Background
VT1021 is a first-in-class therapeutic agent in Phase I clinical studies in solid tumors. In vivo preclinical studies demonstrated that VT1021 inhibited tumor growth via stimulation of p53 and Thrombospondin-1 (Tsp-1) in MDSCs. Moreover, induction of Tsp-1 reprogrammed the tumor microenvironment and induced apoptosis in tumor cells via its cell surface receptors CD36 and CD47. Here we report on the utility of Tsp-1 as a pharmacodynamic biomarker and its correlation with clinical response.

Methods
Tsp-1 protein levels in PBMCs, platelets and plasma were assessed by ELISA following SepMate-based fractionation of subject blood samples. Tsp-1 mRNA levels in peripheral blood cells were analyzed by quantitative RT-PCR following extraction of total RNA from subject whole blood samples via PAXgene Blood RNA kit. Tsp-1 levels in subject biopsy samples were analyzed by immunohistochemistry as described previously.

Results
Up-regulation of Tsp-1 protein was observed in PBMCs, platelets and plasma in all evaluable subjects following treatment with VT1021 across multiple indications in a phase 1 clinical study, indicating that Tsp-1 induction is a pharmacodynamic biomarker for VT1021 (figure 1). Induction of Tsp-1 by VT1021 was also shown at the transcriptional level via RT-PCR measurement of whole blood samples. Strikingly, maximum PBMC Tsp-1 levels induced by VT1021 were higher in subjects with glioblastoma (GBM) that had objective responses (complete or partial response) compared to subjects with stable disease (SD) or progressive disease (PD). Of note, pre-dose levels of Tsp-1 were predictive of response, as subjects with objective responses had higher basal levels of Tsp-1 than those that had stable or progressive disease. For subjects with pancreatic cancer, Tsp-1 induction was higher in SD subjects compared to PD subjects, suggesting that Tsp-1 induction in PBMCs can be a potential prognostic biomarker. In tumor biopsy samples from subjects with pancreatic cancer, increased colocalization of Tsp-1 and CD11b was observed in on-study samples, supporting a role of Tsp-1 in reprogramming the tumor microenvironment (figure 2).

Abstract 375 Figure 1
Up-regulation of Tsp-1 protein levels have been observed in PBMCs (A), platelets (B) and plasma (C) in all evaluable subjects post-dosing with VT1021 across multiple inductions in a phase 1 clinical study.

Abstract 375 Figure 2
Increased colocalization of Tsp-1 and CD11b was observed in tumor microenvironment in tumor biopsy samples from a subject with pancreatic cancer post-dosing with VT1021.
Conclusions Based on both protein and mRNA levels, Tsp-1 induction has the potential to be a useful prognostic pharmacodynamic biomarker for VT1021 in various tumor types. In subjects with GBM, both basal and induced Tsp-1 levels in PBMCs are potential predictive and prognostic biomarkers, respectively. For subjects with pancreatic cancer, Tsp-1 protein induction in PBMCs is a potential prognostic biomarker. The predictive/prognostic utility coupled with the ability to measure levels in peripheral blood makes Tsp-1 a powerful biomarker to assess and predict clinical response to VT1021.

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