Conclusions An early increase in HPV-16 specific T cells (after a single administration of bintrufusp alfa, prior to restaging) was associated with clinical activity in patients with HPV-related cancers undergoing bintrufusp alfa therapy. This evidence, and the pre-clinical finding of enhanced antitumor activity observed when combining bintrufusp 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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A PHASE III 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 a single, open-label, multicenter, phase 1 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

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AGEN2373 IS A CD137 AGONIST ANTIBODY DESIGNED TO LEVERAGE OPTIMAL CD137 AND FcγR 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.1 2 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.3 Preclinical studies using a murine surrogate antibody, clone H3 (CRD-I-binding, rIgG2a), also demonstrated hepatotoxicity that correlated with activation of CD137-expressing myeloid cells and memory CD8+ T cells.4 5 In contrast, utomilumab (CRD-II/III-binding, IgG2) showed acceptable tolerability, but limited clinical efficacy.6 7 These and more recent findings implicate 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 H3, 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...