A Phase 1b Dose-Escalation Study of TRC105 (Endoglin Antibody) in Combination with Axitinib in Patients with Metastatic Renal Cell Carcinoma (mRCC)

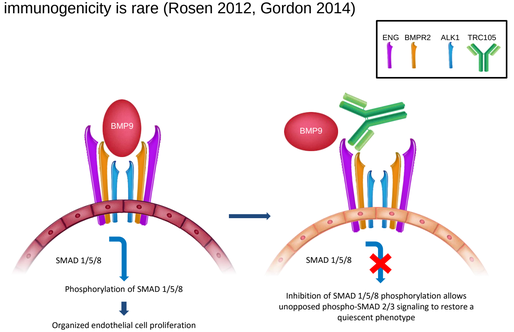
2016 ESMO Abstract # 804P

[1]T.K. Choueiri, [2]M.D. Michaelson, [3]E.M. Posadas, [4]G.P. Sonpavde, [5]D.F. McDermott, [6]A. Nixon, [6]Y. Liu, [6]Z. Yuan, [6]H. Hurwitz, [7]B.K. Seon, [8]M.A. Jivani, [8]B.J. Adams, [8]C.P. Theuer

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Massachusetts General Hospital, Boston, MA; [3]Cedars Sinai Medical Center, Los Angeles, CA; [4]University of Alabama Comprehensive Cancer Center, Birmingham, AL; [5]Beth Israel Deaconess Medical Center, Boston, MA; [6]Duke University Medical Center, Durham, NC; [7]Roswell Park Cancer Institute, Buffalo, NY; [8]TRACON Pharmaceuticals, Inc., San Diego, CA

INTRODUCTION

- Endoglin is a membrane receptor required for angiogenesis (Li 1999) that is highly expressed by proliferating endothelial cells in solid tumors (Seon 2011), and also expressed on renal carcinoma stem cells (Bussolati 2008)
- Preclinical data demonstrate endoglin is an escape pathway that promotes VEGF resistance (Bockhorn 2003, Davis 2004, Anderberg 2013, Liu 2014)
- Endoglin heterozygosity is associated with the Osler-Weber-Rendu syndrome that results in telangiectasia and is associated with improved cancer survival (Duarte 2014)
- TRC105 is a chimeric IgG1 endoglin monoclonal antibody with high avidity (KD = 5 pM) that inhibits angiogenesis (Nolan-Stevaux 2012) and potentiates the activity of VEGF inhibitors in preclinical models, and causes telangiectasia and increased serum VEGF concentrations at its recommended Phase 2 dose (RP2D) (Rosen 2012, Gordon 2014)
- Telangiectasia, a characteristic finding of the Osler-Weber-Rendu syndrome, is observed routinely at the recommended phase 2 dose and immunogenicity is rare (Rosen 2012, Gordon 2014)



STUDY RATIONALE

- Axitinib is an oral VEGF receptor tyrosine kinase inhibitor (VEGFR TKI) that inhibits multiple receptor tyrosine kinases including VEGFR-1, VEGFR-2, and VEGFR-3. Axitinib is approved for the treatment of RCC with an overall response rate of 11% by RECIST 1.1 and progression free survival (PFS) of 4.8 months following treatment with one prior VEGFR TKI
- TRC105 combined safely with bevacizumab, sorafenib, and pazopanib in separate Phase 1/2 studies and demonstrated anti tumor activity (Gordon 2014, Duffy 2015, Attia 2015)
- By targeting a non-VEGF pathway that is upregulated following VEGF inhibition, TRC105 has the potential to complement axitinib in patients with RCC

STUDY DESIGN

PHASE 1B: ENROLLMENT COMPLETE
- Open-label, dose finding (N=18)
- 1° Endpoint: RP2D and safety
- Advanced RCC (all histologies)
- ≥ 1 VEGFR TKI
- Prior immunotherapy and/or mTOR inhibitor allowed
- Axitinib initiated at 5 mg p.o. BID and dose escalation permitted to 10 mg BID
- Multiplex analysis of 23 plasma proteins assessed at baseline and on study

PHASE 2: ENROLLING
- Randomized (N=150)
- 1° Endpoint: PFS
- Advanced or metastatic clear cell RCC (ccRCC)
- Progression on 1 prior VEGF inhibitor
- 1 prior mTOR inhibitor allowed
- 1 prior immunotherapy allowed

COHORT 1
- TRC105 8 mg/kg IV weekly
- Axitinib 5 mg BID
- N = 3

COHORT 2
- TRC105 10 mg/kg IV weekly
- Axitinib 5 mg BID
- N = 3

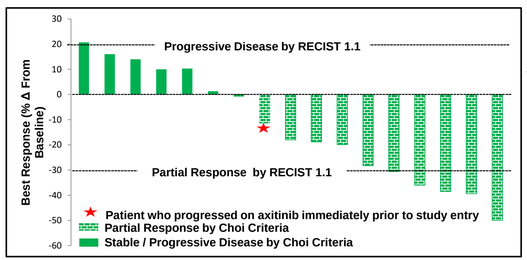
EXPANSION COHORT
- TRC105 10 mg/kg IV weekly
- Axitinib 5 mg BID
- N = 12

Randomization → Axitinib (N=75) / TRC105 + Axitinib (N=75)

RESULTS

Baseline Patient Characteristics (N=18)	
Age	• Median: 61.5 • Range: 35-77
Gender	• Male: 16 • Female: 2
ECOG	• ECOG 0: 14 • ECOG 1: 4
# Prior Therapies	• Median: 3 • Range: 1-6
Histology	• ccRCC: 13 • Other: 5

Best Response (N=17)	
Progressive Disease	2
Stable Disease	10
Partial Response (PR) by RECIST 1.1	5
PR by Modified Choi Criteria	10



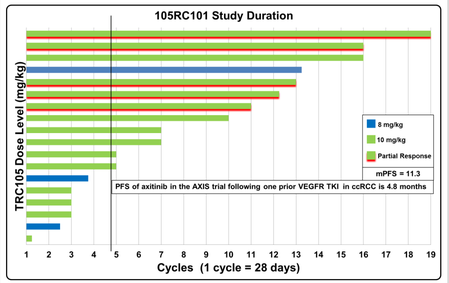
Treatment History of RECIST 1.1 Partial Responders

Subject	Prior Therapies	Best Response	Duration on Prior Therapy (months)	Duration of TRC105 + Axitinib (months)
10221101	High Dose IL-2 Pazopanib Immune checkpoint inhibitor	PD SD SD	<1 24.6 3.7	**14**
10221103	Sunitinib Everolimus Everolimus	PD Unknown SD	4.0 15.9 34	**16.9**
10201104	Sunitinib Pazopanib Immune checkpoint inhibitor	SD PD SD	7 3 7.4	**11.3**
10021102	Sunitinib	PD	5.7	**11.3**
10211103	Temsirolimus Sunitinib Pazopanib	N/A SD PD	<1 9.3 3.5	**9.6**

SUMMARY OF EFFICACY

- Partial response (PR) by RECIST 1.1 occurred in 5 of 17 (29%) patients who progressed on prior VEGFR TKI, 4 of which were in the fourth line setting. None of the RECIST responders had a PR to prior VEGFR TKI treatment. PR by modified Choi criteria occurred in 10 of 17 (59%) patients
- Improved activity was seen in clear cell (8 of 12 patients with modified Choi responses, including 4 partial responses by RECIST 1.1)
- Median PFS (mPFS) overall was 11.3 months in all patients and also 11.3 months in patients with clear cell RCC by Kaplan-Meier
- Axitinib dose-escalation occurred to 7 mg BID in 22.2% of patients and to 10 mg BID in 11.1% of patients

RESULTS



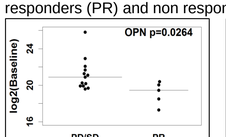
Biomarkers Assessed

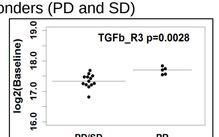
Soluble Angiogenic Factors	VEGF-related Factors	TGFb-related Factors	Inflammation and Matrix-Derived Factors
ANG-2	PlGF	BMP-9	ICAM-1
bFGF	VEGF-A	Endoglin	IL-6
HGF	VEGF-D	TGF-β1	OPN
PDGF-AA	VEGF-R1	TGF-β2	SDF-1
PDGF-BB	VEGF-R2	TGFβ-R3	TIMP-1
TSP-2	VEGF-R3		VCAM-1

Baseline biomarkers significantly correlated with time on study

Biomarker	HR	95% CI	p-value
Ang-2	0.61	0.41-0.92	0.0086
VEGF-R2	0.21	0.04-1.03	0.0402
OPN	1.38	1.01-1.89	0.0403
TGFβ-R3	0.13	0.02-0.99	0.0444

Baseline levels of osteopontin (OPN) and TGF-β receptor 3 (betaglycan) were significantly different between partial responders (PR) and non responders (PD and SD)





CONCLUSION

- TRC105 dose escalation proceeded from 8 mg/kg (n=3) to 10 mg/kg (n=15) without dose limiting toxicity
- TRC105 at its RP2D of 10 mg/kg was well tolerated with axitinib in renal cell carcinoma patients
- Axitinib dose escalation to 10 mg BID was possible with the RP2D of TRC105
- Adverse events characteristic of each drug were not increased in frequency or severity when the two drugs were administered concurrently, and most commonly included epistaxis, headache, fatigue, diarrhea, and gingival bleeding
- Serum concentrations of TRC105 above target concentrations were maintained continuously at the 8 mg/kg and 10 mg/kg TRC105 dose levels
- The combination of TRC105 and axitinib demonstrated encouraging preliminary signs of activity including RECIST 1.1 partial responses (29%) in patients that were prior non-responders and mPFS was more than double that expected for axitinib monotherapy
- Plasma level of TGF-β receptor 3 (betaglycan) at baseline was significantly higher in PR patients, while OPN being significantly lower. Both markers correlated with time on study. Their potential prognostic/predictive value will be investigated in the Phase 2 randomized study
- Study design details are at https://clinicaltrials.gov/show/NCT01806064

REFERENCES

- Anderberg C, The Journal of Experimental Medicine 210:563-79, 2013
- Attia S, ASCO Annual Meeting 2015, Abstract #10514
- Bockhorn M, Clinical Cancer Research 9:4221-4226, 2003
- Bussolati B, FASEB 22:3696-3705, 2008
- Davis DW, Cancer Research 64:4601-4610, 2004
- Duarte CW, Can Epi Bio & Prev 23:117-25, 2014
- Duffy AG, GI ASCO 2015, Abstract # 291
- Gordon MS, Clinical Cancer Research 20:5918-5926, 2014
- Li DY, Science 284:1534-1537, 1999
- Liu Y, Investigational New Drugs 32(5): 851-859, 2014
- 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