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 tumors, 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 (thymoma), 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 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 treatment. VT1021 induced Tsp-1 production in peripheral blood lymphocytes (CTLs). Preclinic al studies showed robust anti-tumor activity and immune responses.

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 0000753 and MD Anderson approval number 00006023.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0374
Conclusions An early increase in HPV-16 specific T cells (after a single administration of bintrafusp alfa, prior to restaging) was associated with clinical activity in patients with HPV-related cancers undergoing bintrafusp alfa therapy. This evidence, and the pre-clinical finding of enhanced antitumor activity observed when combining bintrafusp alfa with an HPV-16 targeted vaccine and an immunostimulatory cytokine have provided the rationale for an ongoing study evaluating this combination in patients with advanced HPV-associated malignancies (NCT04287868).

Ethics Approval All patients provided written informed consent for participation in a clinical trial that was approved by the Institutional Review Board at the National Cancer Institute (NCT02517398, NCT03427411).

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0375

A PHASE I/II STUDY OF LIVE BIOTHERAPEUTIC MRX0518 IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS REFRACTORY TO IMMUNE CHECKPOINT INHIBITORS

Background MRx0518 is a novel, human gut microbiome-derived, single-strain, oral live biotherapeutic. It is a bacterium of the Enterococcus genus that was selected for development in the treatment of solid tumours for its strong in vitro and in vivo immunostimulatory activity. In vivo studies have shown that MRx0518 can inhibit tumour growth in different syngeneic cancer models as monotherapy and in combination with checkpoint inhibitors. MRx0518 has been shown to reduce Treg and increase Th1 and Tc1 lymphocyte differentiation in vitro, and increase intratumoral CD4+ and CD8+ T cells and NK cells in vivo.

Methods The study is being conducted in two parts. Part A is complete and evaluated safety of the combination therapy in a cohort of 12 mRCC and mNSCLC patients. This data was assessed by the Safety Review Committee and it was determined appropriate to proceed to Part B. Part B is now recruiting up to 30 additional patients per indication (RCC, NSCLC or bladder cancer) at several US sites. Patients in both parts must be refractory to checkpoint inhibition. This is defined as having had an initial benefit from PD-1 pathway targeting immune checkpoint inhibition (ICI) but developing disease progression confirmed by two radiological scans ≥4 weeks apart in the absence of rapid clinical progression and within 12 weeks of last dose of ICI. Patients are treated with 1 capsule of MRx0518 (1 × 10^{10} to 1 × 10^{11} CFU) twice daily and pembrolizumab (200 mg every 3 weeks) for up to 35 cycles or until disease progression. Tumour response is assessed every 9 weeks per RECIST. Blood, stool and urine samples are collected throughout the study to evaluate immune markers and microbiome. Patients may choose to consent to tissue biopsies. The primary objective of the study is to evaluate safety of the combination by monitoring toxicities in the first cycle of treatment. Secondary objectives are to evaluate efficacy via ORR, DOR, DCR (CR, PR or SD ≥6 months) and PFS. Exploratory objectives are to evaluate biomarkers of treatment effect, impact on microbiota and OS and correlation of clinical outcome with PD-L1 CPS/TPS.

Results N/A

Conclusions N/A

Trial Registration NCT03637803

Ethics Approval This study was approved by University of Texas MD Anderson’s Institutional Review Board; approval ref. 2018-0290

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0376

AGEN2373 IS A CD137 AGONIST ANTIBODY DESIGNED TO LEVERAGE OPTIMAL CD137 AND FCγR CO-TARGETING TO PROMOTE ANTITUMOR IMMUNOLOGIC EFFECTS

Background CD137 (4-1BB) represents a costimulatory pathway that promotes T, NK, and dendritic cell effector functions favorable for antitumor immunity. The extracellular domain of CD137, comprised of four cysteine-rich domains (CRD-I, CRD-II, CRD-III, CRD-IV), trimerizes upon binding to CD137 ligand (CD137L) to induce cell stimulatory transcriptional and epigenetic changes. The investigation of CD137-targeting agonist antibody, urelumab (CRD-I-binding, IgG4), in human subjects showed immunologic and pharmacodynamic effects, but poor efficacy due to dose-limiting liver toxicity. Preclinical studies using a murine surrogate antibody, clone 3H3 (CRD-I-binding, IgG2a), also demonstrated hepatotoxicity that correlated with activation of CD137-expressing myeloid cells and memory CD8+ T cells. In contrast, utomilumab (CRD-II/III-binding, IgG2) showed acceptable tolerability, but limited clinical efficacy. These and more recent findingsimplicate epitope and Fc gamma receptor (FcγR)-dependent antibody cross-linking as critical factors for CD137 therapeutic antibody design.

Methods We investigated the molecular and cellular effects of AGEN2373 (CRD-IV-binding, IgG1), a conditionally active CD137-targeting agonist antibody designed to bind and induce CD137 signaling upon FcγR cross-linking while permitting ligand binding to CD137. The role of epitope and FcγR binding as critical factors for anti-CD137 therapeutic activity were elucidated in primary cell-based assays and syngeneic tumor-bearing mouse models using anti-mouse antibody clones S3B1 (CRD-IV-binding) and 3H3, surrogates of AGEN2373 and urelumab, respectively. In an ongoing phase 1 trial (NCT04121676), we evaluated the safety and tolerability of AGEN2373.

Results AGEN2373 bound with high-affinity to CD137 CRD-IV and promoted potent agonist activity of CD137 that was...