Clinical update of VT1021, a first-in-class CD36 and CD47 targeting immunomodulating agent, in subjects with pancreatic cancer and other solid tumors stratified by novel biomarkers

Abstract 369

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Background

The immunosuppressive nature of the tumor microenvironment (TME) is a major barrier to the effective treatment of pancreatic cancer. Immunosuppression in the TME is mediated by multiple cell types, including myeloid derived suppressor cells (MDSCs), M2 macrophages, and regulatory T cells (Tregs). Vigeo is addressing this critical unmet need by developing VT1021, a cyclic peptide derived from prosaposin that induces the expression of thrombospondin-1 (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. The induction of TSP-1 in MDSCs reprograms the TME from one that is immunosuppressive and tumor-promoting, to one that activates the adaptive immune system and is tumor-inhibiting. Specifically, TSP-1, via binding 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) (Kaur et al. 2010; Zhang et al. 2009; Russell et al. 2015). High levels of CD36 or CD47 are each poor prognostic indicators for many types of cancers (Enciu et al., 2018; Huang et al., 2020) and there are currently no drugs that target both molecules simultaneously. VT1021 is a first-in-class agent that 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 (NCT03364400). Seven subjects with pancreatic cancer were dosed in Part 1 and 32 were dosed in Part 2, 17 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

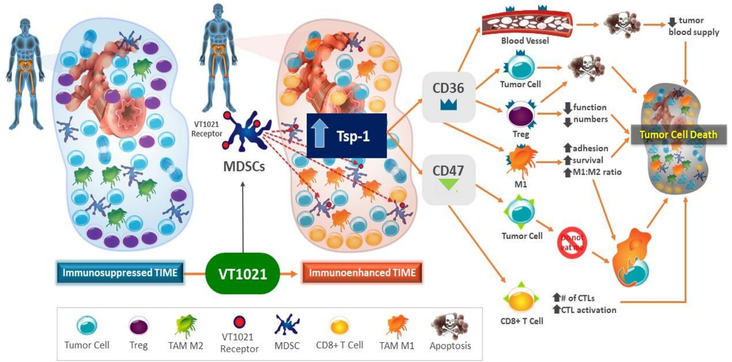

Figure 1. VT1021 reprograms the TME from one that is immunosuppressive to one that is immunoenhanced. The immunosuppressed tumor immune microenvironment (TIME) is characterized by high levels of Tregs, M2 tumor associated macrophages (M2 TAMs) and MDSCs. VT1021 binds to a receptor on MDSCs and induces 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.

Contact

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Safety Profile for Subjects with Pancreatic Cancer

Common AEs in escalation (Part 1) subjects with pancreatic cancer (AEs that occurred in ≥ 2 subjects, all cycles, maximum grade, regardless of toxicity)

AE Term	Total	Grade 1	Grade 2	Grade 3
Abdominal pain	4	3		1
Constipation	2	1		1
Nausea	2	2		
Fatigue	2	2		
Urinary tract infection	2		2	
Infusion related reaction	2		1	1
Thrombosis	2			2

Common AEs in expansion (Part 2) subjects with pancreatic cancer (AEs that occurred in ≥ 6 subjects, all cycles, maximum grade, regardless of toxicity)

AE Term	Total	Grade 1	Grade 2	Grade 3
Anaemia	7	4	2	1
Abdominal pain	16	3	9	4
Constipation	8	4	4	
Diarrhoea	8	5	3	
Nausea	14	10	3	1
Fatigue	14	3	8	3
Pyrexia	6	6		
Alanine aminotransferase increased	6	4		2
Aspartate aminotransferase increased	6	2	2	2
Blood bilirubin increased	7		3	4
Decreased appetite	11	7	2	2
Insomnia	6	6		

Out of 39 pancreatic cancer subjects enrolled and dosed:

- Escalation cohort (Part 1, 7 subjects enrolled)
  - All 7 subjects reported at least one AE (regardless of causality)
  - 4 subjects had at least one AE definitely, probably or possibly related to study drug
  - No dose-limiting toxicity
  - 5 subjects reported at least one SAE (regardless of causality)
  - 2 subjects had SAEs definitely or possibly related to study drug: infusion related reaction (grade 3), altered mental status (grade 2)
- Expansion cohort (Part 2, 32 subjects enrolled)
  - 30 subjects reported at least one AE (regardless of causality)
  - 18 subjects had at least one AE definitely, probably or possibly related to study drug
  - 20 subjects reported at least one SAE (regardless of causality)
  - 2 subjects had SAEs possibly related to study drug: thrombosis (grade 3), fever (grade 1)

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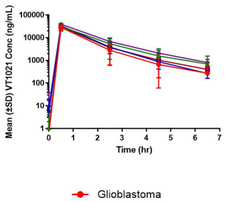


Expression Intensities of CD36 & CD47

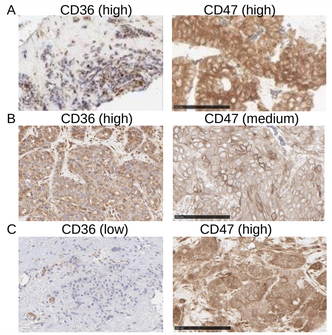


Figure 2. Expression intensities of CD36 and CD47 in subjects with pancreatic cancer. A. Dual high expression of both CD36 and CD47 in an evaluable subject. B. Non-dual high expression of CD36 and CD47 in an evaluable subject. C. Non-dual high expression of CD36 and CD47 in a non-evaluable subject.

Dual High Expression of CD36 & CD47 Correlates with Longer Days on Study and Reduced Tumor Burden

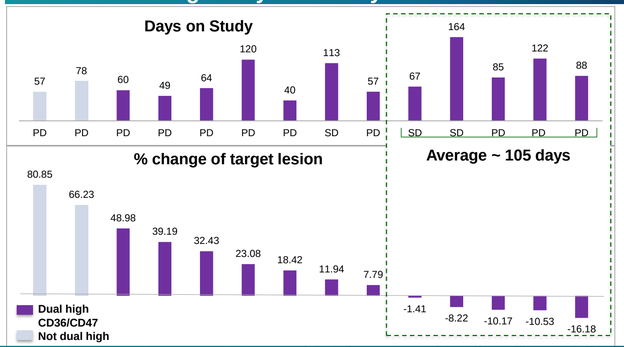


Figure 3. Waterfall plot for changes of tumor burden for 14 subjects in Part 2 with pancreatic cancer with measurable disease. Three out of 3 subjects with stable disease (100%) were dual high. Of the 14 subjects with measurable disease, all 5 subjects with reduction of tumor burden were dual high and remained on study for an average of 105 days.

VT1021 Modulates the TME in Pancreatic Cancer

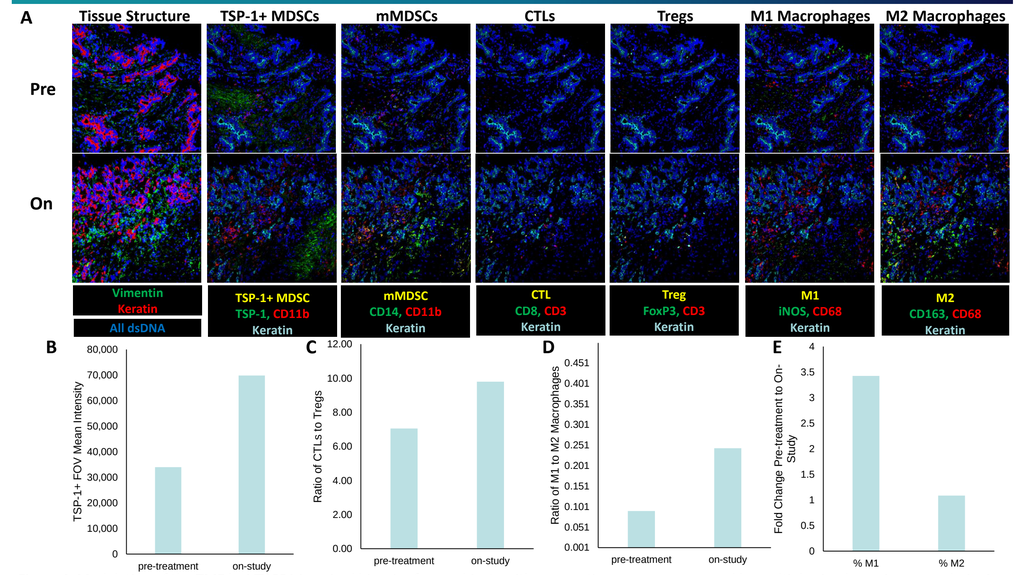
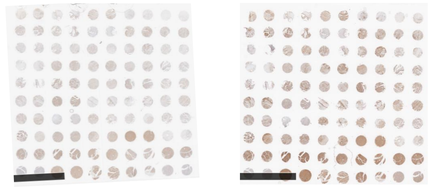


Figure 4. Modulation of the TME by VT1021 in paired biopsies from subjects with pancreatic cancer was assessed by multiplex ion beam image analysis. A. Representative images from 1 of 3 regions of interest in tumor biopsies from a subject obtained pre-treatment (pre) and on-study (on). B. TSP-1+ mean intensity, C. ratio of CTLs to Tregs, D. ratio of M1 to M2 macrophages and E. fold change of percent of M1 macrophages compared to total macrophages were quantified for 8 pairs of biopsies from Parts 1 & 2. TSP-1+ increased >2 fold in on-study biopsies compared to pre-treatment, both the CTL/Treg and M1/M2 macrophage ratios increased and the percent of M1 macrophages increased >3 fold in the TME after treatment with VT1021.

Dual High Expression of CD36 & CD47 Is a Potential Predictive Biomarker for Pancreatic Cancer



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Pancreatic Cancer	Cases	Dual High
All enrolled (Part 2)	32	63%
Evaluable (Part 2)	17	88%
TMA	100	56%
TMA-Stage IV	22	53%

Figure 5. High percentage of dual high CD36 and CD47 is observed in pancreatic cancer. A. Representative images of commercially available pancreatic tumor tissue microarrays stained and scored for dual high CD36 and CD47 B. Subjects in Part 2 with pancreatic cancer with dual high CD36 and CD47 were more likely to be considered evaluable in the Phase 1 study with VT1021.

Conclusions

Pancreatic cancer subjects 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 in the TME and in circulating PBMCs (see poster 375) was confirmed. Remodeling of the TME by VT1021 to be more immune sensitive via increased CTL/Tregs and M1 macrophage accumulation was demonstrated. Based on these findings, the dual high expression of CD36 and CD47 could be a useful predictive biomarker to stratify subjects for inclusion in future trials in pancreatic cancer.

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Clinical trial information: NCT03364400