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TRC105 (Anti-endoglin Antibody) in Combination with Bevacizumab (BEV) and as a Single Agent for Platinum Resistant Ovarian Cancer

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INTRODUCTION

- TRC105 is a chimeric IgG1 anti-endoglin monoclonal antibody with very high avidity (K_D = 5 pM)
- Endoglin is a membrane receptor required for angiogenesis (Li 1999) 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)
- High tumor microvessel density as measured by endoglin immunohistochemistry correlates with poor prognosis across more than 10 solid tumor types including ovarian cancer
- Reduced endoglin expression is associated with the Osler-Weber-Rendu syndrome that results in telangiectasia and is associated with improved cancer survival (Duarte 2013)
- TRC105 inhibits VEGF-driven and bFGF-driven angiogenesis (Nolan-Stevaux 2012) and mediates ADCC
- TRC105 potentiates the activity of VEGF inhibitors in preclinical models
- 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

- Describe the safety and efficacy of intravenous TRC105 given as a single agent and when combined with BEV in patients with advanced metastatic ovarian cancer
- Evaluate pharmacokinetics and immunogenicity

METHODS

- Patients with advanced metastatic ovarian cancer, who were treated with escalating doses of IV TRC105 (3, 6, 8 or 10 mg/kg/wk) plus BEV at 15 mg/kg q3wk or 10 mg/kg q2wk (n=11) in a phase 1b trial were compared with patients with advanced metastatic ovarian cancer, who were treated with 10 mg/kg/wk TRC105 as a single agent (n=23) in a phase 2 trial
- Patients were assessed for safety, PK, immunogenicity and response
- Key Inclusion criteria included: ECOG PS of 0 or 1, adequate organ function, and hemoglobin ≥ 9 g/dL
- Key exclusion criteria included: Prior cancer therapy within 4 weeks, major surgery within 4 weeks, and major bleeding within 6 months

RESULTS

Patient Demographics

	TRC105 Single Agent (N=23)	TRC105 + BEV Combination (N=11)
Age	Median: 63 Range: 26-81	Median: 65 Range: 53-82
Baseline ECOG Performance Status	ECOG PS 0: 19 ECOG PS 1: 4	ECOG PS 0: 6 ECOG PS 1: 5
Number of Prior Regimens	Median: 2 Range: 1-5	Median: 5 Range: 2-9

Pharmacokinetics & Immunogenicity

- Target TRC105 serum concentrations were achieved in all patients who received TRC105 at 10 mg/kg/wk as a single agent or combined with BEV
- Immunogenicity was not observed in any patient who received TRC105 as a single agent or combined with BEV

Safety

TRC105 + BEV Most Common (N >1) and all Grade 3 and 4 TRC105 Related Adverse Events (N=11 Patients)

Preferred Term[a,b,c]	Maximum Grade					Total N=11	
	1	2	3	4	5	n	Percent
Headache	4	3	1			8	73%
Epistaxis	7	1				8	73%
Telangiectasia	6	1				7	64%
Anemia		1	4			5	45%
Flushing	4					4	36%
Face Edema		3				3	27%
Nasal Congestion	2	1				3	27%
Periorbital Edema	1	1				2	18%
Infusion Related Reaction		2				2	18%
Migraine	1	1				2	18%
Dyspnea	2					2	18%
Rash	2					2	18%
Gingival Bleeding	2					2	18%

TRC105 + BEV Most Common (N >1) and all Grade 3 and 4 BEV Related Adverse Events (N=11 Patients)

Preferred Term[a,b,c]	Maximum Grade					Total N=11	
	1	2	3	4	5	n	Percent
Epistaxis	4	1				5	45%
Headache	2	1	1			4	36%
Flushing	3					3	27%
Telangiectasia	2	1				3	27%
Anemia		1	1			2	18%
Infusion Related Reaction	1	1				2	18%
Dyspnea	2					2	18%
Nasal Congestion	1	1				2	18%
Sinus Congestion	2					2	18%
Pulmonary Embolism			1			1	9%

Single Agent Most Common (N >1) and all Grade 3 and 4 TRC105 Related Adverse Events (N=23 Patients)

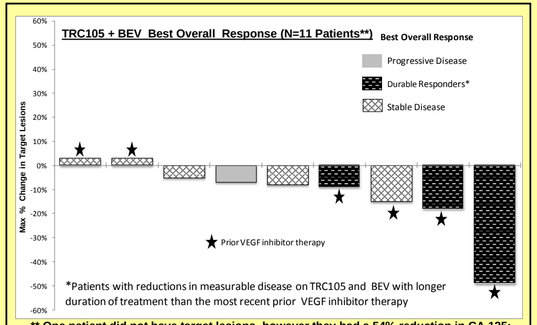
Preferred Term[a,b,c]	Maximum Grade					Total N=23	
	1	2	3	4	5	n	Percent
Epistaxis	15	1	1			17	74%
Headache	5	6	2			13	57%
Gingival Bleeding	10	1				11	48%
Fatigue	6	3	1			10	43%
Telangiectasia	7	1				8	35%
Infusion Related Reaction	3	4				7	30%
Flushing	6					6	26%
Anemia		1	4			5	22%
Diarrhea	2	2				4	17%
Nasal Congestion	4					4	17%
Nausea	2	1				3	13%
Vomiting	3					3	13%
Mucosal Inflammation	1	2				3	13%
Migraine	1	1	1			3	13%
Constipation	2					2	9%
Toothache	2					2	9%
Arthralgia	2					2	9%
Pain in Extremity	1	1				2	9%
Erythema	2					2	9%
Pruritus	2					2	9%

[a]Includes grade 1 or 2 AEs occurring in more than one patient and all grade 3 or higher adverse events
[b]AEs were Drug-Related if they are considered at least possibly related to TRC105 or BEV
[c]AEs were coded by MedDRA dictionary version 14.1

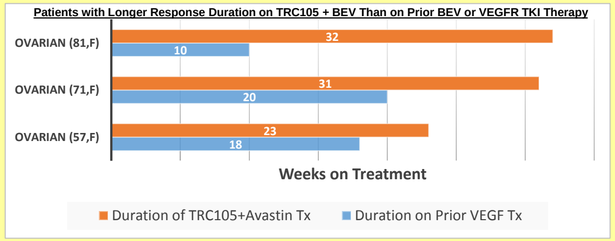
- TRC105 was well tolerated as a single agent at the recommended phase 2 dose of 10 mg/kg/wk
- In the combination study, dose escalation to the recommended phase 2 dose of both drugs was well tolerated when the initial TRC105 dose was split over two days to limit the frequency of headache
- The concurrent administration of BEV and TRC105 did not otherwise potentiate known toxicities of TRC105 or BEV
- Mucocutaneous telangiectasia, a marker of TRC105 target modulation, was observed at higher frequency with the combination of the two drugs (64% vs 35%; P=0.15)

Efficacy

- Reductions in CA-125 were noted in 7 of 20 patients treated with TRC105 as a single agent and 7 of 11 treated with the combination, including 5 of 8 patients who received prior BEV or VEGF receptor tyrosine kinase inhibitor (VEGFR TKI) therapy
- Reductions in tumor volume ≥ 5% were seen in 7 of 9 evaluable patients (78%) treated with the combination, one of whom had a partial response by RECIST 1.1.
- Reductions in tumor volume ≥ 5% were seen in 4 of 8 patients who received prior BEV or VEGFR TKI, including three patients who remained on TRC105 + BEV treatment for longer than the most recent prior treatment with BEV or VEGFR TKI therapy



** One patient did not have target lesions, however they had a 54% reduction in CA-125; one patient did not have an on study efficacy assessment



SUMMARY & CONCLUSIONS

- TRC105 at 10 mg/kg weekly was well tolerated with and without BEV at 10 mg/kg q2wk in patients with advanced platinum resistant ovarian cancer
- In the combination study, antitumor activity (radiographic responses and tumor marker reductions) was observed in patients who progressed on prior BEV or VEGFR TKI, and these patients had longer time on treatment on BEV + TRC105 than on the prior BEV or VEGFR TKI containing regimen
- Further study of TRC105 with BEV in advanced ovarian cancer is justified

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