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Differences in Pharmacokinetics of TRC105 (Anti-endoglin Antibody) when Administered as a Single Agent Versus in Combination with Bevacizumab

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INTRODUCTION

- TRC105 is a chimeric IgG1 anti-endoglin monoclonal antibody with very high avidity (K_D = 5 pM)
- Endoglin is a membrane receptor that is highly expressed by proliferating endothelial cells in solid tumors (Seon 2011). Endoglin is required for angiogenesis and its expression is up-regulated by hypoxia in response to VEGF inhibition (Bockhorn 2003, Davis 2004); mice that lack endoglin die *in utero* (Li 1999)
- High tumor microvessel density as measured by endoglin immunohistochemistry correlates with poor prognosis across more than 10 solid tumor types
- TRC105 inhibits angiogenesis in response to VEGF and basic FGF (Nolan-Stevaux 2012) and induces ADCC
- TRC105 potentiates the activity of VEGF inhibitors in preclinical models
- Endoglin is expressed on renal cell cancer stem cells (Bussolati 2008) and select solid tumors, including sarcoma
- TRC105 is cleared through binding to endoglin expressed on proliferating endothelium when given as a single agent to advanced cancer patients (Spencer 2012)

OBJECTIVE

- Evaluate the pharmacokinetics of TRC105 given as a single agent and when given with bevacizumab (Bev)

Patient Demographics

	Single Agent TRC105 (N=39)	Combination TRC105 + Bevacizumab (N=35)
Age	Median: 64 Range: 26-81	Median: 62 Range: 42-81
Gender	Female: 26 Male: 13	Female: 22 Male: 13
Baseline ECOG Performance Status	ECOG PS 0: 23 ECOG PS 1: 16	ECOG PS 0: 14 ECOG PS 1: 21
Number of Prior Regimens	Median: 3 Range: 1-12	Median: 5 Range: 0-10
Cancer Type	Ovarian: 23 Prostate: 4 Colorectal: 3 Renal: 2 GIST: 2 Lung: 1 Sarcoma: 1 Liver: 1 Mesothelioma: 1 Adenoid cystic: 1	Colorectal: 17 Ovarian: 10 Renal: 1 Hepatocellular: 1 Lung: 1 Cervical : 1 Endometrial : 1 Hemangioendothelioma: 1 Esthesioneuroblastoma: 1 Peritoneal: 1

METHODS

Pharmacokinetic Data

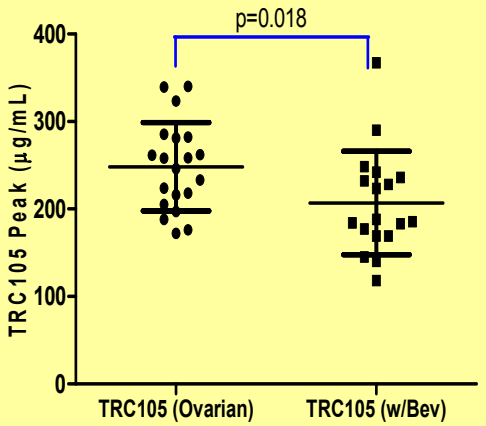
- Serum samples were collected on days of the first and fourth dose at 0, 0.5, 1, 2, 4, 24, 72 and 120 hours following infusion doses of 3, 10 and 15 mg/kg/wk and 10 and 15 mg/kg/2wk of TRC105 dosed as a single agent to patients with advanced solid tumors (N=16). Sparse samples were collected prior to dosing and immediately after dosing during additional dosing days. Additional sparse samples were collected prior to dosing and immediately after dosing following doses of 10 mg/kg/wk as a single agent to patients with advanced ovarian cancer (N=23).
- Sparse samples were collected prior to dosing and immediately after dosing following TRC105 doses of 6, 8 and 10 mg/kg/wk given in combination with Bev at 10 mg/kg/2wk or 15 mg/kg/3wk to patients with advanced solid tumors (N=35).
- TRC105 concentration was determined using a validated ELISA with a LOQ of 78 ng/mL.

Pharmacokinetic Analysis

- Mean peak and trough TRC105 concentrations were compared for patients dosed with TRC105 as a single agent and TRC105 dosed with Bev.
- A two-stage population pharmacokinetic model of TRC105 disposition was built using rich sampling from the single agent solid tumor trial, with sparse data from the single agent ovarian cancer trial and the TRC105+Bev trial included in the base model.
- Bevacizumab administration as a categorical covariate was evaluated simultaneously on all pharmacokinetic parameters in a stepwise process.
- Modeling was implemented with Monolix v.4.2.2.
- A two-compartment model with nonlinear elimination best fit the data, utilizing Michaelis-Menten parameters for saturable clearance.

RESULTS

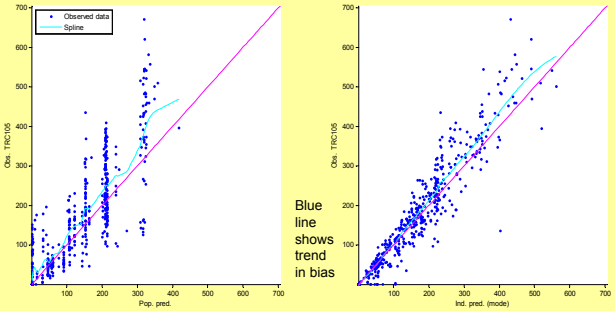
Pharmacokinetics and Pharmacokinetic Modeling Parameters



Reduction in Peak with Bevacizumab

Trial	Dose	Peak (Grand Mean ± SD)	Trough (Grand Mean ± SD)
TRC105 Ovarian (n=20)	10 mg/kg	248.33 ± 50.55	0.69 ± 0.37
TRC105 + Bev (n=18)	10 mg/kg	206.97 ± 59.2	0.54 ± 0.26

Visual goodness-of-fit for observed and model fit data for individual and population parameters



Population Pharmacokinetic Model Parameters of TRC105 (n=74)

PK Parameters		Estimate	Std Error	R.S.E (%)
Vc (mL/kg)	(Volume of Distribution of Central Compartment)	**44.3**	1.9	4
Vmax	(Maximum Elimination Rate) (µg/hr)	**86.3**	14	17
Km	(Michaelis Constant) (µg/mL)	**5.02**	1.6	32
CL_B	(Intercompartmental Binding Clearance) (mL/hr/kg)	**0.33**	0.03	8
V_B	(Binding Distribution Volume)(mL/kg)	**58.3**	11	18
Vc	for Bevacizumab Cohort	**65.8**	4.1	6
Vmax	for Bevacizumab Cohort	**518**	81	16
Km	for Bevacizumab Cohort	**114**	20	17
Variability Parameters				
ω^2_{Vc}	(Single Agent Intra-subject Variance in *Vc*)	**0.051**	0.02	33
$\omega^2_{Vc,Bev}$	(Bevacizumab Cohort Intra-subject Variance in *Vc*)	**0.103**	0.03	31
ω^2_{Vmax}	(Single Agent Intra-subject Variance in *Vmax*)	**0.692**	0.20	29
$\omega^2_{Vmax,Bev}$	(Bevacizumab Cohort Intra-subject Variance in *Vmax*)	**0.25**	0.12	50
ω^2_{Km}	(Single Agent Intra-subject Variance in *Km*)	**2.24**	0.71	32
$\omega^2_{Km,Bev}$	(Bevacizumab Cohort Intra-subject Variance in *Km*)	**0.19**	0.15	80
ω^2_{CLb}	(Intra-subject Variance in CL_B)	**0.084**	0.04	45
ω^2_{Vb}	(Intra-subject Variance in V_B)	**1.28**	0.32	25
$\sigma_{residual}$	(Residual Unexplained Variability)	**0.31**	0.01	4
Bevacizumab Covariate Model Predictions (Coefficients (β))		**Estimate**	**R.S.E (%)**	**P-Value**
(Log $V_C$ind)	= Log $V_C$pop + $\beta_{VcBev,ind}$ + $\eta_{Vc,ind}$	**0.395**	19	**<0.001**
(Log V_{Max}ind)	= Log V_{Max}pop + $\beta_{VmaxBev,ind}$ + $\eta_{Vmax,ind}$	**1.79**	12	**<0.001**
(Log $K_M$ind)	= Log $K_M$pop + $\beta_{KmBev,ind}$ + $\eta_{Km,ind}$	**3.12**	11	**<0.001**

SUMMARY & CONCLUSIONS

- Peak and trough TRC105 serum levels exceed target serum concentrations when given at 10 mg/kg/wk as a single agent or with Bev.
- Central compartment distribution of TRC105 increased when given with Bev as represented by decreased mean peak levels. This was consistent with increased endoglin receptor expression on proliferating endothelium and increased TRC105 binding to endoglin following Bev treatment.
- The maximum rate of elimination (Vmax) also increased, consistent with increased turnover; however, the intrinsic clearance ratio of Vmax/Km remained the same, suggesting no change in endoglin turnover efficiency.
- Future studies will assess whether PK parameters correlate with responses to the combination of TRC105 and Bev in Bev refractory patients.

REFERENCES

- Bockhorn M, Clin Can Res 9:4221-6, 2003
- Bussolati B, FASEB 22:3696-705, 2008
- Davis DW, Cancer Res 64:4601-10, 2004
- Li DY, Science 284:1534-7, 1999
- Nolan-Stevaux O. Plos One 7:e50920, 2012
- Seon BK, Curr Drug Del 8:135-43, 2011
- Spencer SD, ASCO annual meeting, 2012