A Phase 1b Study of TRC105 in Combination with Paclitaxel/Carboplatin and Bevacizumab in Patients with Stage 4 Non-Squamous Non-Small Cell Lung Cancer

Abstract #12978

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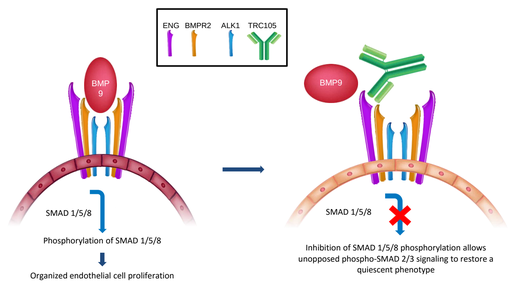
INTRODUCTION

- Endoglin is a membrane receptor required for angiogenesis (Li 1999) that is densely expressed by proliferating endothelial cells in solid tumors (Seon 2011), and is upregulated following vascular endothelial growth factor (VEGF) inhibition.
- Preclinical data demonstrate endoglin is an escape pathway that promotes VEGF resistance (Bockhorn 2003, Davis 2004, Anderberg 2013, Liu 2014)
- TRC105 is a chimeric IgG1 monoclonal antibody that binds endoglin with high avidity (K_D= 5 pM), competitively inhibits binding of BMP-9, inhibits angiogenesis (Nolan-Stevaux 2012), potentiates the activity of VEGF inhibitors in preclinical models, and causes telangiectasia and increased serum VEGF concentrations at its recommended phase 2 dose (Rosen 2012, Gordon 2014, Karzai 2015).
- Endoglin heterozygosity is associated with the Osler-Weber-Rendu syndrome that results in mucocutaneous telangiectasia and is associated with improved cancer survival (Duarte 2014).



STUDY RATIONALE

- Bevacizumab is a monoclonal antibody to VEGF that inhibits angiogenesis and extends survival in non-squamous non-small cell lung cancer (NSCLC) patients when given with paclitaxel/carboplatin.
- TRC105 potentiates bevacizumab activity in pre-clinical models of human angiogenesis (Liu 2014).
- In a phase 1b study, the combination of TRC105 and bevacizumab produced partial responses by RECIST in bevacizumab-refractory patients, and was well tolerated.
- The use of TRC105 with bevacizumab and paclitaxel/carboplatin may more effectively inhibit angiogenesis and improve clinical efficacy over that seen with bevacizumab and paclitaxel/carboplatin.

STUDY DESIGN

PHASE 1B

- Single Center, Open-Label, Nonrandomized, Dose-Finding study (N=18)
- 1° Endpoint: RP2D and safety/tolerability
- Advanced non-squamous NSCLC
- Induction treatment for six 3 week cycles with bevacizumab 15 mg/kg, paclitaxel 200 mg/m^2, carboplatin 6 AUC q3wk and escalating doses of TRC105, followed by maintenance therapy with bevacizumab and TRC105 until disease progression.

Dose Level 1
- TRC105 8 mg/kg weekly IV
- Bevacizumab 15 mg/kg, paclitaxel 200 mg/m^2 and carboplatin 6 AUC q3wk IV
- N = 3 - 6

➡

Dose Level 2
- TRC105 10 mg/kg IV weekly
- Bevacizumab 15 mg/kg, paclitaxel 200 mg/m^2 and carboplatin 6 AUC q3wk IV
- N = 3 - 6

➡

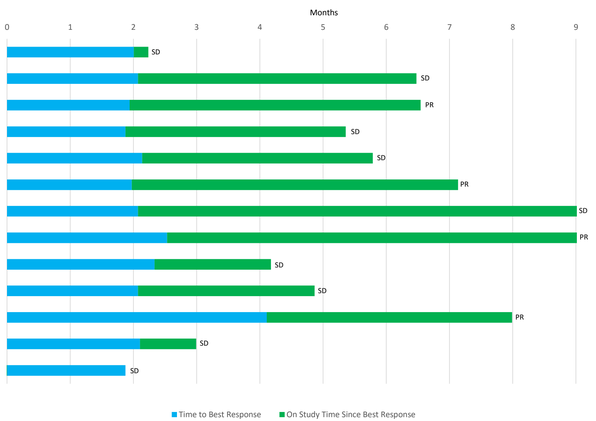
Expansion Cohort
- TRC105 10 mg/kg IV weekly
- Bevacizumab 15 mg/kg, paclitaxel 200 mg/m^2 and carboplatin 6 AUC q3wk IV
- N = 12

RESULTS

Baseline Patient Characteristics (N=15)	
Age	• Median: 67 • Range: 42-80
Gender	• Male: 7 • Female: 8
ECOG	• ECOG 0: 2 • ECOG 1: 13

Best Response (N=13)	
Progressive Disease	0
Stable Disease	9
Partial Response (PR) by RECIST 1.1	4

105LC101 Response and Duration on Study [a,b]



[a]Two patients were not evaluable as they did not have on study scans due to: a DLT of Grade 3 Rash and an unrelated SAE of Grade 3 weakness

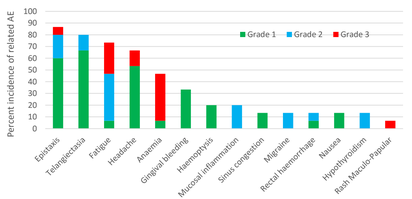
[b]Duration on study is noted as time from informed consent to study discontinuation

SUMMARY OF SAFETY AND EFFICACY

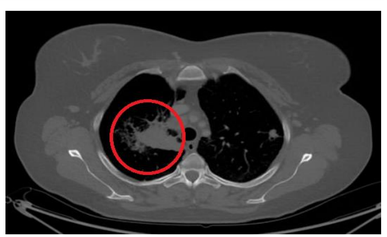
- The RP2D of TRC105 is 10 mg/kg weekly IV when given with standard dose bevacizumab, carboplatin/paclitaxel
- One patient experienced DLT of grade 3 rash at 10 mg/kg TRC105 weekly
- Most common adverse events regardless of relationship were epistaxis, telangiectasia, fatigue, diarrhea, headache, arthralgia and nausea
- Most common TRC105 related adverse events were epistaxis, telangiectasia, fatigue, and headache
- One patient experienced Grade 5 neutropenic sepsis considered unrelated to TRC105 or bevacizumab
- Maintenance therapy with TRC105 and bevacizumab was initiated in 8 of 13 evaluable patients
- Partial response by RECIST 1.1 occurred in 4 of 13 (31%) patients including one patient with a 81% tumor reduction
- Median PFS was 6.54 months

RESULTS

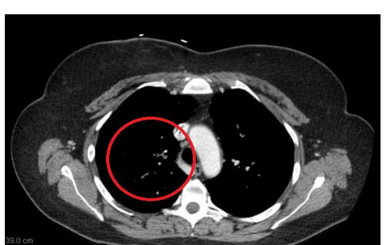
Most Common (n > 1) and all Grade 3 and above TRC105 Related Adverse Events



CHEST CT AT BASELINE AND CYCLE 9 IN PATIENT WITH PARTIAL RESPONSE AND 81% TUMOR REDUCTION



Baseline CT: Right Upper Lobe Mass (4.7 cm x 2.8 cm)



Cycle 9 CT: Right Upper Lobe Mass (0 cm)

Results

Average TRC105 PK Troughs

	8 mg/kg	10 mg/kg
C3D1	56.6 (µg/ml)	103 (µg/ml)
C6D1	72.3 (µg/ml)	113 (µg/ml)
C9D1	59.7 (µg/ml)	78.8 (µg/ml)

- Serum levels of TRC105 exceeded the target concentration (25 µg/ml) following 5 weekly doses (C3D1) of TRC105 at 8 and 10 mg/kg and were subsequently maintained through C9D1
- One of thirteen patients had treatment emergent anti drug antibodies of low titer

CONCLUSION

- TRC105 at its RP2D of 10 mg/kg weekly IV was tolerable with paclitaxel, carboplatin and bevacizumab in non-squamous NSCLC
- The combination of TRC105 and paclitaxel, carboplatin and bevacizumab demonstrated encouraging preliminary signs of activity including a partial response rate of 31% by RECIST
- Maintenance therapy with TRC105 and bevacizumab was achieved in the majority of patients
- Study design details are at https://clinicaltrials.gov/ct2/show/NCT02429843

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