Original Article

Bevacizumab Alone or in Combination With TRC105 for Patients With Refractory Metastatic Renal Cell Cancer

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BACKGROUND: Targeting the vascular endothelial growth factor (VEGF) pathway has improved outcomes in metastatic renal cell carcinoma (RCC); however, resistance inevitably occurs. CD105 (endoglin) is an angiogenic pathway that is strongly upregulated after VEGF inhibition, potentially contributing to resistance. The authors tested whether TRC105, a monoclonal antibody against endoglin, impacted disease control in patients with previously treated RCC who were receiving bevacizumab. **METHODS:** Eligible patients with metastatic RCC who had previously received 1 to 4 prior lines of therapy, including VEGF-targeted agents, were randomized 1:1 to receive bevacizumab 10 mg/kg intravenously every 2 weeks (arm A) or the same plus TRC105 10 mg/kg intravenously every 2 weeks (arm B). The primary endpoint was progression-free survival (PFS) at 12 and 24 weeks. Correlative studies included serum transforming growth factor β (TGFβ) and CD105 levels as well as tissue immunostaining for TGFβ receptors. **RESULTS:** Fifty-nine patients were enrolled (28 on arm A and 31 on arm B), and 1 patient on each arm had a confirmed partial response. The median PFS for bevacizumab alone was 4.6 months compared with 2.8 for bevacizumab plus TRC105 ($P = .09$). Grade ≥ 3 toxicities occurred in 16 patients (57%) who received bevacizumab compared with 19 (61%) who received bevacizumab plus TRC105 ($P = .9$). Baseline serum TGFβ levels below the median (<10.6 ng/mL) were associated with longer median PFS (5.6 vs 2.1 months; $P = .014$). **CONCLUSIONS:** TRC105 failed to improve PFS when added to bevacizumab. TGFβ warrants further study as a biomarker in RCC. ***Cancer* 2017;000:000-000.**

KEYWORDS: angiogenesis, renal cancer, targeted therapy, transforming growth factor β (TGFβ), vascular endothelial growth factor (VEGF).

INTRODUCTION

Renal cell carcinoma (RCC) affected more than 62,000 individuals in the United States in 2016 and is expected to cause more than 14,000 deaths.[1] The prognosis in clear cell RCC has been substantially improved by targeting the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways, based on the biology of von-Hippel Lindau gene inactivation as a driver genomic change.[2-5] Angiogenesis is a foundational developmental process with multiple redundant pathways, which may contribute to innate or acquired resistance to VEGF-targeted therapy. CD105, or endoglin, is 1 of the essential pathways for angiogenesis.[6] Activation of CD105 by transforming growth factor β (TGFβ) results in the stimulation of endothelial cell proliferation through the transmembrane serine/threonine kinase receptor 2 (TBR-II)/activin A receptor like type 1 (ACVRL1)/TGFβ receptor 1 (TGFβR1) heterotetrameric receptor complex.[7] In addition, tumor cells themselves can express CD105, particularly renal cancer cells,[8] and greater expression is associated with poorer outcomes.[9] Tumor microvessels, which remain after exposure to anti-VEGF antibody in animal experiments, exhibit strong expression of CD105,[10] and CD105 is 1 of 3 genes whose expression is upregulated by the suppression of VEGF signaling.[11] Inhibition of CD105 should impede signaling by TGFβ, potentially shutting off an escape pathway during VEGF blockade. TRC105 is a chimeric monoclonal immunoglobulin G1 (IgG1) antibody that binds human CD105 and induces antibody-dependent cellular cytotoxicity and a reduction in the development of

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metastases in colon cancer xenograft models.[12] A phase 1 study identified 10 mg/kg intravenously every week or 15 mg/kg intravenously every 2 weeks as the recommended phase 2 dosing schedules for TRC105, and antitumor effects were reported.[13] Low-grade, first-dose infusion reactions were observed, reflecting antibody-dependent, cell-mediated cytotoxicity and necessitating premedication that was tapered off with repeat dosing. Grade 3 or higher toxicities included anemia (n = 4; 8%), but hypertension and proteinuria were notably absent.

Bevacizumab (Bev) is a humanized monoclonal antibody against VEGF that gained US Food and Drug Administration approval for the treatment of metastatic RCC based on significant prolongation of progression-free survival (PFS) for the combination of Bev plus interferon over interferon alone.[14] Even in a population of previously untreated patients, 20% had primary refractory disease, with a best response of progressive disease on the Bev arm. This has created interest in dual antiangiogenic blockade, although, to date, combination therapy has been limited by excess toxicity.[15,16] A phase 1 trial combining TRC105 with Bev identified a dose-limiting toxicity of headache at doses of 6 mg/kg TRC105 with 15 mg/kg Bev; subsequent adjustments to the TRC105 administration (splitting the first dose and staggering the first dose administration off of the same day as Bev) led to successful escalation of TRC105 to 10 mg/kg with 10 mg/kg Bev.[17] The hypothesis that adding TRC105 to Bev would suppress an escape pathway for VEGF inhibition and result in delay to disease progression led to the development of the current clinical trial of Bev alone or with TRC105 in patients with metastatic RCC. Bev has been more tolerable in vertical and horizontal angiogenesis combinations, whereas toxicity has limited the success of VEGF tyrosine kinase inhibitors in combination studies; this was the rationale for selecting Bev.

MATERIALS AND METHODS

Patients were eligible if they had metastatic RCC with any histologic subtype. Prior treatment with at least 1 targeted therapy for metastatic RCC was required, including cytokine, VEGF, or mTOR agents, with a maximum of 4 prior systemic therapies and excluding prior Bev. Hemoglobin levels $\geq$ 9 g/dL were required for study entry as well as a glomerular filtration rate calculated or measured at >50 mL/minutes, normal bilirubin, and aspartate and alanine aminotransferase levels <2.5 times the institutional upper limit of normal (up to 5 times for patients with liver metastases). Patients who were receiving full-dose anticoagulation were excluded from participation as well as those who had a history of a bleeding diathesis or a venous thromboembolic event within 1 year. Patients were randomized 1:1 to arm A or arm B, stratified to maintain balance with respect to clear-cell versus nonclear-cell disease, and an Eastern Cooperative Oncology Group performance status of 0 or 1 versus 2. Randomization tables for each of the 4 strata, each with a block size of 4, were generated by the statistician, held in confidence at the data-coordinating center, and were accessible to only the 2 registrars. Patients received treatment at the clinical practices constituting the California Cancer Consortium between November 9, 2012, and August 28, 2014. The trial was registered at clinicaltrials.gov (identifier NCT01727089).

Bev was administered at 10 mg/kg intravenously on days 1 and 15 of 28-day cycles as a single agent (arm A) or with TRC105 10 mg/kg intravenously on days 1, 8, 15, and 22 (arm B). The first dose of TRC105 was to be split; thus, patients on arm B received Bev alone on day 1 of cycle 1, day 1; 3 mg/kg TRC105 on day 8; 7 mg/kg TRC105 on day 11; and then the first concurrent full doses of both medications on cycle 1, day 15. These initial doses were infused over 4 hours until the full 10-mg/kg dose was tolerated (ie, cycle 1, day 15 dose), at which point the duration of infusion was decreased, beginning with cycle 1, day 22 (down to 2 hours); and, if that was tolerated, then the infusion time was decreased to 1 hour for all subsequent doses. Premedication with intravenous dexamethasone 20 mg was used until the 1-hour infusion schedule was tolerated; at that point, it was tapered off. Additional required premedications for TRC105 included acetaminophen and H1 and H2 blockers. The first 3 patients on arm B received 8 mg/kg TRC105, split into 3 and 5 mg/kg and staggered; the starting dose was changed to 10 mg/kg once the phase 1 safety data became available. There were no other major changes to eligibility or treatment during the study.

The primary endpoint was PFS, which was evaluated using 2-point analysis (at 12 weeks and 24 weeks), as proposed by Freidlin and coworkers.[18] Withdrawal without radiographic evidence of stable disease or better was included as clinical progression, but this made no qualitative difference in the results. Imaging studies were obtained every 12 weeks ($\pm$1 week). In total, 88 patients were to be randomized to provide 80% power to detect an increase in PFS for the combination therapy from 61% to 78% at 12 weeks and from 37% to 60% at 24 weeks, with $\alpha = .1$. An interim analysis for futility was conducted after 44 patients had 12-week PFS evaluated.

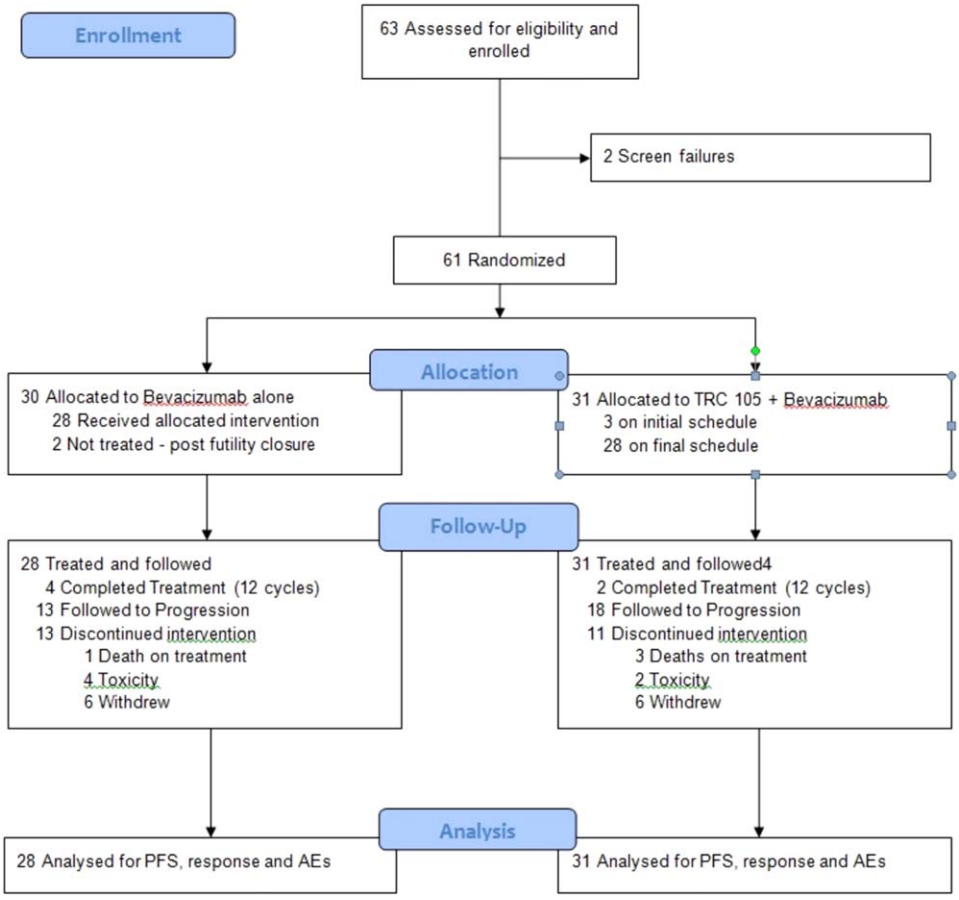

Figure 1. This is a Consolidated Standards of Reporting Trials (CONSORT) diagram depicting patient accrual and randomization in the current study. AEs indicates adverse events; PFS, progression-free survival; TRC, antiendoglin antibody.

Blood for correlative studies was drawn at baseline and before cycles 2 and 4. An enzyme-linked immunosorbent assay was performed using kits from Abcam (Cambridge, UK). Changes in serum TGFβ levels from baseline after treatment were evaluated and compared overall and between arms using a general linear mixed-effects model. Paraffin-embedded tissue samples from biopsy or nephrectomy were evaluated for expression of TGFβR1 and TGFβR2 and ACVRL by immunohistochemistry using antibodies from R&D Systems (Minneapolis, Minnesota). Tissue data and baseline enzyme-linked immunosorbent assay data were evaluated for association with PFS using Kaplan-Meier plots and the log-rank test.

RESULTS

After approval by individual institutional review boards for the participating centers, 59 patients were accrued. Enrollment commenced November 2012 and was halted in September 2014, when an interim analysis for futility revealed that the continuation criterion was unachievable. Accrual is summarized in the Consolidated Standards of Reporting Trials (CONSORT) diagram in Figure 1. Baseline and demographic characteristics are summarized in Table 1. Forty-six patients (78%) had clear cell histology, and 13 (22%) had nonclear cell RCC. Two patients on each arm had received only temsirolimus as their prior therapy, and 1 patient on arm A had only received erlotinib plus ARQ197 (tivantnib) on a clinical trial; otherwise, all patients were VEGF-pretreated. Of the 4 patients who had received only temsirolimus as prior therapy, there was a partial response (PR) with 12-month PFS on arm A, an unconfirmed PR with 12-month PFS on arm B, as well as progression at month 1 on each arm. The patient in arm A patient who had received pretreatment with ARQ197 plus erlotinib had stable disease and progressed at 9 months.

A summary of treatment administration and response is presented in Table 2. One patient on each arm had a confirmed PR, with stable disease in 8 of 28 patients

TABLE 1. Baseline and Demographic Characteristics of the Study Participants

Characteristic	No. of Patients (%)	
	Arm A: Bev Alone. N = 28	Arm B: Bev Plus TRC105, n = 31
Age: Median [range], y	58 [25-82]	65 [24-78]
Sex		
Men	20 (71)	24 (77)
Women	8 (29)	7 (23)
Ethnicity		
Hispanic	6 (21)	4 (13)
Asian	3 (11)	0 (0)
Black	2 (7)	2 (6)
Caucasian	17 (61)	25 (81)
Prior nephrectomy	22 (79)	22 (71)
Histology		
Clear cell	21 (75)	25 (81)
Papillary	2 (7)	1 (3)
Carcinoma, NOS	5 (18)	5 (16)
No. of prior lines of therapy		
1	9 (32)	9 (29)
2	10 (36)	12 (39)
3	8 (29)	7 (22)
4	1 (3)	3 (10)

Abbreviations: Bev, bevacizumab; NOS, not otherwise specified; TRC105, antiendoglin antibody.

TABLE 2. Treatment Summary, Including Cycles of Study Therapy and Best Radiographic Response

Variable	No. of Patients (%)	
	Arm A: Bev Alone, N = 28	Arm B: Bev + TRC105, N = 31
Median no. of cycles [range]	3 [1-12]	3 [1-12]
Reason for discontinuation		
Progression of disease	13 (46)	18 (64)
Toxicity	4 (14)	2 (6)
Treatment completed	4 (14)	2 (6)
Withdrew consent	6 (21)	6 (19)
Death	1 (3)	3 (10)
Best radiographic response		
CR	0 (0)	0 (0)
PR	1 (4)	1 (3)
SD	12 (36)	12 (39)
PD	8 (29)	11 (35)
No repeat imaging	7 (25)	7 (23)
PFS rate [range], %		
At week 12	69 [53-90]	56 [41-77]
At week 24	54 [37-79]	25 [13-47]
PFS: Median [range], mo	4.6 [1.8, NA]	2.8 [2.1-4.2]
Clear cell	3.35 [1.7, NA], n = 21	2.8 [1.9, NA], n = 6
Nonclear cell	5.5 [1.3, NA], n = 7[a]	3.2 [2.1, NA], n = 25

Abbreviations: Bev, bevacizumab; CR, complete response; NA, not applicable; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TRC105, antiendoglin antibody.
[a] This is based on a small number of events (3 of 7 patients in this subgroup).

(28.6%) on arm A and in 6 of 31 patients (19.4%) on arm B on at least 2 evaluations (≥24 weeks). The median PFS for the study population overall was 3.0 months (95% confidence interval [CI], 2.1-5.5 months), or 3.5 months if withdrawals without imaging were censored. The median PFS for Bev alone was 4.6 months, compared with 2.8 for Bev plus TRC105 ($P = .09$). Time-to-failure curves are presented in Figure 2 and are not significantly different (log-rank $P = .09$); this parameter was chosen to eliminate the effect of post-treatment follow-up on patients who did not progress. Because imaging times departed somewhat from the planned 12 and 24 weeks,

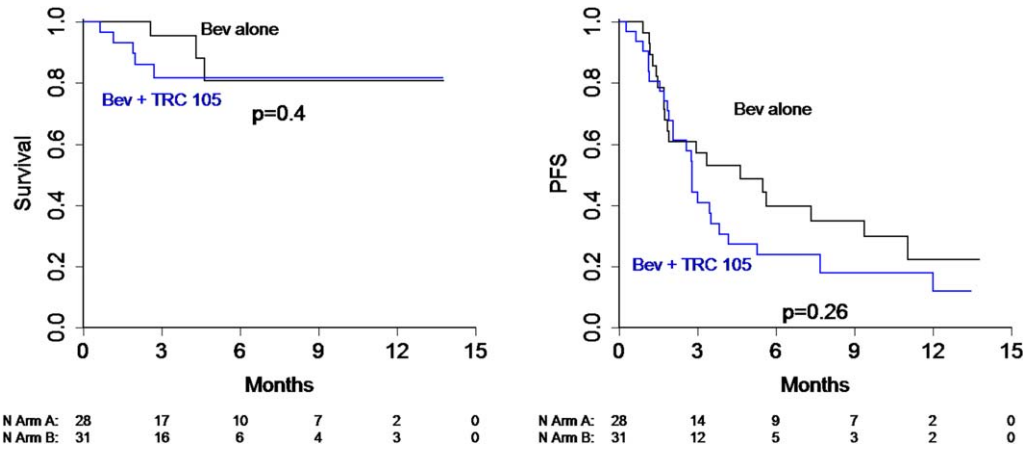

Figure 2. Kaplan-Meier Curves depict (A) overall survival and (B) time to treatment failure for the 2 study arms. Bev indicates bevacizumab; PFS, progression-free survival; TRC, antiendoglin antibody.

we note that 46% of patients receiving Bev alone, versus 42% of those receiving Bev plus TRC105, had a first evaluation of stable disease or better, whereas 29% and 23%, respectively, had a second evaluation of stable disease or better. PFS was similar for patients with clear cell versus nonclear cell histology (median PFS, 2.8 months on arm B vs 4.2 on arm A; log-rank $P = .26$).

Toxicities are summarized in Table 3. Grade 3 or higher toxicities occurred in 16 patients (57%) who received Bev alone compared with 19 (61%) who received Bev plus TRC105 ($P = .9$). Grade 3 or higher anemia, fatigue, pulmonary toxicities, and gastrointestinal toxicities were more common on the Bev plus TRC105 arm; whereas grade 3 or higher cardiac and bleeding events as well as proteinuria were more common with Bev alone. Bleeding from oral mucosa was the most common manifestation of bleeding on the TRC105 arm; whereas, on the Bev monotherapy arm, hemorrhage occurred more commonly from gastrointestinal or respiratory source.

In total, 54 patients (24 in arm A [Bev] and 28 in arm B [Bev plus TRC105]) had baseline serum samples sufficient for correlative study analysis; of these, 14 in arm A and 19 in arm B had both baseline and cycle 2 samples. Results are summarized in Table 4. The mean CD105 level was 82.8 pg/mL (95% CI, 64.6-106.2 pg/mL) at baseline. In patients who received Bev alone, serum CD105 (sCD105) levels did not increase post-treatment (mean, 59.03 pg/mL; 95% CI, 43.20-80.67 pg/mL). Post-treatment sCD105 levels were not evaluated in the Bev plus TRC105 arm because of the potential for assay interference. Mean TGFβ levels were 8.12 ng/mL (95% CI, 6.44-10.25 ng/mL) at baseline in arm A and increased to a mean of 13.24 ng/mL (95% CI, 8.44-20.75 ng/mL) at cycle 4; whereas mean baseline levels were 9.86 ng/mL (95% CI, 7.98-12.20 ng/mL) in arm B and decreased to 8.52 ng/mL (95% CI, 5.60-12.96 ng/mL) at cycle 4. These changes in TGFβ were not significant within groups ($P = .66$), nor were post-treatment levels significantly different between arms ($P = .17$). A baseline serum TGFβ level below the median (<10.6 ng/mL) was associated with longer median PFS (7.3 vs 2.6 months; $P = .02$), whereas the baseline CD105 level was not ($P = .83$). Tissue samples were available for 29 patients. No tissue markers (TGFβR1/TGFβR2 or ACVRL) were associated with longer PFS; except that, in exploratory analysis, higher TGFβR2 staining was associated with longer PFS in patients who received TRC105 (median PFS, 3.8 months for 11 patients with 2 + staining vs 1.8 months for 5 patients with 1 + staining and 2 patients with 0 staining; $P = .03$).

DISCUSSION

The primary endpoint of this randomized study was negative; namely, the addition of TRC105 to Bev failed to increase PFS significantly in a population of heavily pretreated patients with metastatic RCC. Nevertheless, the study yielded several important pieces of information. First, these data provide novel insight into responses and PFS with Bev monotherapy in the second-line setting and beyond. Prospective data have previously been unavailable to practicing physicians and can help inform discussions when considering the use of Bev monotherapy in VEGF-pretreated patients. One retrospective report identified 1 patient who received Bev plus interferon in the third-line

TABLE 3. Number and Percentage of Patients Who Experienced Each Adverse Event, Stratified by Treatment Arm and Severity (Common Toxicity Criteria for Adverse Events Grade 1 or 2 Versus Grade 3 or 4)

	No. of Patients (%)			
	Arm A: Bevacizumab, N = 28		Arm B: Bevacizumab + TRC105, N = 31	
Event	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
Cardiovascular				
Heart failure	2 (7)	0 (0)	0 (0)	0 (0)
Hypertension	8 (28.6)	5 (17.9)	11 (35.5)	4 (12.9)
Constitutional				
Fatigue	6 (21.4)	0 (0)	11 (35.5)	2 (6.5)
Anorexia	6 (21.4)	0 (0)	9 (29)	1 (3.2)
Infusion reaction	1 (3.5)	0 (0)	4 (12.9)	2 (6.5)
Rash	1 (3.5)	0 (0)	12 (38.7)	0 (0)
Gastrointestinal				
Abdominal pain	1 (3.5)	3 (10.7)	3 (9.7)	3 (9.7)
Nausea/vomiting	10 (35.7)	0 (0)	13 (41.9)	5 (16.1)
Hematologic				
Anemia	3 (10.7)	4 (14.3)	8 (25.8)	8 (25.8)
Bleeding	3 (10.7)	2 (7)[a]	9 (29)	0 (0)
Thrombocytopenia	5 (17.9)	0 (0)	2 (6.5)	0 (0)
Metabolic				
Hypercalcemia	4 (14.3)	0 (0)	2 (6.5)	2 (6.5)
Hyponatremia	0 (0)	1 (3.5)	9 (29)	2 (6.5)
Neurologic				
Dizziness	6 (21.4)	0 (0)	4 (12.9)	0 (0)
Headache	0 (0)	0 (0)	5 (16.1)	0 (0)
Renal				
Increased creatinine	6 (21.4)	0 (0)	4 (12.9)	0 (0)
Hematuria	4 (14.3)	0 (0)	2 (6.5)	0 (0)
Proteinuria	9 (32.1)	2 (7)	5 (16.1)	0 (0)

[a] One event was grade 5.

TABLE 4. Summary of Correlative Blood and Tissue Markers and Relation to Progression-Free Survival for All Patients (Both Arms Combined)

		PFS: Mean ± SD		
Correlate and Grouping for Analysis	No. of Patients	12-Week PFS	24-Week PFS	*P*[a]
TGF-β R1 (IHC staining)				
0	14	0.55 ± 0.14	0.46 ± 0.14	0.76
1-2	15	0.43 ± 0.13	0.32 ± 0.14	
TGF-β R2 (IHC staining)				
0-1	15	0.40 ± 0.13	0.30 ± 0.13	0.36
2	15	0.55 ± 0.14	0.46 ± 0.14	
ACVRL (IHC staining)				
0-1	16	0.38 ± 0.12	0.38 ± 0.12	0.43
2	13	0.57 ± 0.15	0.46 ± 0.16	
CD105 (ELISA), pg/mL				
<64.07	24	0.53 ± 0.11	0.37 ± 0.11	0.83
>64.07	24	0.57 ± 0.10	0.32 ± 0.11	
TGF-β (ELISA), ng/mL				
<10.60	24	0.78 ± 0.09	0.49 ± 0.12	0.022
>10.60	24	0.30 ± 0.10	0.19 ± 0.09	

Abbreviations: ACVRL, activin receptor-like kinase; CD105, cluster of differentiation 105 (endoglin); ELISA, enzyme-linked immunosorbent assay; IHC, immunohistochemistry; PFS, progression-free survival; SD, standard deviation; TGF-β R1, transforming growth factor β receptor 1; TGF-β R2, transforming growth factor β receptor 2.
[a] Log-rank *P* values are shown for the association with PFS.

setting with a PFS of 3 months, 2 treated in the fourth-line setting with a PFS of 1.6 months, and 5 treated in the fifth-line setting with a PFS of 26.2 months.[19] For benchmarking purposes, there has been a randomized trial in the third-line setting comparing 2 VEGF tyrosine kinase inhibitors, dovitinib and sorafenib, in which the median PFS was 3.6 months.[20] Thus, in the current trial, the overall population PFS of 3.5 months with Bev-based therapy

appears to be similar to the reported PFS attained using other agents in the salvage setting.

Second, the current trial included a substantial population of patients with nonclear cell RCC and presented unique data about the response to Bev in this group. Patients with mixed clear cell and nonclear cell were allowed on the registration trial of Bev/interferon, but outcomes were not reported separately for these groups.[14] In the current study, disease stabilization did occur in patients with nonclear cell RCC who received Bev alone or in combination, with similar PFS. Third, the toxicity profile in this study is notable for relatively few constitutional and gastrointestinal side effects, which contrasts with VEGF tyrosine kinase inhibitor therapy. This may become more relevant now, because there are increasing options for patients who have had previous exposure to VEGF therapy, and it may be useful to patients and physicians who are weighing the relative risks and benefits of treatment options.

In the current study, the high rate of patients (25%) who stopped therapy before radiographic evaluation may reflect the enrollment of rapidly progressing patients, who are less likely to benefit. Nevertheless, several hypotheses may also account for the negative trial results and the numerically inferior PFS in the combination group (2.8 months compared with 4.6 months for Bev alone). One possibility would be interference of the 2 antibodies with each other in vivo, which would explain the trend toward lower PFS rates at 12 and 24 weeks in the combination arm. However, the finding of no significant difference between arms in VEGF on-target toxicities, such as hypertension and proteinuria, argues against this hypothesis. Furthermore, the observation of responses and disease stabilization in the combination arm and the Bev-alone arm, without statistical inferiority, also suggests that VEGF inhibition occurred in the combination group. An unexpected pro-growth effect of TRC105 would be another possible explanation, but this is unlikely, because phase 1 and ongoing clinical trial data have not identified an increased risk of disease progression in patients who receive this agent. Serum CD105 levels actually decreased after treatment with Bev rather than increasing, contrary to the tissue preclinical data, in which CD105 expression is upregulated by VEGF inhibition. This could be an issue of targeting VEGF ligand rather than receptor, or tissue may be a better place to look for receptor signaling changes. An ongoing study of axitinib alone or in combination with TRC105 will provide further data regarding the utility of targeting CD105 upregulation as a way of preventing resistance to VEGF suppression (NCT01806064). A phase 1b study indicated that full-dose axitinib was tolerable with TRC105 dosed at 10 mg/kg and exhibited promising activity with a PR according to Response Evaluation Criteria in Solid Tumor (RECIST) reported in 5 of 17 patients (29%), some of whom were heavily pretreated.[21]

We also tested the hypothesis that tissue levels of TGFβ receptor expression would be related to treatment response: Because CD105 is required for heterodimerization and signaling activation by TGFβ, it was postulated that tumors using more TGFβ would be more sensitive to CD105 inhibition. Although the current study had limited power to detect differences, because relatively few patients had long PFS, and not all patients' samples were available for analysis, there was a hypothesis-generating finding of longer PFS among patients who had higher TGFβR2 expression when they received treatment with TRC105. Although it was not significantly different, the rise in mean serum TGFβ in arm A (without TRC105), compared with the decrease in arm B, suggests decreased TGFβ signaling with CD105 inhibition. This is provocative in terms of proof of concept, although the comparison was underpowered, and fits with emerging data from the study of TRC105 plus axitinib, in which investigators observed that higher plasma levels of TGFβR3 were associated with a greater likelihood of response.[22] Overall, these data support further study of TGFβ pathway expression to yield potential predictive markers in future studies of patients with advanced RCC, particularly in the setting of treatment with TRC105.

Conclusions

TRC105 added to Bev was not associated with longer PFS compared with Bev alone in the second-line through fourth-line treatment setting for patients with metastatic RCC. Bev is associated with poor activity in this population. TGFβ warrants further study as a biomarker in RCC.

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CONFLICT OF INTEREST DISCLOSURES

Tanya B. Dorff reports personal fees from Astellas, Bayer, Dendreon, Exelixis, Genentech, and Pfizer outside the submitted work. Sumata K. Pal reports personal fees from Alkermes, Aveo,

Dendreon, Eisai, Exelixis, Genentech, Ipsen, Medivation, Novartis, Pfizer, and Roche outside the submitted work. Walter M. Stadler reports personal fees from Alkermes, Bayer, Dendreon, Genentech, and Medivation. Mayer N. Fishman reports personal fees from Novartis; personal fees and research support from Alkermes, Bayer, Exelixis, Genentech, GlaxoSmithKline, and Pfizer; and research support from Amgen, Altor Bioscience, Astra-Zeneca, Aveo, Bristol-Myers Squibb, Eisai, Merck, Prometheus, and Tracon outside the submitted work. Ulka N. Vaishampayan reports personal fees from Aeterna-Zentaris, Astellas, Bayer, Dendreon, Janssen, and Millennium outside the submitted work. Amol Rao reports personal fees from Aeterna-Zentaris, Astellas, Bayer, Dendreon, Janssen, and Millennium outside the submitted work. Jacek K. Pinski reports personal fees from Aeterna-Zentaris, Amgen, Astellas, Bayer, Dendreon, Janssen, and Millennium outside the submitted work. James S. Hu reports personal fees from Eisai outside the submitted work. David I. Quinn reports personal fees from Exelixis, Genentech, Pfizer, Bayer, Peleton, and Merck outside the submitted work. Primo N. Lara, Jr, reports personal fees from Genentech and research support from Tracon outside the submitted work

AUTHOR CONTRIBUTIONS

Tanya B. Dorff: Clinical trial design, data curation–clinical, planning and analyzing correlative laboratory studies, provided input for statistical analyses, primary responsibility for day-to-day clinical trial management, writing–original draft, writing–review and editing, and project administration. **Jeff A. Longmate**: Clinical trial design, data curation–correlative, conducted main statistical analysis, writing–original draft, and writing–review and editing. **Sumanta K. Pal**: Day-to-day clinical trial management and writing–review and editing. **Walter M. Stadler**: Day-to-day clinical trial management and writing–review and editing. **Mayer N. Fishman**: Day-to-day clinical trial management and writing–review and editing. **Ulka N. Vaishampayan**: Provided input for statistical analyses and writing–review and editing. **Amol Rao**: Day-to-day clinical trial management and writing–review and editing. **Jacek K. Pinksi**: Performed correlative laboratory studies, day-to-day clinical trial management, and writing–review and editing. **James S. Hu**: Clinical trial design, day-to-day clinical trial management, and writing–review and editing. **David I. Quinn**: Clinical trial design, provided input for statistical analyses, day-to-day clinical trial management, writing–review and editing, and funding acquisition (with support from the California Cancer Consortium. **Primo N. Lara, Jr**: Clinical trial design, provided input for statistical analyses, day-to-day clinical trial management, writing–review and editing, and funding acquisition (with support from the California Cancer Consortium.

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