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### A FIRST-IN-HUMAN PHASE 1/2 OPEN LABEL TRIAL EVALUATING THE SAFETY, PHARMACOLOGY, AND PRELIMINARY EFFICACY OF VT1021 IN SUBJECTS WITH ADVANCED SOLID TUMORS

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**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 (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 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 00001313, South Texas Accelerated Research Therapeutic IRB, approval number 00003657, University of Oklahoma Health Sciences Center IRB, approval number 00006075, Cleveland Clinic IRB, approval number 00000536, Florida Cancer Specialists IRB, approval number 00006075, Case Western IRB, approval number 00000536, Beth Israel Deaconess Hospital and Dana Farber Cancer Institute IRB, approval number 00000753 and MD Anderson IRB, approval number 00006023.

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### EXPANSION OF HPV-16 SPECIFIC T CELLS IN PATIENTS WITH HPV-RELATED CANCERS TREATED WITH BINTRAFUSP ALFA

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**Background** The safety and efficacy of bintrafusp alfa, a first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF- $\beta$ RII receptor (a TGF- $\beta$  ‘trap’) fused to a human IgG1 mAb blocking PD-L1, have been demonstrated in patients with human papillomavirus (HPV)-related cancers in an open label, multicenter phase 1 trial (NCT02517398), and an open-label, single center phase 2 trial (NCT03427411). The current study aimed to investigate whether HPV-16-specific T cells are expanded with therapy and associate with the clinical response of patients in these trials. We also present pre-clinical evidence from a mouse model of HPV-associated cancer supporting the combination of bintrafusp alfa with an HPV-16 targeted therapeutic vaccine and an immunostimulatory cytokine.

**Methods** Peripheral blood mononuclear cells (PBMC) were obtained from 33 patients prior to and 2 weeks after 1 and/or 3 cycles of bintrafusp alfa and evaluated for HPV-16 specific CD4+ and CD8+ T cells. PBMCs were stimulated with 15-mer peptide pools of the HPV-16 E6 and E7 oncoproteins, and T cell responses were assessed for the production of cytokines (TNF $\alpha$ , IFN $\gamma$ , IL-2) and positivity for the degranulation marker CD107a. Multifunctional T cells, positive for >2 measures, were also enumerated. For pre-clinical studies, a syngeneic mouse model of TC-1 carcinoma was treated with bintrafusp alfa alone or in combination with a liposomal-based HPV-16 therapeutic vaccine (PDS 0101) and a tumor targeting immunocytokine (NHS-muIL12) and evaluated for anti-tumor activity and immune responses.

**Results** HPV-16 specific T cells were increased after 1 cycle of bintrafusp alfa in a greater proportion of responders (9/14) than non-responders (4/17) (p=0.03). In addition, the magnitude of HPV-16 specific T cells was greater after 1 (p=0.04) and 3 (p<0.0001) cycles of bintrafusp alfa in responders than non-responders. Multifunctional HPV-16-specific T cells were also increased to a greater extent in responders than non-responders. Preclinical studies demonstrated that the combination of bintrafusp alfa with an HPV-16-targeted therapeutic vaccine along with an immunocytokine resulted in maximal anti-tumor activity and T cell responses.

**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)

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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  $\geq 6$  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

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

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**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. This phase I/II clinical study is evaluating the combination of MRx0518 and pembrolizumab in a cohort of heavily pre-treated patients refractory to immune checkpoint inhibitors (ICIs) to assess whether it is safe and can provide a clinical benefit.

**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  $\geq 4$  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 ( $1 \times 10^{10}$  to  $1 \times 10^{11}$  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

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### AGEN2373 IS A CD137 AGONIST ANTIBODY DESIGNED TO LEVERAGE OPTIMAL CD137 AND FC $\gamma$ R CO-TARGETING TO PROMOTE ANTITUMOR IMMUNOLOGIC EFFECTS

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**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.<sup>1-2</sup> 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.<sup>3</sup> Preclinical studies using a murine surrogate antibody, clone 3H3 (CRD-I-binding, rIgG2a), also demonstrated hepatotoxicity that correlated with activation of CD137-expressing myeloid cells and memory CD8+ T cells.<sup>4-5</sup> In contrast, utomilumab (CRD-II/III-binding, IgG2) showed acceptable tolerability, but limited clinical efficacy.<sup>6-7</sup> These and more recent findings implicate epitope and Fc gamma receptor (Fc $\gamma$ R)-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 Fc $\gamma$ R cross-linking while permitting ligand binding to CD137. The role of epitope and Fc $\gamma$ R 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 3S3B1 (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