AN OPEN LABEL PHASE 1B DOSE ESCALATION STUDY OF TRC105 (ANTI-ENDOGLIN ANTIBODY) COMBINED WITH STANDARD DOSE BEVACIZUMAB FOR ADVANCED SOLID TUMORS

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Abstract: 3059

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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
- 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 standard dose bevacizumab in patients with advanced solid tumors
- Evaluate pharmacokinetics, immunogenicity, and tumor response

METHODS

Study Design

- Phase 1b, open-label, dose-escalation study conducted at 4 institutions in the United States

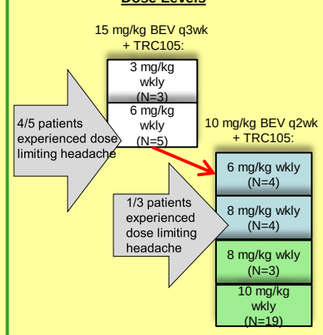
Key Inclusion Criteria

- Advanced incurable solid cancer
- ECOG PS of 0 or 1
- Adequate organ function
- Hemoglobin ≥ 9 g/dL

Key Exclusion Criteria

- Lung cancer with central tumor
- Prior cancer therapy within 3 wks
- Major surgery within 4 wks
- Major bleeding within 6 mo

Dose Levels



TRC105 wkly + 15 mg/kg Bev q3wk

TRC105 wkly + 10 mg/kg Bev q2wk (1st dose of TRC105 staggered 1 week after 1st Bev dose)

TRC105 wkly + 10 mg/kg Bev q2wk (1st dose of TRC105 staggered 1 week AND split over 2 days)

RESULTS

Demographics

Baseline Patient Characteristics (N=38)	
Age	Median: 64 Range: 43-83
Gender	Female: 23 Male: 15
Baseline ECOG Performance Status	ECOG PS 0: 14 ECOG PS 1: 24
Number of Prior Regimens	Median: 4 Range: 0-9
Cancer Type	Colorectal: 17 Ovarian: 11 Renal Cell: 2 Hepatocellular: 2 Non-Small Cell Lung: 1 Cervical: 1 Endometrial: 1 Hemangioendothelioma: 1 Esthesioneuroblastoma: 1 Peritoneal: 1

Immunogenicity

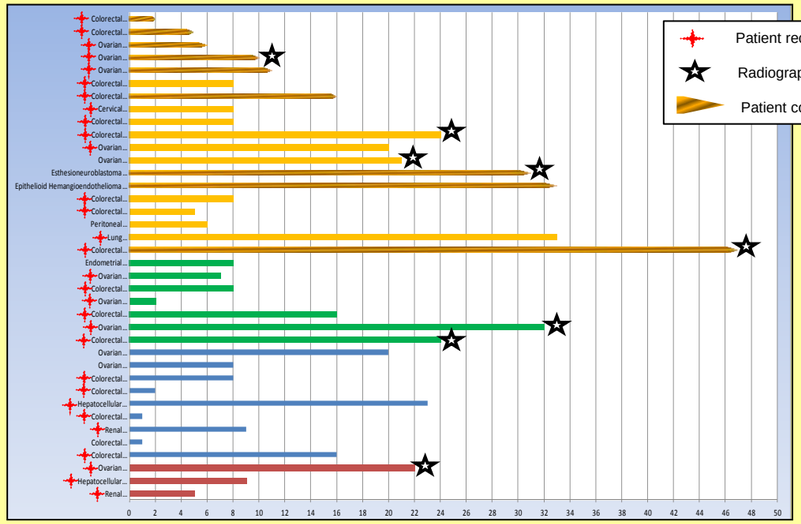
HAMA Positive	HACA Positive
2 of 30 (7%)	2 of 30 (7%)

Pharmacokinetics

	Mean TRC105 Peak Concentration (µg/mL)	Mean TRC105 Trough Concentration (µg/mL)
3 mg/kg/wk TRC105+Bev (n=4)	38.65 ± 27.63	0 ± 0
6 mg/kg/wk TRC105+Bev (n=9)	61.59 ± 18.02	0.35 ± 0.35
8 mg/kg/wk TRC105+Bev (n=7)	134.5 ± 32.39	0.53 ± 0.36
10 mg/kg/wk TRC105+Bev (n=16)	191.1 ± 50.30	0.60 ± 0.22

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

Duration of Participation (Wks)

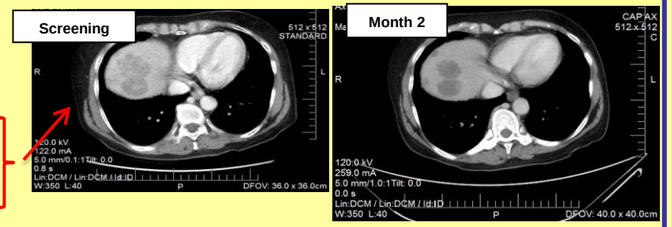


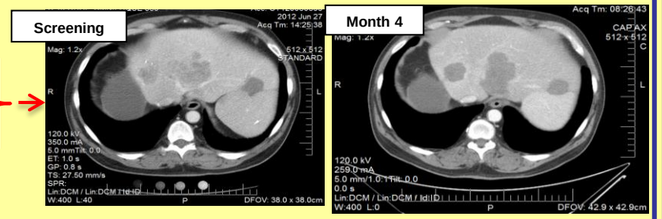
- **Radiographic responses were noted in 8 of 30 (27%) evaluable pts including in 6 of 23 (26%) patients who progressed following prior Bev or VEGF TKI treatment**
- **9 patients remain on treatment with TRC105 + Bev (range: 1 to 11 months)**

Efficacy

Radiographic responses in patients who progressed on prior Bev/VEGF TKI

- 57 yo woman with OVCA treated with 7 prior regimens, incl. Bev + Doxil (PD after 4 mo), had TTP of 5 mo with a 10% tumor reduction at 3 mg/kg TRC105 + Bev
- 66 yo woman with CRC treated with 7 prior regimens (Bev given with 4 prior regimens), who progressed after 1 mo of treatment with Cetuximab + Bev had TTP of 5 mo with a 35% decrease in CEA and 16% tumor reduction at 8 mg/kg TRC105 + Bev
- 71 yo woman with OVCA treated with 5 prior regimens, (PD on VEGFR TKI after 5 mo), had TTP of 7 mo with a 17% reduction in tumor burden at 8 mg/kg TRC105 + Bev
- 56 yo man with CRC treated with 3 prior regimens, who failed FOLFOX + Bev and FOLFIRI + Bev had TTP of 5 mo with a 12% tumor reduction at 10 mg/kg TRC105 + Bev
- 53 yo man with CRC failed FOLFIRI + Bev and then irinotecan + Bev immediately prior to study entry is ongoing in mo 11 of treatment with a 82% decrease in CEA (to normal) and 25% tumor reduction at 10 mg/kg TRC105 + Bev
- 81 yo woman with OVCA treated with 7 prior regimens, including Bev + Topotecan for 3 mo, is ongoing at month 3 of treatment with a 35% decrease in CA125 and 24% tumor reduction at 10 mg/kg TRC105 + Bev





Safety

Most Common (N >1) and all Grade 3 and 4 TRC105 Drug-Related Adverse Events (N=36 Patients)

Preferred Term[a,b,c]	Maximum Grade				Total N = 36	
	1	2	3	4	n	Percent
Headache	14	10	4*		28	77.80%
Anaemia	1	4	3		8	22.20%
Infusion related reaction		9	1		10	27.80%
Fatigue		5	1		6	16.70%
Decreased appetite		2	1		3	8.30%
Face oedema	1	4			5	13.90%
Epistaxis	18	2			20	55.60%
Telangiectasia	15	1			16	44.40%
Flushing	6	1			7	19.40%
Diarrhoea	2	1			3	8.30%
Nausea	2	1			3	8.30%
Gingival bleeding	8				8	22.20%
Rash	3				3	8.30%
Oral pain	2				2	5.60%
Migraine	2				2	5.60%
Sinus headache	2				2	5.60%
Erythema	2				2	5.60%

*All Grade 3 headaches 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 are 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 when the TRC105 dose was staggered by one week following the initial Bev dose and split over two days.
- Grade 3 headache was the only dose limiting toxicity observed and occurred only prior to splitting the initial TRC105 dose over two days
- Low grade headaches at the recommended Phase 2 doses of both drugs were treated with acetaminophen and NSAIDs
- Telangiectasia (with associated epistaxis and gingival bleeding), an on-target manifestation of endoglin receptor modulation, was dose dependent
- Rare low grade adverse events included anemia, infusion reaction, and fatigue

SUMMARY & CONCLUSIONS

- 10 mg/kg TRC105 and 10 mg/kg Bev were well tolerated when delaying the initial dose of TRC105 by one week and splitting the initial dose over two days
- Continuous TRC105 serum levels above the target concentration were maintained continuously in all patients 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
- Antitumor activity (radiographic responses with tumor marker reductions) was observed in patients who progressed on prior Bev, and these patients had longer time to tumor progression on Bev + TRC105 than on the prior Bev containing regimen
- Based on the results of this study of TRC105 + Bev, TRC105 is now being studied in two randomized Phase 2b studies with Bev in renal cell cancer and glioblastoma (NCT01727089 and NCT01648348)

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