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AN OPEN LABEL PHASE 1B DOSE-FINDING STUDY OF TRC105 (ANTI-ENDOGLIN ANTIBODY) COMBINED WITH CAPECITABINE FOR PROGRESSIVE OR RECURRENT METASTATIC BREAST CANCER

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INTRODUCTION

- TRC105 is a chimeric IgG1 anti-endoglin monoclonal antibody with high avidity (K_D = 5 pM)
- Endoglin is a membrane receptor that is highly expressed by proliferating endothelial cells in solid tumors (Seon 2011). Endoglin is required for angiogenesis and its expression is up-regulated by hypoxia in response to VEGF inhibition (Bockhorn 2003, Davis 2004); mice that lack endoglin die *in utero* (Li 1999)
- High tumor microvessel density as measured by endoglin immunohistochemistry correlates with poor prognosis in more than 10 solid tumor types, including breast cancer
- TRC105 inhibits angiogenesis in response to VEGF and basic FGF (Nolan-Stevaux 2012) and induces ADCC
- TRC105 potentiates the activity of VEGF inhibitors in preclinical models
- Endoglin is expressed on renal cell cancer stem cells (Bussolati 2008) and select solid tumors, including sarcoma
- The MTD of TRC105 given as a single agent was 10 mg/kg by weekly intravenous infusion. Dose escalation was limited by anemia, an on-target effect of TRC105 treatment, without significant hypertension or proteinuria. Telangiectasia, a characteristic finding of endoglin receptor modulation, were observed routinely at the MTD and immunogenicity was not observed (Rosen 2012)

OBJECTIVES

- Evaluate the safety and tolerability of escalating doses of intravenous TRC105 when added to capecitabine in patients with advanced solid tumors (dose escalation) and then in patients with Her-2-negative breast cancer (expansion cohort)
- Evaluate pharmacokinetics, immunogenicity, and tumor response

METHODS

Study Design

- Phase 1b, open-label, 3 + 3 dose-escalation study conducted at 2 US centers
- Dose expansion in patients with Her-2-neu negative breast cancer was permitted following identification of MTD

Key Inclusion Criteria

- Advanced incurable solid cancer (dose escalation portion)
- Her-2-negative breast cancer (expansion cohort)
- ECOG PS of 0 or 1
- Adequate organ function
- Hemoglobin ≥ 9 g/dL

Dose Levels

Cohort	TRC105 Weekly (21 Day Cycle)	Capecitabine Days 1-14 (21 Day Cycle)
1	7.5 mg/kg	1,000 mg/m^2 BID
2	10 mg/kg	1,000 mg/m^2 BID

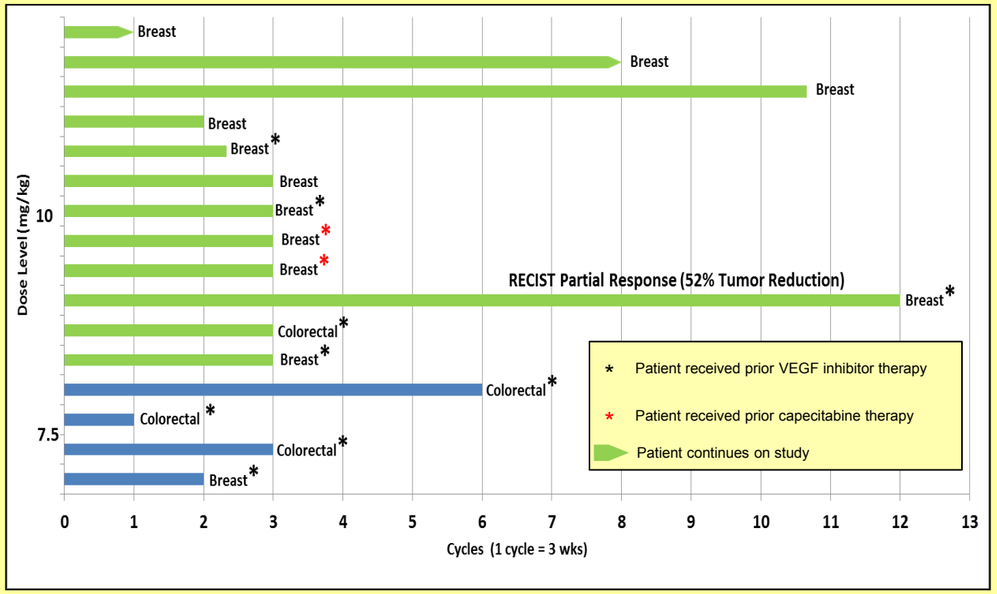
Key Exclusion Criteria

- CNS disease
- Prior treatment with more than one systemic chemotherapy regimen for metastatic disease (expansion cohort)
- Prior cancer therapy within 4 wks
- Major surgery within 4 wks
- Major bleeding within 6 mo

RESULTS

Duration of Participation

(Four patients were enrolled at 7.5 mg/kg TRC105 and three patients were enrolled at 10 mg/kg TRC105 prior to dose expansion at 10 mg/kg)



Patient Demographics

Baseline Patient Characteristics (N=16)	
Age	Median: 51 Range: 33-70
Gender	Female: 12 Male: 4
Baseline ECOG Performance Status	ECOG PS 0: 7 ECOG PS 1: 9
Number of Prior Regimens	Median: 3 Range: 1-8
Cancer Type	Breast: 12 Colorectal: 4

Immunogenicity

HAMA Positive	HACA Positive
1 of 11 (9%)	0 of 11 (0%)

Pharmacokinetics

	Mean Peak TRC105 Concentration (µg/mL)	Mean Trough TRC105 Concentration (µg/mL)
7.5 mg/kg/wk TRC105 +Capecitabine (n=4)	128.3 ± 60.27	0.563 ± 0.261
10 mg/kg/wk TRC105 +Capecitabine (n=11)	239.7 ± 94.64	9.72 ± 18.90

TRC105 serum levels above the target concentration of 200 ng/mL (Rosen 2012) were observed continuously in all patients dosed with 10 mg/kg of TRC105

Efficacy

- RECIST-defined partial response occurred in a heavily pretreated 53 year old male breast cancer patient who remained on study for 9 months
  - The patient received 6 prior regimens, and progressed within 2.5 months on each regimen
  - Progression on the most recent regimen (bevacizumab/paclitaxel) occurred after 6 weeks
- Stable disease beyond 9 weeks was observed in three additional patients

Safety

Most Common (N >1) and all Grade 3 and 4 TRC105 Drug-Related Adverse Events

	Maximum Grade				Total N = 15	
Preferred Term[a,b,c]	Grade 1	Grade 2	Grade 3	Grade 4	n	Percent
Headache	2	3	1*		5	33%
Vomiting	2		1		3	20%
Blood alkaline phosphatase increased			1		1	7%
Fatigue	2	3			5	33%
Nausea	1	2			3	20%
Infusion related reaction	1	2			3	20%
Rash	1	1			2	13%
Epistaxis	7				7	47%
Gingival bleeding	6				6	40%
Onychoclasis	2				2	13%
Flushing	2				2	13%
Telangiectasia	2				2	13%

*A Grade 3 headache occurred prior to splitting the first dose of TRC105 over 2 days
[a]Includes grade 1 or 2 AEs occurring in more than one patient and all grade 3 or higher adverse events
[b]Adverse Events were Drug-Related if they were considered at least possibly related to TRC105
[c]Adverse Events were coded by using MedDRA dictionary version 14.1

- Dose escalation to the recommended Phase 2 dose of both drugs was well tolerated
- Adverse events characteristic of each individual drug were not increased in frequency or severity when the two drugs were administered together
- A single dose limiting toxicity of Grade 3 headache was observed in one patient in the expansion cohort; as a result, the initial TRC105 dose was split over two days, and Grade 3 headache did not recur
- Low grade headaches were treated with acetaminophen and NSAIDs
- Mucocutaneous telangiectasia (or associated epistaxis and gingival bleeding), an on-target manifestation of endoglin receptor modulation, were observed consistently at the top dose level of 10 mg/kg of TRC105
- Rare low grade adverse events included infusion reaction and fatigue

SUMMARY & CONCLUSIONS

- The combination of 10 mg/kg TRC105 and 1,000 mg/m^2 capecitabine was well tolerated
- TRC105 serum levels above the target concentration were maintained continuously at the 10 mg/kg dose level
- Telangiectasia, an on-target manifestation of endoglin receptor modulation, was dose dependent
- Immunogenicity was rarely observed and was not associated with clinical sequelae
- Partial response by RECIST was observed in a heavily pretreated male breast cancer patient and stable disease was observed in three additional patients
- TRC105 was combined safely with capecitabine; the combination treatment could be advanced in HER-2-negative breast cancer or colorectal cancer

REFERENCES

- Bockhorn M, Clinical Cancer Research 9:4221-4226, 2003
- Bussolati B, FASEB 22:3696-3705, 2008
- Davis DW, Cancer Research 64:4601-4610, 2004
- Li DY, Science 284:1534-1537, 1999
- Nolan-Stevaux O, PLOS One e50920, 7:1-12, 2012
- Rosen L, Clinical Cancer Research 18:4820-9, 2012
- Seon BK, Current Drug Delivery 8:135-143, 2011