Clinical efficacy and biomarker assessment of VT1021, a CD36/CD47 dual-targeting agent, in recurrent glioblastoma

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Abstract CTIM-06

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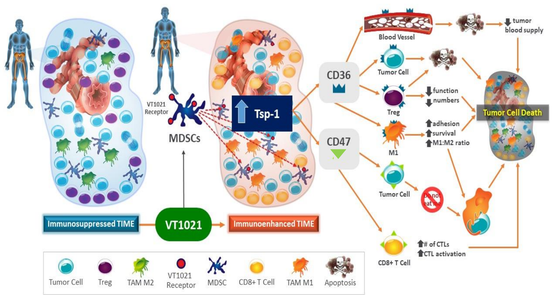
Background

- One of the major barriers to the effective treatment of glioblastoma (GBM) is the immunosuppressive nature of the tumor microenvironment (TME), which is mediated by myeloid derived suppressor cells (MDSCs), M2 macrophages, and regulatory T cells (Tregs).
- High levels of CD36 and CD47 are associated with poor prognostic outcome for many types of cancers (Enciu et al., 2018; Huang et al., 2020); no drugs currently target both molecules simultaneously.
- Thrombodspondin-1 (TSP-1) binds to the cell surface receptors CD36 and CD47 to induce apoptosis in tumor and endothelial cells, blocks the "do-not-eat-me" signal, increases the M1:M2 macrophage ratio, and activates cytotoxic T lymphocytes (CTLs) (Dawson et al 1996, Martin-Manso et al 2008, Russell et al. 2015).
- Vigeo developed VT1021, a first in class agent, which is a cyclic peptide derived from prosaposin that induces the expression of TSP-1 in MDSCs that are recruited to the TME (Kang et al, 2009; Catena et al. 2013; Wang et al. 2016).
- Preclinical studies of VT1021 have shown robust anti-tumor activity in multiple animal models of ovarian, pancreatic, and breast cancer.
- VT1021 was evaluated in a recently completed phase I/II open-label, multicenter, dose escalation (Part 1) and expansion (Part 2) clinical study in advanced, refractory, solid tumors including recurrent GBM (rGBM) (NCT03364400).
- Thirty-two subjects with rGBM were dosed in Part 2, 22 of which were considered evaluable as having completed ≥1 cycle of VT1021 treatment and tumor imaging during cycle 2.
- VT1021 had no major adverse events (AEs) and a predictable pharmacokinetic profile.

VT1021 Modulates the TME via CD36 and CD47



VT1021 reprograms the TME from one that is immunosuppressive to one that is immunoenhanced. The immunosuppressed tumor immune microenvironment is characterized by high levels of Tregs, M2 tumor associated macrophages (M2 TAMs) and MDSCs. VT1021 binds to a receptor on MDSCs and induces expression of TSP-1. TSP-1 binding to one of its receptors, CD36, inhibits angiogenesis, induces apoptosis in tumor cells, endothelial cells and Tregs, and increases M1 macrophage adhesion, survival, and the M1:M2 ratio. TSP-1 binding to its other major receptor, CD47, blocks the "do-not-eat-me" signal allowing macrophage phagocytosis of tumor cells and increases CTL infiltration and activity resulting in tumor cell death.

Baseline Characteristics

		Statistics	Total (N=32)
Age (years)		Mean (STD)	56.6 (14.8)
		Median (Min, Max)	59.5 (24, 82)
Age Group:	18 <= to <= 65	n (%)	21 (65.6%)
	66 <= to <= 75	n (%)	9 (28.1%)
	> 75	n (%)	2 (6.3%)
Gender:	Female	n (%)	16 (50%)
	Male	n (%)	16 (50%)

In the rGBM cohort of the expansion phase, of the 32 subjects dosed, the median age was 60 years and 50% were female.

Contact

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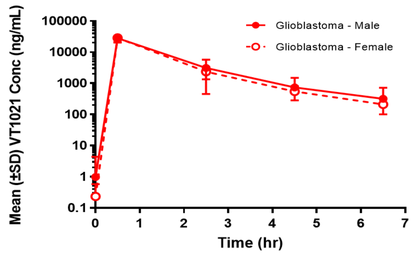
Safety Profile

Common Adverse Events: 32 Subjects
(All cycles, maximum grade, regardless of causality)

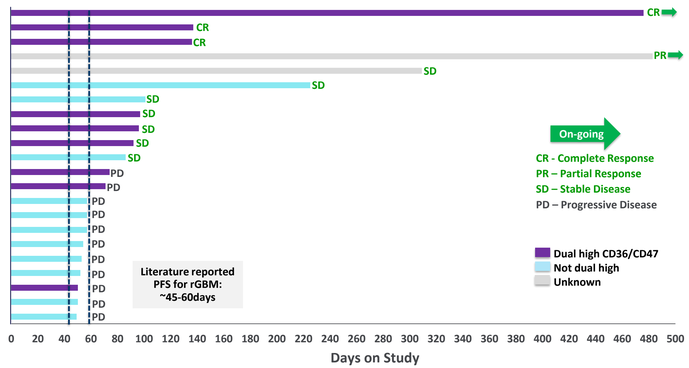
	All Grades	Grade 1-2	Grade 3-4
Abdominal Pain	5	5	-
Diarrhea	4	4	-
Nausea	3	3	-
Vomiting	3	2	1
Fall	9	9	-
Infusion reaction	3	3	-

- There were 373 AE events reported in all GBM subjects treated (N=32), of which 35 were SAEs
- **NO SAE was considered by site PIs and by sponsor monitor to be related to study drug**

PK Profile

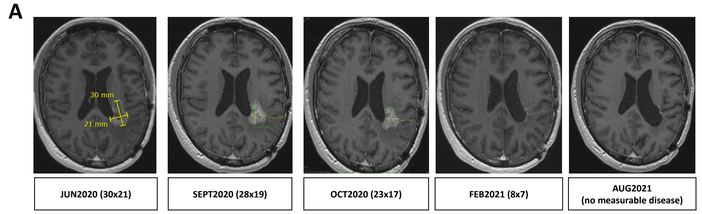


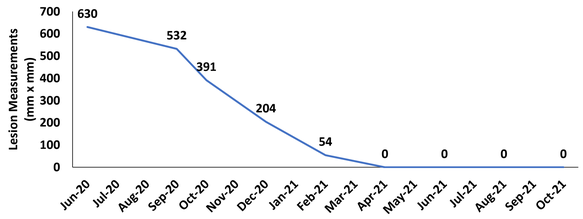
Dual High CD36/CD47 Correlates with Clinical Response & Duration of Treatment

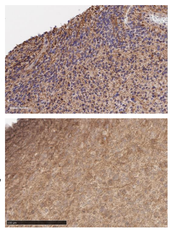


Dual high expression of CD36 and CD47 correlates with clinical response and longer duration of treatment. Among 22 evaluable rGBM subjects, 3 had complete response (CR), 1 had partial response (PR), and 7 had stable disease (SD) with an average study duration of over 203 days. The overall disease control rate (DCR) was 50%. Nine of the 20 (45%) evaluable subjects with available biopsy samples showed high expression levels of both CD36 AND CD47. Among the 9 dual-high subjects, 3 achieved CR, representing an overall response rate of 33.3%, with another 3 subjects achieving SD for a DCR of 67%. Of the 11 CR/PR/SDs, 6 were dual high (55%). Days on study are as of 10/31/21.

VT1021 Induces Complete Response in rGBM Subjects

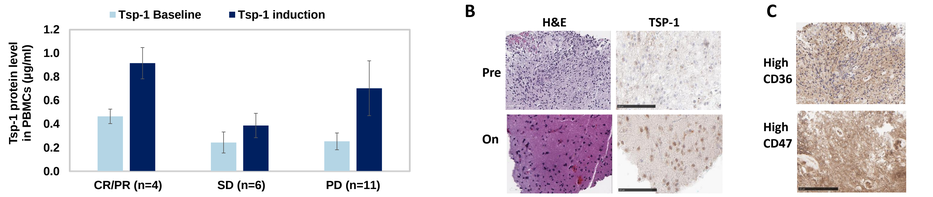






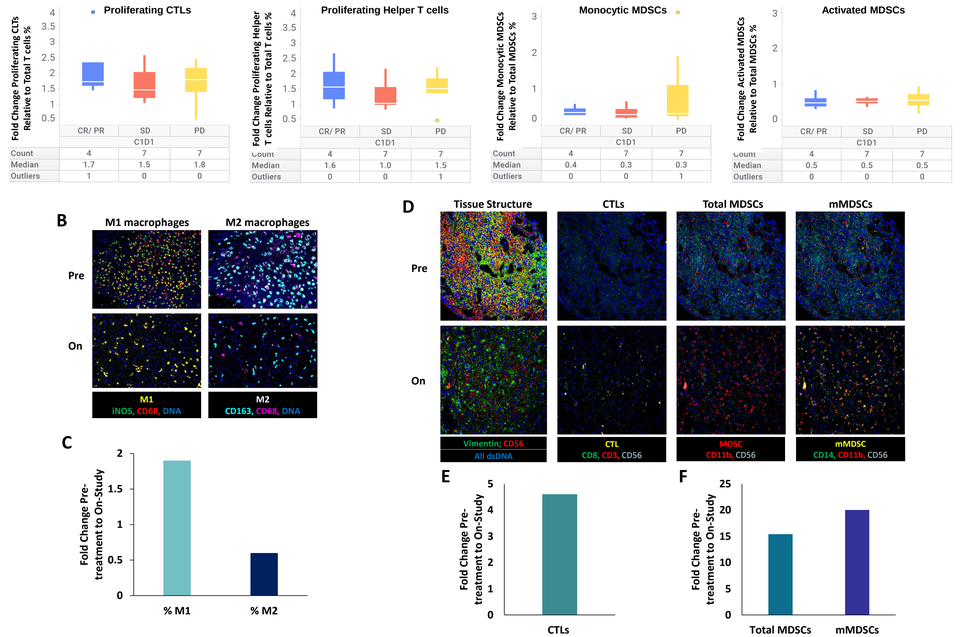
Complete response scan images and lesion shrinkage for 1 of 3 subjects who achieved CR. A. Lesion measurements and scan images for 1 CR subject who has been on study for 476 days and is still on-going. B. The lesion steadily decreased until no longer measurable after 9 cycles of treatment. C. Dual high expression of CD36 and CD47 by IHC analysis of the pre-treatment biopsy.

VT1021 Induces TSP-1 in the Circulation and in the TME



VT1021 induces TSP-1 expression both in circulation and in the TME. A. TSP-1 protein measured from peripheral blood mononuclear cells (PBMCs) was induced by VT1021 in all evaluable subjects with rGBM. B. TSP-1 induction in the on-study (on) biopsy from a subject with rGBM who achieved CR. No tumor cells were detected by pathological examination of the on-study biopsy. C. Dual high expression intensities of CD36 and CD47 in a pre-treatment (pre) biopsy from the same subject in B.

Profiling the Modulation of the Immune System by VT1021 in Circulation and in TME



VT1021 modulated the immune profile in both circulation and in the TME. A. Immune cells isolated from whole blood collected before and after 6 hours of treatment with VT1021 on Cycle 1 Day 1 were analyzed by flow cytometry. Proliferating CTLs increased ≥1.5 fold regardless of clinical response, proliferating helper T cells increased ≥1.5 fold in CR/PR and PD subjects while monocytic MDSCs (mMDSCs) and activated MDSCs decreased ≤0.5 fold in all evaluable subjects. B. IHC for M1 and M2 macrophages on tumor biopsies obtained pre-treatment (pre) and on-study (on) from a subject with rGBM who achieved CR. C. Fold change of M1 and M2 macrophages were quantified for the biopsy pair in B. Percent of M1 increased 1.9-fold while M2 decreased 0.6-fold after treatment. D. Representative in tumor biopsies obtained pre-treatment and on-study from the subject in B. assessed by multiplex ion beam imaging. E. Fold change of CTLs and of F. total and mMDSCs were quantified for the biopsy pair in D. CTLs increased >4 fold while total and mMDSCs increased >15 fold in the on-study biopsy compared to pre-treatment.

Conclusions

- VT1021 demonstrates promising single-agent clinical activity in rGBM, particularly in subjects with high expression levels of CD36 and CD47.
- Subjects with rGBM who were dual high for CD36 and CD47 were more likely to have a reduction in tumor burden and stay on study longer than non-dual high subjects.
- Increased TSP-1 expression was observed in circulating PBMCs and in the TME.
- VT1021 remodeled the TME to be more immune enhanced via increased M1 macrophages and CTLs.
- Dual high expression of CD36 and CD47 is a putative predictive biomarker to stratify subjects for inclusion in future clinical trials in GBM.
- A Phase 2/3 study will be initiated in 1H2022 to further investigate the efficacy of VT1021 in GBM; additional clinical studies are planned for other solid tumor indications.

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Clinical trial information: NCT03364400