A PHASE 1B DOSE-ESCALATION STUDY OF TRC105 (ANTI-ENDOGLIN ANTIBODY) IN COMBINATION WITH PAZOPANIB IN PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA (STS)

S. Attia[1], R.F. Riedel[2], S.I. Robinson[3], R.M. Conry[4], K.K. Sankhala[5], B.K. Seon[6], D. Alvarez[7], B.J. Adams[7], R. Shazer[7], C.P. Theuer[7], R.G. Maki[8]

[1]Mayo Clinic, Jacksonville, FL; [2]Duke University Medical Center, Durham, NC; [3]Mayo Clinic, Rochester, MN; [4]The University of Alabama at Birmingham, Birmingham, AL; [5]Sarcoma Oncology Center, Santa Monica, CA; [6]Roswell Park Cancer Institute, Buffalo, NY; [7]TRACON Pharmaceuticals, Inc., San Diego, CA; [8]Icahn School of Medicine at Mount Sinai, New York, NY

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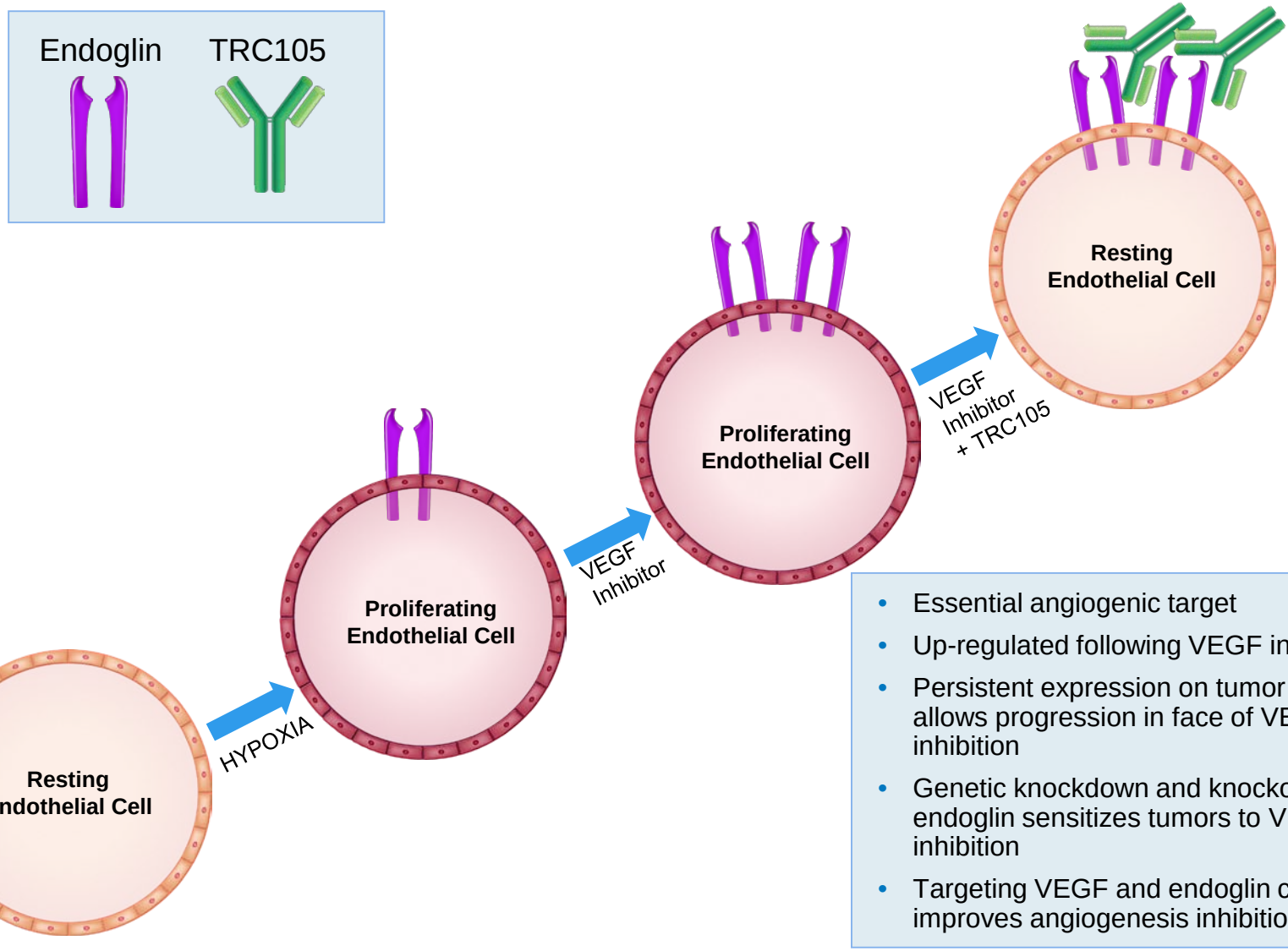
Endoglin is Expressed on Tumor Vessels and Targeting Endoglin Complements VEGF Inhibition



- Essential angiogenic target
- Up-regulated following VEGF inhibition
- Persistent expression on tumor vessels allows progression in face of VEGF inhibition
- Genetic knockdown and knockout of endoglin sensitizes tumors to VEGF inhibition
- Targeting VEGF and endoglin concurrently improves angiogenesis inhibition

Endoglin (CD105) Expression on STS

Tumor Type	Number Patient Samples	CD105 IHC 3+	CD105 IHC 2+	CD105 IHC 1+	Tumor vessels CD105+
Chondrosarcoma	19				13/14
Ewing sarcoma	7		1	5	7/7
Osteosarcoma	20		2	2	20/20
Leiomyosarcoma (non-gynecologic)	20		2	1	20/20
Gynecologic leiomyosarcoma	20	2	1	3	18/20
Synovial sarcoma	20			3	20/20
Angiosarcoma	20	13	3	3	17/17
Undifferentiated pleomorphic sarcoma	20	1	4	3	20/20

- Endoglin is densely expressed on certain STS, particularly angiosarcoma

Fritchie K, Attia S, Okuno SH, Arndt CAS, Robinson SI, *CD105 - A Therapeutic Target for Sarcomas*. EORTC-AACR-NCI, 2013.

Study Rationale

- Pazopanib is an oral multikinase VEGFR inhibitor 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 1.1 following treatment with chemotherapy in the pivotal PALETTE study.

- Endoglin is densely expressed on tumor vessels and on certain STS tumor tissue, particularly angiosarcoma, by immunohistochemistry (IHC).

- By targeting the endoglin pathway that is upregulated following VEGF inhibition and is expressed directly on sarcoma tissue, TRC105 may complement pazopanib, particularly in angiosarcoma.

- Tumor endoglin expression by IHC may serve as a biomarker that predicts highly responsive STS subtypes.

Phase 1b Sarcoma: Study Design

- **ENROLLMENT COMPLETE**
- Open-label, dose finding (N=18)
- Unresectable STS that progressed following chemotherapy
- GIST & adipocytic sarcomas excluded
- Prior pazopanib allowed
- 1° Endpoint: Recommended Phase 2 Dose (RP2D) and safety

COHORT 1 (N=3)

- TRC105 8 mg/kg IV weekly
- Pazopanib 800 mg/day PO

(2-4 week run-in period)

COHORT 2 (N=3)

- TRC105 10 mg/kg IV weekly
- Pazopanib 800 mg/day PO

(2-4 week run-in period)

RP2D EXPANSION COHORT (N=12)

- TRC105 10 mg/kg IV weekly
- Pazopanib 800 mg/day PO

(2-4 week run-in period)

Phase 1b Sarcoma: Study Results

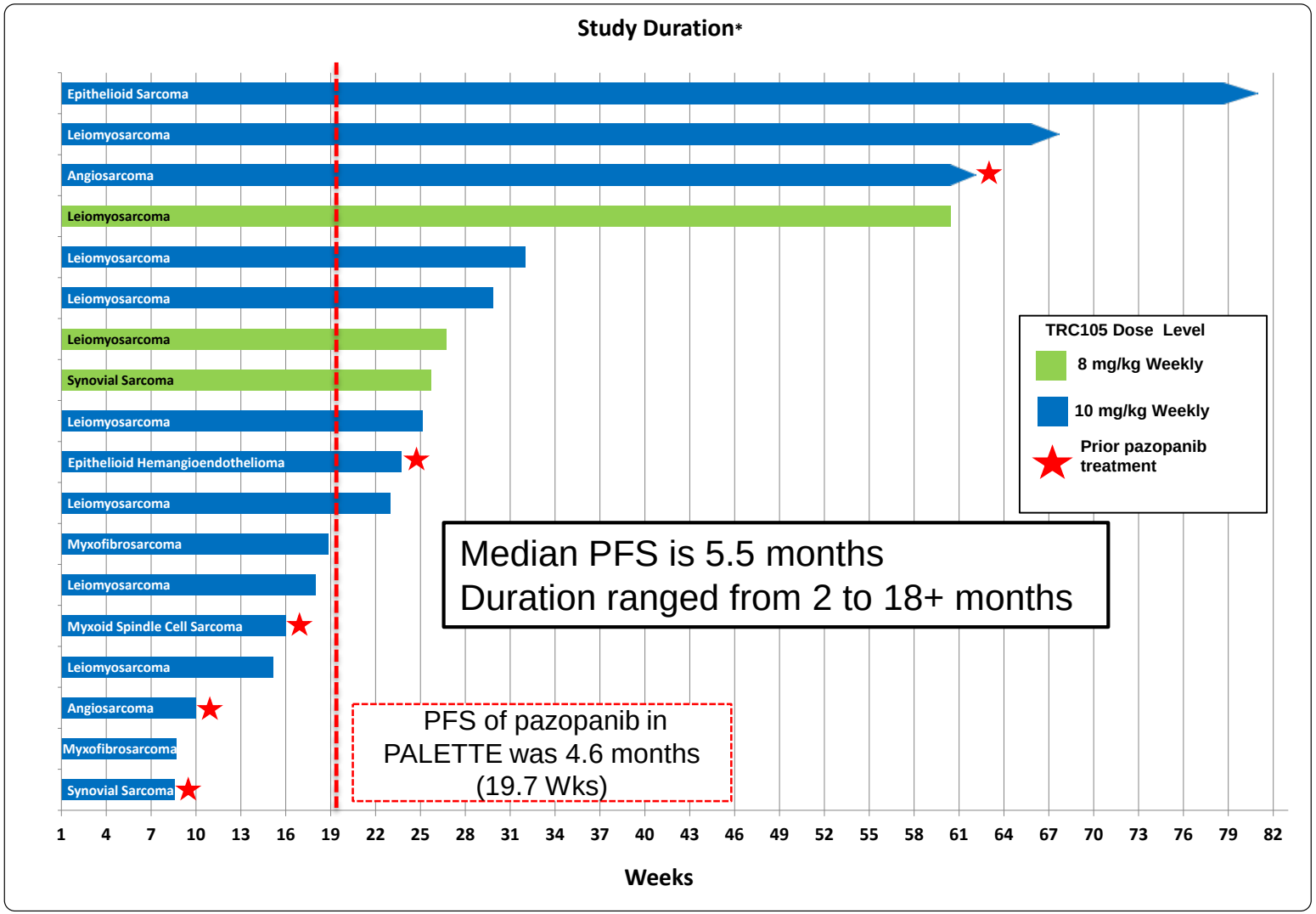
Baseline Patient Characteristics (N=18)	
Age (years)	• Median: 55 • Range: 25-71
Gender	• Male: 8 • Female: 10
ECOG	• ECOG 0: 7 • ECOG 1: 11
Number of Lines of Previous Systemic Therapies	• Median: 2 • Range: 1-7
Histology	• Leiomyosarcoma: 9 • Angiosarcoma: 2 • Synovial Sarcoma: 2 • Myxofibrosarcoma: 2 • Epithelioid Sarcoma: 1 • Epithelioid Hemangioendothelioma: 1 • Myxoid Spindle Cell Sarcoma: 1

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 = 18	
Preferred Term	**Gr 1**	**Gr 2**	**Gr 3**	**Gr 4**	**Gr 5**	**n**	**Percent**
Epistaxis	12	3	0	0	0	15	(83%)
Anemia	0	4	5	0	0	9	(50%)
Gingival bleeding	8	1	0	0	0	9	(50%)
Headache	7	1	0	0	0	8	(44%)
Fatigue	2	3	0	0	0	5	(28%)
Flushing	4	0	0	0	0	4	(22%)
Gingival pain	2	2	0	0	0	4	(22%)
Decreased appetite	2	1	0	0	0	3	(17%)
Dysgeusia	3	0	0	0	0	3	(17%)
Nausea	2	1	0	0	0	3	(17%)
Vomiting	2	1	0	0	0	3	(17%)
Dyspnea	2	0	0	0	0	2	(11%)
Erythema	2	0	0	0	0	2	(11%)
Insomnia	2	0	0	0	0	2	(11%)
Stomatitis	2	0	0	0	0	2	(11%)
Hypertension	0	0	1	0	0	1	(6%)
Hyponatremia	0	0	1	0	0	1	(6%)
Lymphocyte count decreased	0	0	1	0	0	1	(6%)

- Dose limiting toxicity was not observed
- Expected events of epistaxis, gingival bleeding and headache are known features of the Osler-Weber-Rendu syndrome of endoglin heterozygosity
- Anemia reflects endoglin expression on the proerythroblast, an erythrocyte precursor

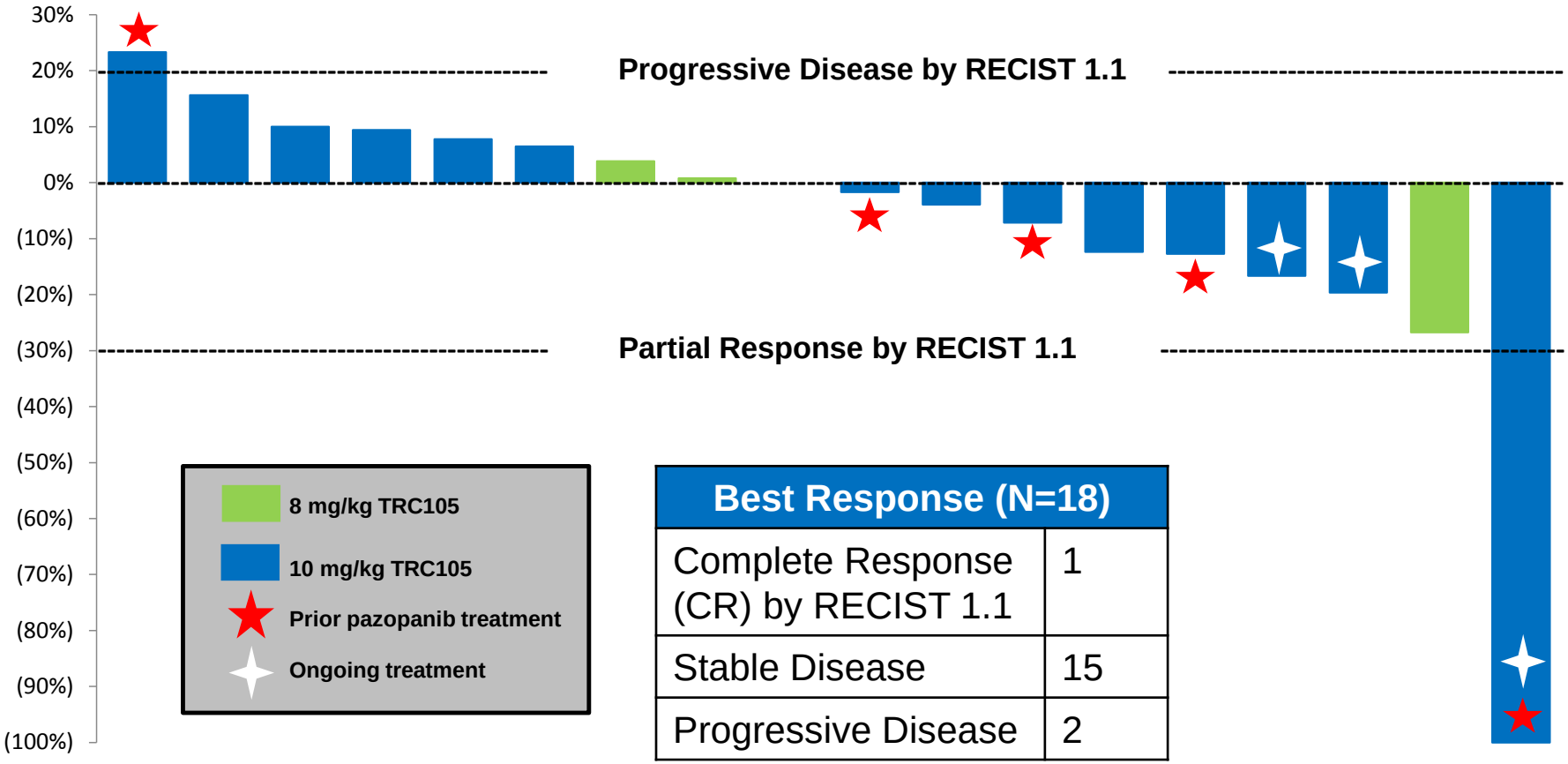
Phase 1b Sarcoma: Study Results



* Duration on study is calculated from date of consent to date of withdrawal or most recent visit if pt is ongoing

Phase 1b Sarcoma: Study Results

Maximum percentage change in target lesion size



Best Response (N=18)	
Complete Response (CR) by RECIST 1.1	1
Stable Disease	15
Progressive Disease	2

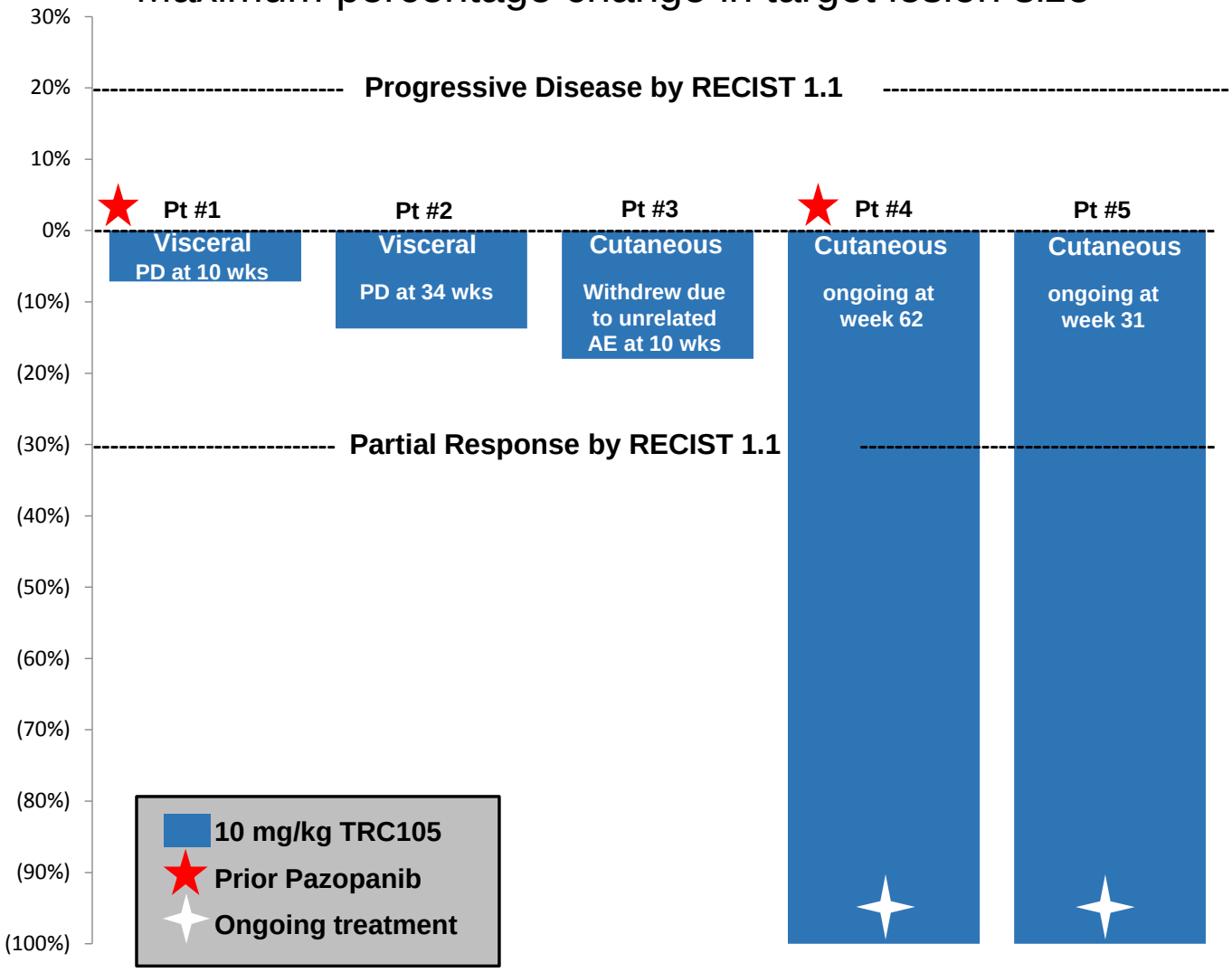
Phase 2 Sarcoma: Study Design

- Open-label, non-randomized, metastatic STS
- Progression following anthracycline chemotherapy, up to four prior lines of systemic therapy
- TRC105 RP2D of 10 mg/kg weekly with pazopanib at 800 mg/day
- 1° Endpoint: PFS, stratified by tumor endoglin expression by IHC

- Enrollment ongoing, 62 of 63 patients enrolled
- Angiosarcoma cohort added (N=13)

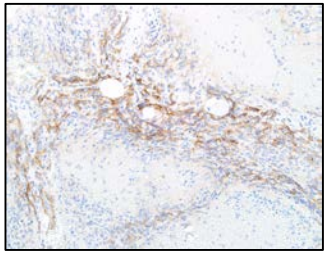
Phase 1b/2: Angiosarcoma Experience

Maximum percentage change in target lesion size

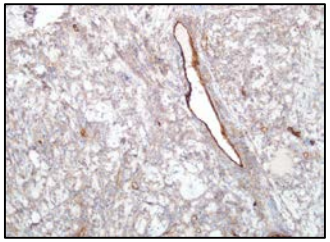


Positive IHC staining in 3/3 patients with available samples

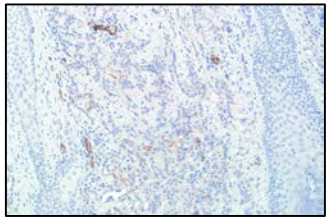
Pt #1: CD105, IHC 2+



Pt #3: CD105, IHC 3+

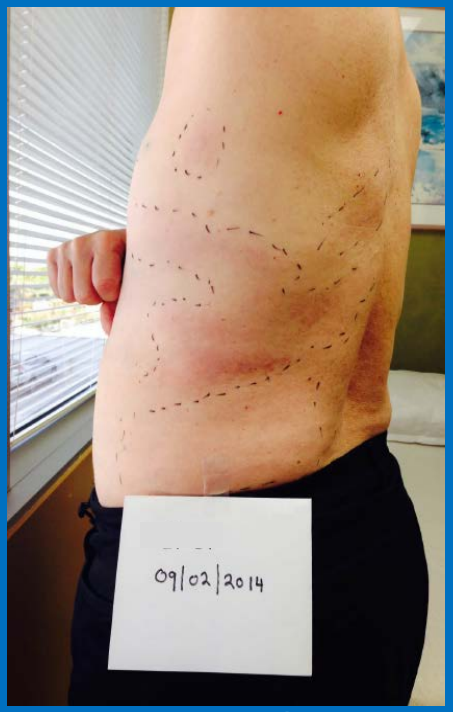


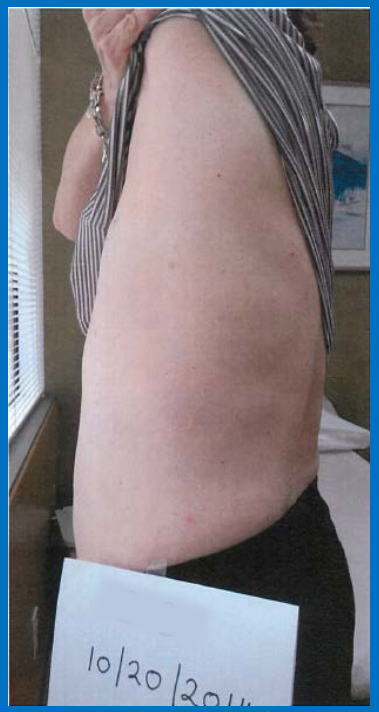
Pt #5: CD105, IHC 1+



Phase 1b/2 Angiosarcoma: Durable Complete Responses

Phase 1b Angiosarcoma patient with CR at TRC105 RP2D

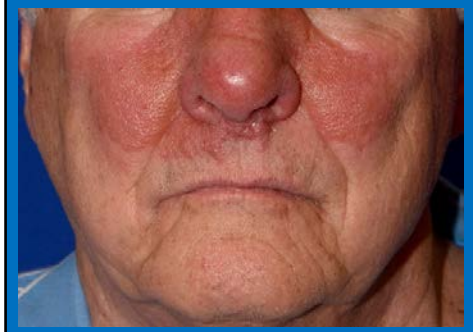




Day 0 Day 48

Ongoing CR at week 62

Phase 2 Angiosarcoma patient with CR at TRC105 RP2D



Day 0 Day 37

Ongoing CR at week 31

Conclusions

- TRC105 at its RP2D of 10 mg/kg weekly was well tolerated with pazopanib without dose limiting toxicity
- Adverse events characteristic of each individual drug were not increased in frequency or severity when the two drugs were administrated concurrently
- TRC105 and pazopanib demonstrated encouraging preliminary signs of activity in a highly pretreated population, including durable complete responses in patients with cutaneous angiosarcoma
- A randomized phase 3 trial of TRC105 and pazopanib is planned in angiosarcoma

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