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Abstract: A2

Exploratory Evaluation of the Combination of TRC105 (anti-Endoglin Monoclonal Antibody) and Bevacizumab (BEV) Indicates Partial Response by Choi Criteria in BEV Refractory Advanced Cancer Patients and Identifies Candidate Textural Analysis Imaging Markers of Response

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INTRODUCTION

- TRC105 is a chimeric IgG1 anti-endoglin monoclonal antibody with high avidity (KD = 5 pM)
- Endoglin is a membrane receptor highly expressed by proliferating endothelial cells in solid tumors (Seon 2011), required for angiogenesis, and up-regulated by hypoxia in response to VEGF inhibition (Bockhorn 2003)
- 10 mg/kg TRC105 and 10 mg/kg Bev were well tolerated when delaying the initial dose of TRC105 by one week and splitting the initial dose over two days
- Continuous TRC105 serum levels above the target concentration were maintained continuously in all patients at the 10 mg/kg dose level
- Telangiectasia, an on-target manifestation of endoglin receptor modulation, was dose dependent
- Immunogenicity was rarely observed and was not associated with clinical sequelae
- Patients who progressed on prior Bev therapy responded with tumor reductions and prolonged progression free survival following treatment with TRC105 + Bev (Rosen 2013)

OBJECTIVES

- Evaluation of predictive response biomarkers using Quantitative Textural Analysis (QTA) on selected CT scans

METHODS

- Central radiographic review was performed at baseline and cycle 2 day 22 (follow-up) scans for 5 patients with prolonged PFS who received TRC105 + Bev
- Selected target lesion (TL) diameter, whole lesion density and tumor volume were measured at baseline and on follow-up scans
- Each subject was assessed for response by RECIST 1.1 and Choi response criteria (Choi 2007)
- Quantitative textural analysis (QTA) was assessed on the same TL using 6 different filter levels on baseline and follow-up scans
- Statistical analysis was performed using non-parametric evaluation and regression modeling
- Significance was defined as p-value <0.05 (two-tailed)

RESULTS

Patient Demographics and Efficacy

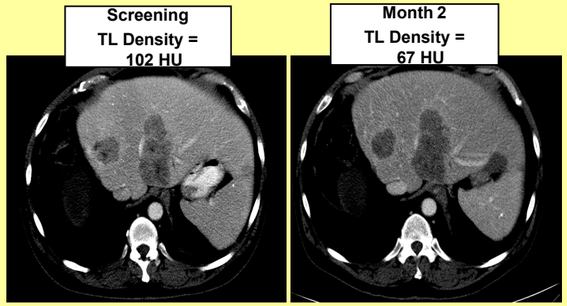
Subject	Cancer Type	Gender	Age	Baseline ECOG Performance Status	Prior Cancer Regimens	TTP on Previous VEGF/TKI Therapy	TTP on TRC105 + Bev Therapy
10015001	Ovarian	Female	57	1	8	18 weeks	23 weeks
10028001	Colorectal	Female	66	1	7	9 weeks	24 weeks
10028101	Colorectal	Male	53	1	6	67 weeks	65 weeks +
10038103	Colorectal	Male	55	1	3	23 weeks	27 weeks
10158103	Ovarian	Female	66	1	4	N/A	20 weeks

+ Subject remains on TRC105 + Bev therapy

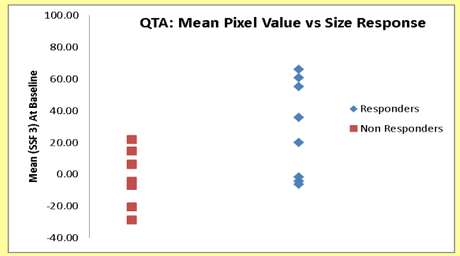
Subject	Best TL Response	RECIST	CHOI
1001-5001	-14.00%	SD	PR
1002-8001	-5.10%	SD	SD*
1002-8101	1.40%	SD	PR
1003-8103	0.10%	SD	PR
1015-8103	-0.70%	SD	PR

Example of Radiographic Response by Choi Criteria in a Patient Who Progressed on Prior Bevacizumab

10028101: 53 yo man with CRC failed FOLFIRI + Bev and then irinotecan + Erbitux is ongoing at week 65 of treatment with a 82% decrease in CEA (to normal) and 30% tumor reduction at 10 mg/kg TRC105 + Bev. Follow-up CT scan at 2 month indicated decreased tumor density of hepatic metastases that met the Choi criteria for partial response

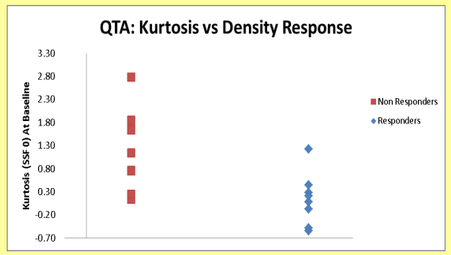


Qualitative Textural Analysis (QTA) Biomarker Assessment



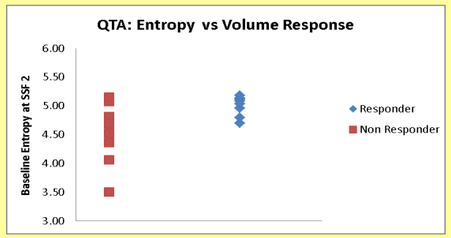
Mean pixel value at baseline, a measure of tumor density, correlated reduction in tumor volume by ≥ 20%

Mean (SSF 3)	Non Responders	Responder
Minimum	-28.880	-6.490
25% Quartile	-7.100	-2.588
Median	-4.340	27.705
75% Quartile	6.540	56.403
Maximum	21.690	65.790
T Test (p Value)	0.031	



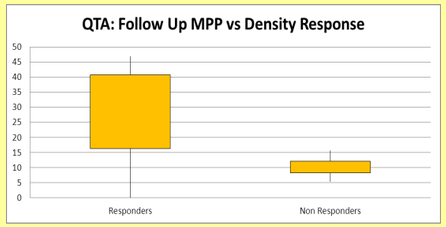
Mean kurtosis at baseline, a measure of tumor heterogeneity (i.e., a measure of flow voids, hypoxia and scattered pockets of necrosis) correlated with ≥ 15% reduction in tumor density

Kurtosis (ssf 0)	Non Responders	Responders
Minimum	0.147	-0.541
25% Quartile	0.754	-0.175
Median	1.142	0.152
75% Quartile	1.742	0.324
Maximum	2.781	1.221
T test (p-value)	0.007	



Mean entropy at baseline, a measure of tumor heterogeneity (i.e., a measure of flow voids, hypoxia and scattered pockets of necrosis), correlated with reduction in tumor volume by ≥ 20%

Entropy (SSF 2)	Non Responders	Responder
Minimum	3.505	4.696
25% Quartile	4.359	4.916
Median	4.690	5.059
75% Quartile	4.818	5.118
Maximum	5.153	5.182
T test (p-value)	0.031	



Mean positive pixel (MPP) value at 2 months, a measure of tumor hypoxia, correlated with ≥ 15% reduction in tumor density

MPP (ssf 6)	Responders	Non Responders
Minimum	0.00	5.33
25% Quartile	16.26	8.22
Median	23.87	10.11
75% Quartile	40.88	12.20
Maximum	47.00	15.72
T-test (p-value)	0.035	

Spearman's Correlation for Change in Density vs. Change in MPP: Rs = -0.638, p-value = 0.021

SUMMARY & CONCLUSIONS

- Antitumor activity (radiographic partial responses by Choi criteria based on decreased tumor size or decreased tumor density) was observed in patients who progressed on prior Bev, and these patients had longer time to tumor progression on Bev + TRC105 than on the prior Bev containing regimen
- Qualitative Textural Analysis (QTA) identified potential lesion-based predictors of response, based on morphologic changes in size and density
- Both mean pixel density and kurtosis (measures associated with tumor heterogeneity (i.e., a measure of flow voids, hypoxia and necrosis)) on baseline CT scan correlated with decrease in lesion volume and density, respectively, on follow-up CT scan
- Mean positive pixel (MPP) (a measure associated with hypoxia) at follow-up CT scan was correlated with decreased tumor density
- QTA may provide predictive biomarkers of response and responding lesions tend to have an alteration of hypoxia.

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- Seon BK, Current Drug Delivery 8:135-143, 2011