Background VT1021, a cyclic pentapeptide, reprograms myeloid-derived suppressor cells (MDSCs) and induces the production of thrombospondin-1 (Tsp-1) in the tumor microenvironment (TME). Tsp-1, via binding to CD36 and CD47, induces 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). Preclinical studies showed robust anti-tumor activities of VT1021 in multiple animal models.

Methods This is a first-in-human, Ph 1/2, open-label, multicenter dose escalation and expansion study in advanced solid tumors. The primary objectives are to determine the recommended Phase 2 dose (RP2D) and characterize the safety and tolerability of VT1021. Secondary objectives are to characterize the adverse event (AE) profile, evaluate pharmacokinetics (PK), and describe preliminary efficacy. Exploratory objectives include evaluation of pharmacodynamic effects of VT1021 in tumor, TME, and peripheral blood. The expansion phase focuses on ovarian, pancreatic, triple negative breast cancer, glioblastoma, and a basket cohort with high CD36-expressing tumors.

Results In the escalation phase, 46 subjects received between 0.5–15.6 mg/kg of VT1021 by IV infusion twice weekly. VT1021 has been well tolerated through all doses tested. One patient dosed at 1.0 mg/kg developed a grade 3 infusion reaction and 3 patients dosed at 1.0, 6.6, and 8.8 mg/kg respectively developed grade 2 infusion reactions. Other drug related AEs included grade 1–2 fatigue (n=7), nausea (n=4), constipation (n=2), increased aspartate aminotransferase (n=2) and blood bilirubin (n=2), hypomagnesaemia (n=2), and dizziness (n=2). Dose proportionality was observed in PK analysis. Among 28 evaluable subjects, one partial response (thyroma, 372+ days on treatment) and 11 stable disease (SD) in 9 different solid tumors have been observed for a disease control rate of 43%. Seven of eleven SDs had high CD36 AND high CD47 expression with an average duration of 162 days on study. VT1021 induced Tsp-1 production in peripheral blood cells at most dose levels. In addition, on-study biopsies exhibited increased Tsp-1 expression in the TME by activation of p53 in MDSCs, increased CTL infiltration, increased M1:M2 macrophage ratio, and reduced regulatory T cells in the TME. The RP2D was declared to be 11.8 mg/kg and enrollment in tumor-specific expansions is on-going.

Conclusions Through all doses tested, VT1021 was safe and well tolerated, with dose proportional PK properties. In addition, VT1021 has demonstrated activities in reprogramming the TME which resulted in a high disease control rate in subjects with tumors expressing both high CD36 and high CD47.

Trial Registration NCT03364400

Ethics Approval The study was approved by Northwestern University Medical School institutional review board (IRB), approval number 00000418, Horizon Oncology Center IRB, approval number 0001313, South Texas Accelerated Research Therapeutic IRB, approval number 00003657, University of Oklahoma Health Sciences Center IRB, approval number 0006075, Cleveland Clinic IRB, approval number 0000536, Florida Cancer Specialists IRB, approval number 0006075, Case Western IRB, approval number 0000536, Beth Israel Deaconess Hospital and Dana Farber Cancer Institute IRB, approval number 00000573 and MD Anderson IRB, approval number 0006023.

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