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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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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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 designed to assess the efficacy 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

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, rIgG2a), 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 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 tumour-bearing mouse models using anti-mouse antibody clones S3B1 (CRD-IV-binding) and 3H3, surrogate 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
conditionally dependent on Fc-dependent antibody cross-linking. AGEN2373 surrogate, S3B1, showed comparable binding and cross-link dependent agonist activity. In CT26 tumor-bearing mice, S3B1 and 3H3 demonstrated complete tumor control that was not reproducible with a Fc-silent S3B1 antibody. The Fc-dependent activity of S3B1 correlated with induced immunologic changes in the TME including CD8 T cell expansion, NK cell activation, and Treg depletion. Patients with advanced solid cancers, treated with AGEN2373 up to 1 mg/kg every 4 weeks, demonstrate clinical activity with no evidence of hepatotoxicity.

Conclusions Conditional and potent agonist activity of AGEN2373 is dependent on binding to CD137 CRD-IV and FcγR. Preclinically, our data demonstrate that AGEN2373-like murine surrogate antibodies promote potent immune activation and anti-tumor immunity. Phase 1 clinical trials investigating the safety and efficacy of AGEN2373, alone or combination with basilimumab (anti- PD-1), are underway.

Trial Registration NCT04121676

REFERENCES


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A FIRST IN-HUMAN, MULTICENTER, OPEN-LABEL, DOSE-FINDING PHASE 1 STUDY OF THE IMMUNE STIMULATOR ANTIBODY CONJUGATE NJH395 IN PATIENTS WITH NONBREAST HER2+ ADVANCED MALIGNANCIES

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Background NJH395 is a first-in-class immune stimulator antibody conjugate (ISAC) consisting of a toll-like receptor 7 (TLR7) agonist conjugated to an anti-HER2 antibody. Antibody-mediated delivery of TLR7 may limit systemic toxicities previously seen with TLR agonists, while enhancing long-lasting antitumor immune response. In preclinical studies, NJH395 showed promising activity in HER2 expressing xenograft mouse models, and demonstrated immunogenicity and cytokine release in mice and nonhuman primates.

Methods This phase 1, first-in-human, open-label, multicenter study (NCT03696771) is evaluating the safety, tolerability, pharmacokinetics, and preliminary efficacy of NJH395 in patients with nonbreast HER2+ advanced malignancies. The study design includes two parts: single-ascending dose (SAD), followed by multiple-ascending dose. Primary endpoint is safety; key secondary endpoints include assessment of pharmacokinetics, immunogenicity, and overall response rate. Tumor response was evaluated 3 weeks after treatment in SAD. Evaluation of pharmacodynamic markers including tumor-infiltrating lymphocytes is the key exploratory objective.

Results Here, we report the results of the SAD part of this phase 1 study. As of July 01, 2020, 18 patients (10 males, 8 females; median age, 52.5 years [range, 42–74 years]) were enrolled in 5 dose cohorts (0.1–1.6 mg/kg). The tumor types included HER2+ colorectal cancer (N=11), gastroesophageal adenocarcinoma (N=2), non–small cell lung cancer (N=1), nasopharynx adenocarcinoma (N=1), pancreatic adenocarcinoma (N=1), bladder cancer (N=1), and small intestine adenocarcinoma (N=1). Seventeen patients reported 124 treatment-related adverse events. The most common (occurring in ≥20%) adverse events (AEs) of any grade (G) regardless of study drug relationship were cytokine release syndrome (55.6%, G=2), pyrexia (44.4%), nausea (44.4%), vomiting (33.3%), headache (33.3%), increased aspartate aminotransferase (AST, 33.3%), increased alanine aminotransferase (ALT, 27.8%), and lymphopenia/lymphocyte count decrease (27.8%). The most common ≥G3 AEs (occurring in ≥10%) were lymphopenia/lymphocyte count decrease (27.8%) and increased AST (11.1%). Five dose-limiting toxicities, all G3, were reported in 3 patients: 2 cases of AST increase (1 at 0.2 mg/kg; 1 at 1.6 mg/kg), 1 ALT increase (1.6 mg/kg), 1 aseptic meningitis (1.6 mg/kg), and 1 meningism (1.6 mg/kg). No complete/partial response was seen; 9 patients had stable disease by RECIST v1.1 at 3 weeks post treatment. An increase in CD8+T-cells was detected in on-treatment tumor biopsies in 5 patients. Pharmacokinetics showed a greater than dose proportional exposure of NJH395; anti-drug antibodies were detected in all tested patients (14/14).

Conclusions Single dosing of NJH395 showed significant but manageable toxicities in patients with nonbreast HER2+ advanced malignancies. Biomarker analysis is ongoing.

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Trial Registration ClinicalTrials.gov Identifier: NCT03696771

Ethics Approval The study was performed in accordance with ethical principles of the declaration of Helsinki and good clinical practice guidelines. The protocol and its amendments were approved by institutional review boards of each participating site.

Consent Written informed consent was obtained from each patient prior to enrolment in the study.

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