/embolism	1	—
Vascular access, thrombosis/embolism	1	—
Ventricular arrhythmia NOS	—	1
Vomiting	2	—
Weight gain	1	—
Wound, noninfectious	—	1
Maximum grade	22	5

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; GI = gastrointestinal; NOS = not otherwise specified; PTT = partial thromboplastin time.

Supplemental Table 2 H Score (Categorical 2 Level by Upper Tertile) by Clinical Benefit Status

Tertile	Clinical Benefit Status[a]		
	No SD by Cycle 4	SD by Cycle 4	Total
1-2	7 (41.18%)	10 (58.82%)	17
3	1 (11.11%)	8 (88.89%)	9
Total	8	18	26

Frequency missing = 14

$P = .190$ (Fisher's exact, underpowered).
Abbreviation: SD = stable disease.
[a]Data are presented as score upper tertiles and frequency row percentages.