INTERIM RESULTS OF A FIRST-IN-HUMAN PHASE 1 DOSE-ESCALATION TRIAL OF TAK-102, A GLYPICAN-3 TARGETED ARMORED CHIMERIC ANTIGEN RECEPTOR T-CELL IMMUNOTHERAPY IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background Glypican 3 (GPC3) is a member of the glypican family of heparan sulfate (HS) proteoglycans that are attached to the cell surface by a glycosylphosphatidylinositol (GPI) anchor. High GPC3 expression rates are present in numerous cancer types with high unmet medical needs, including hepatocellular carcinoma, squamous non-small cell lung cancer, upper gastrointestinal cancers, cervical cancer, and undifferentiated sarcomas. TAK-102 is a GPC3-targeted, interleukin (IL)-7- and CC chemokine ligand 19 (CCL19)-expressing autologous chimeric antigen receptor (CAR) T-cell immunotherapy. The addition of IL-7 and CCL19 to the construct is expected to support the expansion of memory subsets and persistence of CAR T cells. This is hypothesized to help overcome the challenges associated with an immunosuppressive tumor microenvironment, one of the foremost pathogenic mechanisms likely limiting the activity of non-armored CAR T-cell therapies in solid tumors. In vivo antitumor activity of TAK-102 was confirmed in NOD scid gamma mice engrafted with GPC3-positive human HepG2 cells.

Methods The first-in-human, Phase 1 dose-escalation study is evaluating TAK-102 in patients with GPC3-expressing solid tumors who are refractory or intolerant to standard treatments. TAK-102 is administered via a single infusion on 3 dose cohorts after lymphodepleting chemotherapy (fludarabine and cyclophosphamide): Cohort 1 (starting cohort), 1x10^7 CAR+ cells/body; Cohort 2, 1x10^8 CAR+ cells/body; Cohort 3, 1x10^9 CAR+ cells/body. Objectives include evaluation of safety, dose-limiting toxicity (DLT), recommended Phase 2 dose, cellular kinetic (CK) parameters, pharmacodynamic (PD) effects, and antitumor activity based on RECIST 1.1.

Results As of March 25, 2022, 4 patients were enrolled and infused with TAK-102 (Cohort 1: 3 patients, one each with gastric neuroendocrine carcinoma, liposarcoma, and hepatocellular carcinoma; Cohort 2: 1 patient with liposarcoma). No DLT, cytokine release syndrome, or neurotoxicity were observed in any of the patients. Two patients, one with hepatocellular carcinoma and the other with liposarcoma, achieved stable disease (SD). There was a dose-dependent increase in expansion and persistence based on peripherally measured TAK-102 transgene levels. Peripheral blood CK also trended with some of the cytokines’ kinetics, including interferon-γ, IL-12/23p40, and IL-10. Pre-/post-treatment paired tumor biopsies from a patient with hepatocellular carcinoma who was administered TAK-102 showed significant increase in endogenous T-cell infiltration and activation markers (CD69, granzyme B). The observed SD and accompanying changes in relevant tumor biomarker levels (alpha-fetoprotein, lactate dehydrogenase) are encouraging.

Conclusions TAK-102 is an autologous GPC3-targeted IL-7/CCL19 armored CAR T-cell immunotherapy. Preliminary data show an encouraging safety profile and CK/PD results. The dose-escalation study is ongoing (NCT04405778).

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Trial Registration www.clinicaltrials.gov; NCT04405778

Ethics Approval The study was approved by National Cancer Center Institution’s Ethics Board on 27 May 2020.