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 balstilimab (anti-PD-1), are underway.

Trial Registration NCT04121676

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378 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 $\geq$ 20%) adverse events (AEs) of any grade (G), regardless of study drug relationship were cytokine release syndrome (55.6%, G $\leq$ 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 $\geq$ G3 AEs (occurring in $\geq$ 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-positive 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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