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A Phase 1b / Phase 2a Study of TRC105 (Endoglin Antibody) in Combination with Pazopanib (P) in Patients (pts) with Advanced Soft Tissue Sarcoma (STS)

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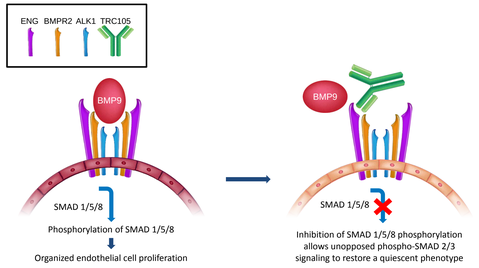
INTRODUCTION

- Endoglin is a membrane receptor required for angiogenesis (Li 1999) that is highly expressed by proliferating endothelial cells in solid tumors (Seon 2011), and is upregulated following VEGF inhibition.
- Endoglin expression allows continued angiogenesis despite VEGF inhibition (Bockhorn 2003, Davis 2004, Anderberg 2013).
- 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 (K_D = 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).
- TRC105 combined safely and demonstrated anti-tumor activity with bevacizumab, sorafenib and axitinib in separate phase 1/2 studies (Gordon 2014, Duffy 2015, Choueiri 2015).
- TRC105 received Orphan Drug Designation for soft tissue sarcoma (STS) in the US on Jan 21, 2016 and EU on Apr 28, 2016.



STUDY RATIONALE

- Pazopanib is an inhibitor of multiple kinases including VEGF receptors that is approved for the treatment of STS and demonstrated a partial response rate of 4% and progression free survival (PFS) of 4.6 months by RECIST 1.0 following treatment with chemotherapy in the pivotal PALETTE study.
- Endoglin is densely expressed on the malignant cells of certain STS, particularly angiosarcoma, by immunohistochemistry (Fritchie 2013), and endoglin expression is associated with poor prognosis in STS (Pardali 2011).
- Angiosarcoma is a rare and aggressive form of STS of endothelial cell origin associated with poor PFS and overall survival. No complete responses (CRs) were reported in a retrospective analysis of 30 angiosarcoma patients treated with single agent pazopanib, and median PFS was 3.02 months (Kollar 2015).
- By targeting a non-VEGF pathway that is upregulated following VEGF inhibition and is expressed directly on malignant cells, TRC105 may complement pazopanib, particularly in angiosarcoma.

STUDY DESIGN

PHASE 1B: N=18

- Open-label, dose finding of 8 mg/kg (N=3) and then 10 mg/kg weekly of TRC105 (N=15) with pazopanib 800 mg qD
- Unresectable STS (other than GIST/adipocytic)
- Prior pazopanib allowed
- 1° Endpoint: RP2D and safety

PHASE 2: N=63

- Open-label, single arm trial at RP2D of 10 mg/kg weekly of TRC105 with pazopanib 800 mg qD
- Metastatic STS (other than GIST/adipocytic)
- Progression following anthracycline chemotherapy
- Up to four prior lines of systemic therapy
- 1° Endpoint: PFS by RECIST 1.1

ANGIOSARCOMA COHORT added as an amendment to the original Phase 1b/2 trial: N= up to 13

- Open-label, at RP2D of 10 mg/kg weekly of TRC105 with pazopanib 800 mg qD (n=4) *or* 10 mg/kg weekly of single agent TRC105 with transition to combination with pazopanib 800 mg qD at progression (n=5)
- Advanced or metastatic angiosarcoma
- Progression following chemotherapy
- Prior pazopanib allowed
- Up to four prior lines of systemic therapy
- 1° Endpoint: ORR by RECIST 1.1

KEY ENROLLMENT CRITERIA: Measurable disease by RECIST 1.1, ECOG ≤ 1

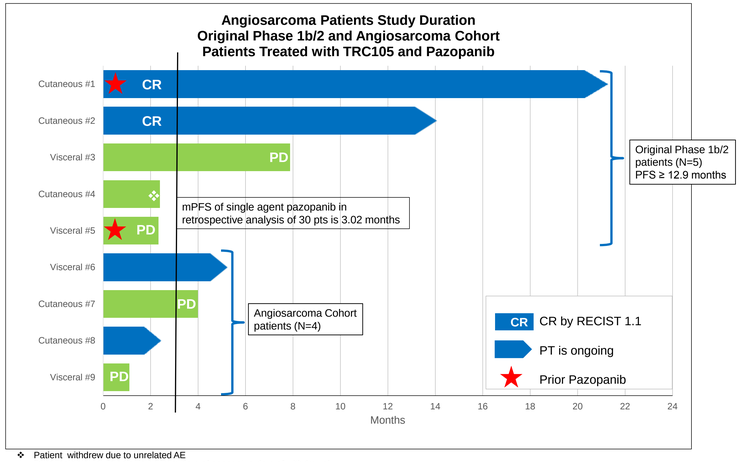
RESULTS

Baseline Patient Characteristics (N=81)	
Age (years)	• Median: 57 • Range: 19 - 89
Gender	• Male: 36 • Female: 45
ECOG	• ECOG 0: 28 • ECOG 1: 53
Number of Lines of Previous Systemic Therapies	• Median: 2 • Range: 1-7
Histology	• Leiomyosarcoma: 35 • Undifferentiated Pleomorphic Sarcoma (UPS): 18 • Synovial Sarcoma: 7 • Myxofibrosarcoma: 6 • Angiosarcoma: 5 • Epithelioid Sarcoma: 5 • Epithelioid Hemangioendothelioma: 2 • Other: 3

Phase 1b/2 Median PFS, months, 95% CI		
Overall	n=77	3.95 (3.25, 5.52)
Histology	• Angiosarcoma (n=5)*	≥12.9[f] (2.1, NA)
	• Leiomyosarcoma (n=33)	5.26 (2.20, 7.36)
	• Synovial Sarcoma (n=6)	5.19 (1.87, NA)
	• Myxofibrosarcoma (n=5)	3.88 (2.01, NA)
	• UPS (n=18)**	3.73 (2.20, 3.95)
	• Epithelioid Sarcoma (n=5)	2.53 (1.97, NA)
Tumor Endoglin Expression	• Positive (n=15)	3.88 (2.20, 3.91)
	• Negative (n=51)	4.04 (2.53, 5.95)

*2 CRs ongoing at month 21 and month 14
**1 CR ongoing at month 15
[f]Last response assessment used as date of progression for the two ongoing pts with CR to calculate mPFS

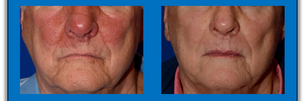
Ph1b/2 Best Response by RECIST 1.1 (N=81)	
Complete Response (CR)	3
Partial Response (PR)	1
Stable Disease (SD)	46
Progressive Disease (PD)	27
Not Evaluable	4



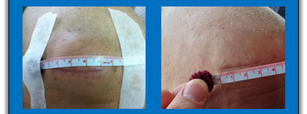
❖ Patient withdrew due to unrelated AE
• Duration on study is calculated from date of consent to date of withdrawal

Patient #1 ongoing at month 21 with a CR

Patient #2 ongoing at month 14 with a CR



Patient #6 ongoing at month 5 with significant tumor reduction



RESULTS

- TRC105 at its RP2D of 10 mg/kg weekly was well tolerated with pazopanib at its approved dose in STS patients.
- Adverse events characteristic of each individual drug were not increased in frequency or severity when the two drugs were administrated concurrently.
- Pazopanib steady state PK when dosed with TRC105 was similar to that reported following dosing as a single agent.
- Median PFS = 3.95 months in all STS patients, by Kaplan-Meier (N=77).
- Median PFS ≥12.9 months for the 5 angiosarcoma patients enrolled in the original Phase 1b/2 trial. Tumor reductions or clinical improvement were observed in 8 of 9 (88%) angiosarcoma patients treated with the combination of TRC105 and pazopanib in the original phase 1b/2 trial (n=5) or the angiosarcoma specific cohort (n=4), including two ongoing CRs.
- Patient #1 with cutaneous angiosarcoma and a CR by RECIST 1.1 continues on study in month 21. The patient progressed within 15 weeks of treatment with docetaxel combined with pazopanib.
- Patient #2 with cutaneous angiosarcoma and a CR by RECIST 1.1 continues on study in month 14. The patient progressed within 4 weeks of treatment with doxorubicin.
- Patient #6 with visceral angiosarcoma demonstrated disappearance of the non-target lesion and significant reduction in a target lesion and continues on study in month 5. The patient progressed within 4 weeks of treatment with gemcitabine, doxorubicin, and docetaxel.
- Five angiosarcoma pts were initially treated with TRC105 monotherapy in the angiosarcoma specific cohort, of whom 4 remain on study with either TRC105 monotherapy or TRC105 and pazopanib combination treatment.
- A patient with undifferentiated pleomorphic sarcoma (UPS) experienced a CR by RECIST 1.1 and continues on study in month 15.
- Endoglin expression on archival tumor tissue was not associated with improved PFS.

Safety

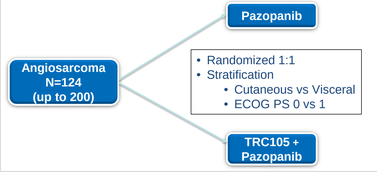
Most Common (n > 1) and all Grade 3 and Above TRC105 Drug-Related Adverse Events by Preferred Term and by Grade

	Maximum Grade					Total N = 81	
Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	n	Percent
Epistaxis	46	4	1	0	0	51	63%
Headache	33	13	0	0	0	46	57%
Fatigue	17	15	3	0	0	35	43%
Gingival Bleeding	28	0	0	0	0	28	35%
Anemia	1	8	17	0	0	26	32%
Infusion Related Reaction	7	10	2	0	0	19	23%
Nausea	17	2	0	0	0	19	23%
Vomiting	12	3	1	0	0	16	20%
Periodontal Disease*	12	3	0	0	0	15	19%
Flushing	13	1	0	0	0	14	17%
Stomatitis	12	2	0	0	0	14	17%
Decreased Appetite	10	2	1	0	0	13	16%
Telangiectasia	9	0	0	0	0	9	11%
Dysgeusia	9	0	0	0	0	9	11%
Diarrhea	5	2	2	0	0	9	11%

* Periodontal disease includes gingival pain, gingival disorder, gingival swelling, gingivitis and gingival infection
- Table shows frequencies and percentages of TRC105 Drug-related Adverse Events occurring in > 1 patients or at Grade 3 or above in phase 1 and phase 2 patients who have taken TRC105. Percentages are computed by using the number of patients in the safety population as the denominator.
- Adverse Events are coded by using MedDRA dictionary version 14.1.
- If more than one event of a type is recorded for a patient, the patient is only counted once at the highest grade

CONCLUSION

- TRC105 combined with pazopanib demonstrated encouraging activity in angiosarcoma patients, including durable CRs by RECIST 1.1 and median PFS of 12.9 months.
- Clinical safety profile of the combination was tolerable and allowed for prolonged dosing.
- PFS in non-angiosarcoma STS patients was not significantly different from PFS expected with pazopanib.
- PFS was not increased in non-angiosarcoma STS patients with tumor endoglin expression on archival tumor specimens, possibly reflecting the effect of subsequent therapies and tumor heterogeneity on tumor endoglin expression.
- Endoglin tumor expression on circulating tumor cells may be explored as a biomarker in future STS studies.
- A randomized phase 3 study with TRC105 in combination with pazopanib compared to single agent pazopanib in pts with angiosarcoma is planned in 2016 to confirm the activity seen in this study.



REFERENCES

- Anderberg C, J Exp Med 210:563-79, 2013
- Bockhorn M, Clin Cancer Res 9:4221-26, 2003
- Choueiri T, GU ASCO 2015
- Davis DW, Cancer Res 64:4601-10, 2004
- Duarte CW, Can Epi Bio & Prev 23:117-25, 2014
- Duffy AG, GI ASCO 2015
- Fritchie K, EORTC-AACR-NCI 2013
- Gordon MS, Clin Cancer Res 20:5918-26, 2014
- Karzai FH, BJU Intl 116:546-55, 2015
- Kollar A, EORTC STBSG, 2015
- Li DY, Science 284:1534-37, 1999
- Nolan-Stevaux O, PLOS One 7:1-12, 2012
- Pardali E, Oncogene 30:334-45, 2011
- Rosen L, Clin Cancer Res 18:4820-9, 2012
- Seon BK, Current Drug Del 8:135-43, 2011