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

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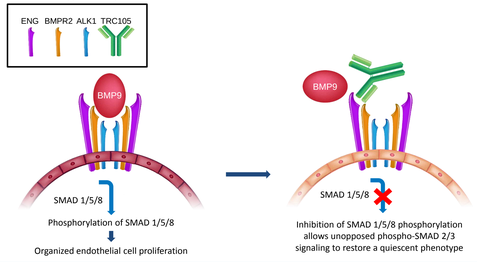
INTRODUCTION

- TRC105 is a chimeric IgG1 anti-endoglin monoclonal antibody with high avidity (K_D = 5 pM) that inhibits angiogenesis by competitively inhibiting bone morphogenic protein (BMP) binding to endoglin (Nolan-Stevaux 2012)
- 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)
- Reduced endoglin expression is associated with the Osler-Weber-Rendu syndrome that results in telangiectasia and is associated with improved cancer survival (Duarte 2013)
- Endoglin expression is up-regulated by hypoxia in response to VEGF inhibition (Bockhorn 2003, Davis 2004) and TRC105 potentiates the activity of VEGF inhibitors in preclinical models
- The recommended phase 2 dose (RP2D) of TRC105 given as a single agent or when given with bevacizumab is 10 mg/kg by weekly intravenous infusion. TRC105 treatment is not associated with hypertension or proteinuria
- 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 and with sorafenib in separate Phase 1/2 studies and demonstrated anti tumor activity (Gordon 2014, Duffy 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)
- ≥ 1VEFGR TKI
- Prior immunotherapy and/or mTOR inhibitor allowed
- Axitinib initiated at 5 mg p.o. BID and dose escalation permitted to 10 mg p.o. BID

KEY ENROLLMENT CRITERIA:

- ✓ Advanced renal cell carcinoma
- ✓ Measurable disease by RECIST 1.1
- ✓ ECOG ≤ 1
- ✓ Adequate organ function

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

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

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

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

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

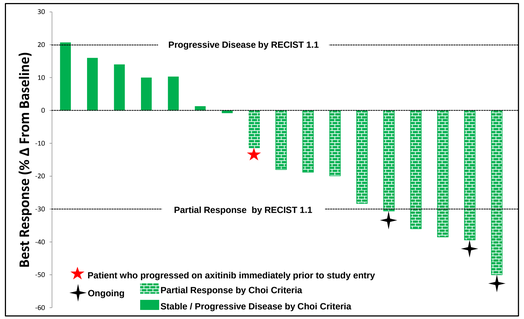
RESULTS

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 by RECIST 1.1	5
Partial Response by Modified Choi Criteria	10



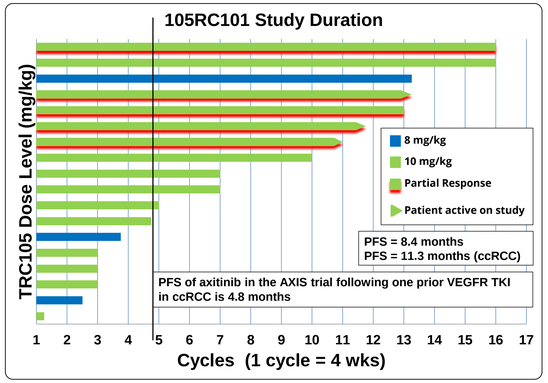
RECIST 1.1 Responses Occurred in 29% of Patients

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 25 3.7	**14.2**
10221103	Sunitinib Everolimus Everolimus	PD Unknown SD	4.0 16.1 34.5	**11✓**
10201104	Sunitinib Pazopanib Immune checkpoint inhibitor	SD PD SD	7.1 3 7.5	**11.4**
10021102	Sunitinib	PD	5.8	**10.1✓**
10211103	Temsirolimus Sunitinib Pazopanib	N/A SD PD	<1 9.4 3.5	**9.1✓**

✓Active on study

- **SUMMARY OF EFFICACY**
  - Partial response (PR) by RECIST 1.1 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 Choi criteria occurred in 10 of 17 (59%) patients
  - Improved activity in clear cell (8 of 12 patients with Choi responses, including 4 partial responses by RECIST)
  - To date, median PFS overall was 8.4 months in all patients and 11.3 months in patients with clear cell RCC by Kaplan-Meier
  - Axitinib dose-escalation occurred to 7 mg p.o. BID in 23.5% of patients and to 10 mg p.o. BID in 5.9% of patients

RESULTS



Most Common (n > 2) and all Grade 3 and Above TRC105 Possibly Drug-Related Adverse Events by Preferred Term and by Grade

Preferred Term	Maximum Grade					Total N = 18	
	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5	n	Percent
Epistaxis	13	1	0	0	0	14	77.8%
Headache	10	1	2	0	0	13	72.2%
Fatigue	7	4	0	0	0	11	61.1%
Diarrhea	7	2	1	0	0	10	55.6%
Nausea	7	1	0	0	0	8	44.4%
Gingival bleeding	8	0	0	0	0	8	44.4%
Vomiting	4	1	0	0	0	5	27.8%
Anemia	2	1	1	0	0	4	22.2%
Hypertension	1	2	1	0	0	4	22.2%
Mucosal inflammation	3	0	0	0	0	3	16.7%
Pyrexia	2	1	0	0	0	3	16.7%
Aspartate aminotransferase increased	3	0	0	0	0	3	16.7%
Decreased appetite	3	0	0	0	0	3	16.7%
Dehydration	1	2	0	0	0	3	16.7%
Hypernatremia	3	0	0	0	0	3	16.7%
Dermatitis acneiform	2	1	0	0	0	3	16.7%
Palmar-plantar erythrodysesthesia syndrome	1	2	0	0	0	3	16.7%
Rash	3	0	0	0	0	3	16.7%
Skin infection	0	0	1	0	0	1	5.6%

Table shows frequencies and percents of TRC105 Drug-related Adverse Events occurring in > 2 patients or at Grade 3 or above in the safety population.
Percents 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 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 p.o. b.i.d. was possible with the RP2D of TRC105
- The most common adverse events were generally low grade and included diarrhea, nausea, fatigue, headache, epistaxis, and gingival bleeding
- Adverse events characteristic of each individual drug were not increased in frequency or severity when the two drugs were administrated together
- Serum concentrations of TRC105 above target concentrations were maintained continuously at the 8 mg/kg and 10 mg/kg TRC105 dose levels
- TRC105 and axitinib demonstrated encouraging preliminary signs of activity including RECIST partial responses (29%) in patients that were prior non-responders and longer PFS than expected with axitinib as a single agent
- A multicenter randomized Phase 2 trial of axitinib +/- TRC105 is accruing at this time that will enroll 150 patients in the US at approximately 25 sites
- Study design details are at https://clinicaltrials.gov/show/NCT01806064

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