Introduction

Angiogenesis is a complex process that is regulated by multiple pathways (1, 2). Approved antiangiogenic drugs such as bevacizumab, sorafenib, sunitinib, and pazopanib primarily target the VEGF signaling pathway and are associated with modest survival advantages in select indications (3–8). Inhibition of non-VEGF pathways is a strategy that may improve antitumor activity and address resistance to anti-VEGF therapies.

CD105 is a homodimeric TGF-β coreceptor expressed on proliferating vascular endothelium in solid tumors (9). CD105 is selectively expressed at high density on angiogenic endothelial cells and is upregulated by hypoxia through induction of hypoxia-inducible factor-1-α (HIF-1-α; refs. 9, 10). CD105 expression is also upregulated on tumor endothelial cells following inhibition of the VEGF pathway (11, 12).

CD105 is essential for normal vascular development (13), and heterozygous expression of CD105 is associated with hereditary hemorrhagic telangiectasia type 1 (HHT-1, Rendu–Osler–Webber syndrome), a human disease characterized by ectatic blood vessel formation (14). In patients with solid tumors, high tumor microvessel density, as assessed by CD105 immunohistochemistry, has been correlated with poor prognosis (15, 16).

TRC105 (TRACON Pharmaceuticals, Inc.) is a chimeric IgG1 antibody that binds human CD105 with high avidity and induces antibody-dependent cellular cytotoxicity (ADCC) and apoptosis of human umbilical vein endothelial cells (HUVEC) and CD105-positive tumor cells (9). In preclinical experiments, SN6j, the murine parental
Translational Relevance

TRC105 is a therapeutic monoclonal antibody to CD105, a target that is expressed at high levels on endothelial cells. CD105 is the gold standard for measuring tumor microvessel density and promotes angiogenesis by altering TGF-β and BMP-9 signaling. By binding CD105, TRC105 inhibits angiogenesis and seems to have a safety profile distinct from VEGF inhibitors. This phase I first-in-human study presents safety, pharmacokinetics, and antitumor activity data in patients with advanced solid tumors that supports ongoing phase Ib and phase II studies of TRC105 in combination with chemotherapy, with VEGF inhibitors, and as a single agent in patients with advanced prostate, ovarian, breast, bladder, and hepatocellular cancer. More studies are planned in 2012, including randomized controlled studies in malignant glioma and renal cell cancer, and the results of this study will provide a valuable resource to clinicians involved in TRC105 clinical development.

monoclonal antibody (mAb) of TRC105 inhibited tumor growth and tumor angiogenesis (17, 18). The growth of human and syngeneic breast and colorectal cancer cell line xenografts was inhibited by monotherapy, whereas the antibody potentiated chemotherapy and was well tolerated, without dose-limiting toxicity, in animal models. TRC105 also showed synergy with bevacizumab in models of human angiogenesis.

Here we report the results of a first-in-human, open-label, phase I clinical study that assessed the safety, tolerability, pharmacokinetics, and antitumor activity of TRC105 in adult patients with advanced refractory solid tumors.

Patients and Methods

Patient eligibility

Eligible patients had histologically proven advanced or metastatic solid cancer for which curative therapy was unavailable, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function as shown by an absolute neutrophil count ≥1,500 cells/μL, hemoglobin ≥10 g/dL, platelets ≥100,000/μL, prothrombin time, or international normalized ratio ≤1.5 times the institutional upper limit of normal (ULN), creatinine ≤1.5 times the ULN, bilirubin ≤1.5 mg/dL, and aspartate and alanine transaminases ≤2.5 times the ULN (or ≤5 times the ULN in patients with liver metastases). Patients were excluded if they had a known history of central nervous system disease, lung cancer with a central chest lesion, thromboembolic disease, clinically significant ascites or pleural effusions, uncontrolled hypertension, required anticoagulation, or had received cancer therapy within 4 weeks before study entry. Patients were also excluded if they had a history of hemorrhage or unhealed surgical wounds within 30 days of study entry or were pregnant or lactating. All patients signed an Institutional Review Board–approved informed consent form before undertaking study-related procedures. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice (GCP) guidelines and all applicable local regulatory requirements and laws.

Study design and treatments

This was a multicenter first-in-human, phase I, open-label study (NCT00582985). The starting dose was calculated on the basis of the avidity of TRC105 for human CD105 (Kd = 5 pmol/L) and expected serum concentrations (based on drug distribution in cynomolgus monkeys) to deliver a dose that would bind target but not immediately saturate CD105-binding sites within the vasculature (19). The TRC105 dose was escalated in serial cohorts of patients using a standard 3 + 3 design, whereby if one of the initial 3 patients in a cohort developed dose-limiting toxicity, the cohort was expanded to evaluate 6 patients. Dose-limiting toxicity was defined as any grade 3 or higher hematologic or nonhematologic adverse event related to TRC105. The maximum tolerated dose (MTD) was defined as the highest dose that had an observed incidence of dose-limiting toxicity of less than 33% of patients per cohort. Patients who discontinued for reasons other than dose-limiting toxicity before completion of 28 days of therapy were replaced to ensure an adequate safety assessment of each cohort. TRC105 therapy continued until disease progression, unacceptable toxicity, or withdrawal of consent. Intrapatient dose escalation was not permitted. Patients were allowed to dose reduce for adverse events that resolved to grade 1 or baseline and were allowed to interrupt TRC105 dosing for up to 4 weeks following the 4 week dose-limiting toxicity evaluation period.

TRC105 was supplied as a PBS solution in single-use glass vials for intravenous administration. Before infusion, the agent was diluted in normal saline and infused using an in-line 0.2-micron low protein binding filter. The first 21 patients (cohorts 1 to 5A) were administered material produced in mouse myeloma NS0 cells at doses of 0.01, 0.03, 0.1, 0.3, and 1 mg/kg every 2 weeks infused over 1 hour without premedication. The last 29 patients (cohorts 4B to 12) were administered material produced in Chinese hamster ovary (CHO) cells at doses of 0.3, 1, 3, 10, and 15 mg/kg every 2 weeks (and also weekly at 10 and 15 mg/kg) infused over 1 to 4 hours and medicated for infusion reaction prophylaxis. The premedication regimen included acetaminophen 650 mg, diphenhydramine 50 mg (or similar H1 receptor antagonist), famotidine 20 mg (or similar H2 receptor antagonist), and dexamethasone (up to 24 mg in divided doses). The dexamethasone dose was gradually lowered and discontinued as tolerated.

Safety assessments

Safety was evaluated at regular intervals at baseline, during treatment, and for 28 days after completing study therapy. Vitals signs were recorded before and after every
infusion and weekly. Physical examination was done every 2 weeks. Hematology, serum chemistry, and coagulation parameters were analyzed weekly during the initial 4-week cycle and every 2 weeks thereafter.Urinalysis was carried out before dosing and every 4 weeks thereafter. Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Pharmacokinetics and immunogenicity
Sample serum samples for pharmacokinetic parameters were collected on days of the first and fourth dose before dosing, during infusion, immediately after infusion, and at 1, 2, 4 and 24, 72 and 120 hours following infusion. Samples were also collected before dosing and immediately after dosing during all additional dosing days and 4 weeks following the end-of-study visit. TRC105 concentration was determined using a validated ELISA with a limit of quantitation of 78 ng/mL (20). Pharmacokinetic parameters were estimated using serum concentration data following initial dosing in 16 patients at 3, 10, and 15 mg/kg. Observed parameters for each dose were the maximum serum concentration (Cmax), time of maximum serum concentration (Tmax), area under the serum concentration versus time curve extrapolated from time of the last measurable concentration to infinity (AUC0-∞), terminal half-life (t1/2), and clearance (CL). Serum for assessment of human antibody formation to the murine portion of TRC105 (human anti-murine antibody, HAMA) and human portion of TRC105 (human anti-chimeric antibody, HACA) was collected before dosing, every 4 weeks thereafter, and approximately 4 and 12 weeks following the last dose of TRC105. HAMA and HACA concentrations were determined by validated ELISA.

Evaluation of tumor response
Tumor responses were evaluated using CT or MRI per Response Evaluation Criteria in Solid Tumors (RECIST; ref. 21). Evaluations were carried out at 2-month intervals or earlier if disease progression was suspected. Serum tumor markers as appropriate for the tumor type were assessed at baseline and monthly thereafter.

Statistical analysis
The safety population included all patients who received at least a portion of the initial TRC105 infusion. The evaluable population for determination of response included all patients with a baseline and a follow-up radiographic assessment for response at designated time points (e.g., 2 and 4 months). Descriptive statistics (means, medians, SDs, and ranges for continuous data and percentages for categorical data) were used to summarize patient characteristics, treatment administration, safety, efficacy, pharmacokinetic, and pharmacodynamic parameters.

Results
Patient characteristics and disposition
Between January 2008 and November 2010, 50 patients with advanced or metastatic solid tumors were enrolled at 4 sites in the United States and treated with escalating doses of TRC105 at 0.01, 0.03, 0.1, 0.3, 1, 3, 10, and 15 mg/kg weekly every 2 weeks and then 10 and 15 mg/kg weekly. All received at least a portion of the first dose of TRC105, and 48 of 50 completed the 28-day dose-limiting toxicity evaluation period. Reasons for not completing the dose-limiting toxicity evaluation period were rapidly progressive disease in one patient at 15 mg/kg every 2 weeks who had subclinical brain metastases at baseline, and persistent grade 2 headache in a patient at 15 mg/kg weekly. Patients who were dosed every 2 weeks received a median of 4 TRC105 infusions, and patients who were dosed weekly received a median of 8 infusions. Baseline patient characteristics are presented in Table 1. At the time of this analysis, 33 patients had discontinued study therapy because of disease progression (confirmed radiographically in 27), 8 due to adverse events, 5 at the recommendation of the investigator, one per protocol for a dosing delay, and one who withdrew consent. Two patients, one with metastatic prostate cancer and one with metastatic uterine carcinosarcoma, remain on treatment at 48 and 18 months, respectively.

MTD and dose-limiting toxicity
Dose escalation proceeded stepwise until the top dose was reached. The MTD was exceeded at 13 mg/kg weekly, and the recommended phase II dose of TRC105 was, therefore, determined to be 10 mg/kg weekly. Three of 4 patients at 15 mg/kg weekly developed grade 3 hypoproliferative anemia (without leukopenia or thrombocytopenia) in month 2, and one of the 3 progressed to grade 4 in month 3. Bone marrow aspiration attempts in the patient with grade 4 anemia yielded insufficient material to permit evaluation of the cause of anemia. The patient was removed from study and his anemia resolved following discontinuation of treatment. Anemia was associated with accumulation of TRC105 and characterized by a low reticulocyte production index. Additional laboratory and clinical evaluations excluded common causes of anemia including blood loss, hemolysis, plasma volume expansion, inadequate erythropoietin, iron deficiency, and vitamin B-12 or folate deficiency. Anemia was manageable with standard supportive measures, including erythropoietin and blood transfusion. One patient required dose reduction from 10 to 7.5 mg/kg weekly for grade 3 anemia at month 12 and continues on therapy without further grade 3 anemia at month 18.

Safety and tolerability
Treatment-related adverse events occurring in more than one patient and all grade 3 and higher adverse events are listed by dose level in Table 2. The majority of treatment-related adverse events were grade 1 or 2. Infusion reactions, among the most common adverse events, were usually with the initial TRC105 dose and included one or more of the following signs or symptoms: rigors, bronchospasm, urticaria, hypertension, hypotension, tachycardia, or bradycardia. Infusion reactions were reported in 9 patients, including 6 with grade 2 (requiring
than was considered to be dose proportional (Table 3).

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Table 1. Baseline patient characteristics (N = 50)

| Age Median: 63 | Gender Female: 16 | Male: 34 |
| ECOG PS 0: 15 | Baseline ECOG performance status | ECOG PS 1: 35 |
| Cancer type Colon: 10 | Baseline number of prior regimens | Female: 16 |
| Prostate: 9 | Male: 34 | Male: 34 |
| Renal: 5 | Baseline number of prior regimens | Number of prior regimens |
| Lung: 4 | Median: 4 | Range: 1-13 |
| Ovarian: 3 | Cancer type | Other: 12 |
| Sarcoma: 3 | Breast: 2 | Other: 12 |
| Breast: 2 | Pancreatic: 2 | Other: 12 |

temporary interruption of the infusion) and 3 with grade 3 reactions (requiring discontinuation of the infusion).

Infusion reactions were initially reported at 1 mg/kg every 2 weeks for patients receiving TRC105 produced in NS0 cells without premedication. TRC105 produced in CHO cells was known to more potently engage ADCC in vitro than TRC105 produced in NS0 cells. Because of this, the initial dose level for patients receiving CHO-produced TRC105 was deescalated to 0.3 mg/kg. Despite dose deescalation, the first 2 patients at 0.3 mg/kg treated with CHO-produced TRC105 experienced grade 2 and grade 3 infusion reactions with the first dose in the absence of premedication. The protocol was therefore amended to require a dexamethasone-based premedication regimen and extend the initial infusion duration from 1 to 4 hours.

The amendment mandating premedication and an extended initial infusion duration successfully reduced the frequency and severity of infusion reactions and allowed dose escalation to continue. One additional patient who received CHO-produced TRC105 at 1 mg/kg developed a grade 3 infusion reaction with the third dose given over 2 hours. This patient had experienced a grade 2 infusion reaction when the dose was administered over 4 hours. In all 3 patients with grade 3 infusion reactions, TRC105 was not detectable in serum at the time of dosing, which allowed de novo binding of TRC105 to CD105 expressing endothelium within the vasculature. Grade 3 infusion reactions were not observed in patients dosed at 10 or 15 mg/kg who maintained TRC105 serum levels known to saturate CD105-binding sites for the full dosing interval. At dose levels at which continuous TRC105 serum levels were achieved, dexamethasone was safely discontinued and the infusion duration reduced to 1 hour.

Three patients developed grade 1 cutaneous telangiectasias on the trunk early in the course of therapy, all at dose levels of 10 or 15 mg/kg weekly that resulted in continuous serum levels of TRC105 known to saturate CD105 sites on human endothelium. Grade 1 or 2 hemorrhage was reported, including intermittent postcoital vaginal bleeding (that also occurred before TRC105 treatment), epistaxis, and superficial gingival bleeding.

Grade 1 or 2 headaches were observed, mainly in patients treated at doses of TRC105 above 3 mg/kg (Table 2). Headaches began the day following infusion and were generally manageable with acetaminophen. However, grade 2 headache in one patient at 15 mg/kg weekly prompted discontinuation before completion of the dose-limiting toxicity evaluation period. Fatigue was one of the more common adverse events attributable to TRC105 and was more prevalent at doses above 3 mg/kg (Table 2).

Classic toxicities associated with VEGF inhibition, including hypertension, proteinuria, and thrombosis, were not prominent. One patient with recurrent anal cancer treated at 0.1 mg/kg developed proteinuria considered possibly related to TRC105, but proteinuria was also noted before TRC105 dosing. Transient hypertension (156/112) without QT changes occurred in a single patient one day following infusion of 15 mg/kg and was controlled by a single dose of oral antihypertensive medication. There were no arterial or venous thromboembolic events nor gastrointestinal or other perforations in these patients.

One patient developed dose-limiting toxicity of grade 4 hemorrhage presenting as melena from a gastric ulcer within 5 days of the initial TRC105 infusion at 0.1 mg/kg. He discontinued TRC105 treatment, was transfused 2 units of packed red blood cells, and the bleeding resolved with nonsurgical management by the time of upper endoscopy. Serious bleeding was not observed following protocol amendment to exclude patients with a history of peptic ulcer disease (unless healing was documented) and patients on ulcerogenic medications, including nonsteroidal anti-inflammatory drugs.

Pharmacokinetics and immunogenicity

TRC105 was detectable at all dose levels immediately after intravenous infusion. In patients enrolled at doses below 0.3 mg/kg every 2 weeks, circulating TRC105 was detectable but not measurable above the lower limit of quantitation of the assay (78 ng/mL). On an every 2-week schedule, TRC105 was measurable above the target concentration that saturates CD105 receptors (200 ng/mL) for a duration of 4 hours at a TRC105 dose of 0.3 mg/kg, for 24 hours at 1 mg/kg, 120 hours at 3 mg/kg, and 188 hours at 10 mg/kg (Fig. 1). The observed terminal t1/2 was considerably prolonged following a single dose of 15 mg/kg compared with 3 and 10 mg/kg (Table 3). Serum concentrations expected to saturate CD105 binding sites (> 200 ng/mL) were achieved continuously at 15 mg/kg dosed every 2 weeks and 10 mg/kg dosed weekly, and TRC105 accumulated at 15 mg/kg dosed weekly (Fig. 1). At doses above 1 mg/kg, AUC increased supraproportionally with dose, whereas the Cmax seemed to be dose proportional (Table 3 and Fig. 1).
Table 2. Possibly related adverse events in more than one patient and all grade 3 and 4 events (N = 50)

<table>
<thead>
<tr>
<th>Drug supply</th>
<th>Adverse event</th>
<th>Infusion reaction</th>
<th>Anemia</th>
<th>Fatigue/malaise</th>
<th>Headache</th>
<th>Telangiectasia</th>
<th>Epistaxis</th>
<th>Pain</th>
<th>Vomiting</th>
<th>Arthralgia</th>
<th>Constipation</th>
<th>Diarrhea</th>
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NOTE: Dose-limiting toxicities are given in bold and italicized. qwk, every week.
In patients administered NS0-produced TRC105 (0.01 to 1 mg/kg), HAMA and HACA were detected in 9.5% and 35% of patients, respectively. The presence of HAMA or HACA did not correlate with infusion reactions or other clinical adverse events. In patients treated with CHO-produced TRC105 (0.3 to 15 mg/kg), neither HAMA nor HACA were detected.

Antitumor activity

Overall, 21 of 45 evaluable patients were progression free at 2 months and 6 of 44 were progression free at 4 months. One patient with castrate-refractory prostate cancer remains on TRC105 therapy at 48 months at 0.01 mg/kg every 2 weeks with normalization of prostate specific antigen (PSA) levels, resolution of bone pain and significant improvement on bone scan. This 63 year old man underwent radical prostatectomy, pelvic lymph node dissection, and postoperative pelvic external beam radiation therapy for non-metastatic prostate cancer. He developed a rising PSA and diffuse skeletal metastases while being treated with leuprolide and bicalutamide that continued to rise over the subsequent five weeks following discontinuation of bicalutamide up to a maximum value of 155. Within 2 months of initiating TRC105 therapy, the bone scan markedly improved and the PSA became undetectable. The patient remains on study therapy with an undetectable PSA and improved bone scan at 48 months (Fig. 2). PSA decreases (25 and 49%) were noted in two of the five other prostate cancer patients for whom PSA data were available, all of whom were castrate-resistant and chemotherapy treated, but who progressed between two and five months following initiation of treatment with TRC105.

A patient with metastatic chemotherapy-refractory uterine carcinosarcoma remained on TRC105 at 18 months with an ongoing minor radiographic response first detected 2 months after initiation of treatment as reductions in the diameters of each of 5 pulmonary metastases (Fig. 3). An overall reduction in the sum of tumor diameters between 7% and 13% has been noted during treatment. She was enrolled at 10 mg/kg weekly and was dose reduced to 7.5 mg/kg weekly at month 12 for grade 3 anemia. The duration of TRC105 treatment has exceeded the duration of 3 prior treatments: carboplatin and paclitaxel (4 months), anastrozole (8 months) and ifosfamide (2 months), each of which was discontinued for progressive disease.

Reductions in serum CEA (3%–11%), PSA (25%–99%), or CA-125 (17%–35%) levels were noted in 7 of 21 evaluable patients with relevant tumor markers, including a patient with metastatic ovarian cancer who progressed following platinum-based chemotherapy, pegylated liposomal doxorubicin and topotecan and showed stable

<p>| Table 3. TRC105 pharmacokinetic at 3, 10, and 15 mg/kg |</p>
<table>
<thead>
<tr>
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<th>3 mg/kg</th>
<th>10 mg/kg</th>
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<td>$C_{\text{max}}, \text{µg/mL}$</td>
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<tr>
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<tr>
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disease by CT scan for 6 months following initiation of TRC105 treatment.

Discussion

This is the first human study of TRC105, a novel IgG1 mAb to human CD105. CD105 is a proangiogenic TGF-β membrane coreceptor that is selectively expressed at very high density on proliferating endothelial cells (9).

On-target effects of TRC105 administration were observed, including hypoproliferative anemia, infusion reactions, and telangiectasias that were sometimes associated with mild superficial mucosal bleeding. The dose-limiting toxicity of single-agent TRC105 was hypoproliferative anemia associated with drug accumulation at 15 mg/kg weekly. The anemia is believed to result from TRC105-mediated suppression of proerythroblasts, the only cells in the bone marrow known to express substantial levels of CD105 (22). The anemia was easily monitorable, reversible, and treatable without adverse sequelae.

Three patients developed grade 1 cutaneous telangiectasias early in the course of therapy, at 10 and 15 mg/kg weekly. Telangiectasias are a notable clinical feature of patients with HHT-1, a genetically inherited disease.
characterized by mutation of one copy of the CD105 gene (23). This condition of CD105 haplotype insufficiency results in the development of cutaneous and mucosal telangiectasias that commonly lead to epistaxis and gingival bleeding. Telangiectasias have also been reported with developmental therapeutics that target the CD105 signaling axis, including an antibody to ALK1 and an ALK1 receptor IgG1 fusion protein (24, 25). Development of telangiectasias may represent a class effect for therapies targeting the CD105 pathway and serve as a pharmacodynamic confirmation of on-target effects. Interestingly, HHT-1 has been treated successfully with bevacizumab, suggesting potentially complementary roles for VEGF and TGF-β superfamily signaling in angiogenesis and a potential role for a combination therapy approach (26).

Three patients developed grade 3 infusion reactions. Infusion reactions are a known risk of therapeutic antibodies that bind cellular targets, and the risk may be highest for antibodies with potent cytotoxic activity against intravascular cellular targets (e.g., rituximab in chronic lymphocytic leukemia). TRC105 is an IgG1 antibody that engages ADCC at low concentrations in vitro upon binding proliferating endothelium. Modest infusion reactions were expected during dose escalation in the absence of premedication and were evident at doses of 0.3 to 1 mg/kg. These events generally occurred early in the course of therapy, usually with the initial TRC105 dose. Infusion reactions were more prominent with CHO-produced TRC105 that has a higher degree of afucosylated glycans and therefore more potent ADCC activity than TRC105 from NS0 cells. Infusion reactions were not observed in patients with measurable TRC105 serum levels at the time of redosing, where de novo binding of target did not occur.

Infusion reactions beyond the initial doses, or those associated with hypersensitivity to TRC105 that might be manifestations of immunogenicity, were not observed in the trial. Host anti-TRC105 antibodies were detected in patients administered NS0-produced TRC105 but not in patients treated with CHO-produced TRC105 that is being used in phase Ib and phase II trials. The immunogenicity of NS0-produced TRC105 was not surprising because the glycosylation of antibodies produced in NS0 cells results in the attachment of immunogenic oligosaccharides (e.g., galactose-α-1,3-galactose) that are not present in antibodies manufactured from CHO cells (27). In general, the risk of immunogenicity to therapeutic chimeric antibodies produced in CHO cells is small (<10%), and the clinical significance of immunogenicity is not well understood (28).

TRC105 pharmacokinetic analyses revealed continuous serum levels at a dose and schedule of 10 mg/kg weekly and 15 mg/kg every 2 weeks, and both dose levels are being studied in ongoing phase II trials. Notably, the development of telangiectasias and other on-target effects including tumor burden reductions were noted with continuous or prolonged dosing.

TRC105 treatment resulted in durable stable disease in a variety of refractory tumor types. Two patients, one patient with castrate-resistant prostate cancer and one with metastatic uterine carcinosarcoma, continue to derive clinical benefit from ongoing TRC105 therapy for more than 1 year. The response in the patient with prostate cancer was particularly dramatic and is ongoing at 4 years.

Reductions in CA-125 were noted in ovarian cancer patients, and a patient with metastatic uterine carcinosarcoma showed a minor response that exceeded the duration of treatment of 3 prior regimens. CD105 expression has been detected on ovarian cancer cells in addition to the tumor vasculature (29). Melanoma, renal cell carcinoma, extramedullary plasmacytoma, immature B-lineage acute lymphoblastic leukemia, and acute myelomonocytic leukemia represent other malignancies in which CD105 expression has been reported on tumor cells in addition to the tumor vasculature (30–33).

In summary, TRC105 is a novel targeted therapy that is well-tolerated at clinically relevant doses. On the basis of results from this phase 1 trial, multiple phase II clinical studies are ongoing to evaluate TRC105 alone and in
combination with other agents in a wide variety of cancer types. Adverse events commonly associated with VEGF inhibitors (e.g., hypertension, proteinuria, and thrombosis) were not associated with TRC105, suggesting that TRC105 may be combined safely with VEGF-targeted agents to enhance clinical benefit. Ongoing studies are testing TRC105 in combination with chemotherapy and VEGF inhibitors and as a single agent in patients with advanced prostate, ovarian, bladder, breast, and hepatocellular cancer. CD105 has been shown to be a useful marker for imaging tumor angiogenesis and further planned clinical studies incorporate positron emission tomography and MRI to further assess effects of TRC105 on the tumor vasculature (34).

Disclosure of Potential Conflicts of Interest
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Authors’ Contributions

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