493 FIRST-IN-HUMAN PHASE 1/2 TRIAL TO EVALUATE THE SAFETY AND INITIAL CLINICAL ACTIVITY OF DUOBODY®-CD40×4–1BB (GEN1042) IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background Despite the preclinical promise of CD40 and 4-1BB as immuno-oncologic targets, clinical efforts evaluating these agonists as monotherapy have had limited success due to minimal efficacy and/or severe toxicity. DuoBody-CD40×4-1BB (GEN1042) is a first-in-class, bispecific, agonistic antibody that combines targeting and conditional activation of CD40 and 4-1BB on immune cells, resulting in enhanced priming and (re-)activation of tumor-specific immunity. Furthermore, preclinical data suggest that combination with anti–PD-1 can enhance antitumor activity. We present preliminary data from the ongoing, first-in-human, open-label, phase 1/2 trial of DuoBody-CD40×4-1BB in advanced solid tumors (NCT04083599).

Methods During dose escalation, patients with metastatic/unresectable non-CNS solid tumors who had exhausted standard therapies received flat-dose DuoBody-CD40×4-1BB (0.1–400 mg) intravenously every 3 weeks until disease progression or unacceptable toxicity. Primary endpoint was dose-limiting toxicity (DLT). Secondary endpoints included adverse events (AEs), pharmacokinetic parameters, and preliminary antitumor activity (RECIST v1.1). Pharmacodynamic biomarkers were assessed as exploratory endpoints.

Results As of June 11, 2021, 50 patients were enrolled (median age, 57 years). The most common cancer types were colorectal (22%), melanoma (20%), and non–small-cell lung cancer (8%). Patients received a median (range) of 2.5 (1–21) treatment cycles; Cmax was observed shortly after end of infusion. Treatment-related AEs occurring in ≥10% of patients (all grades; grade ≥3) were fatigue (22%; 0%), pyrexia (16%; 0%), nausea (10%; 0%), and transaminase elevation (10%; 6%). Maximum tolerated dose was not reached. One DLT of elevated transaminases (grade 4) was observed at the 200-mg dose that resolved upon corticosteroid administration. No drug-related grade ≥3 thrombocytopenia events were reported. Disease control, defined as best overall response of complete/partial response and stable disease, was achieved in 51% of patients (25/49), including 2 confirmed partial responses per RECIST v1.1 in melanoma and neuroendocrine lung cancer. Modulation of pharmacodynamic endpoints was observed across dose levels, with more pronounced effects near the 100-mg dose. Increases in peripheral IFN-γ, TARC (monocyte/DC chemokine), and proliferating CD8+ total and effector memory T cells were observed during cycle 1. Using physiologically based pharmacokinetic/pharmacodynamic modeling and available safety, efficacy, and pharmacodynamic data, 100 mg every 3 weeks was identified as the expansion dose for further evaluation.

Conclusions DuoBody-CD40×4-1BB demonstrated biologic and early antitumor activity with a favorable safety profile in patients with advanced solid tumors. Expansion cohorts, including combination therapy with PD-1 inhibitors, are currently enrolling.

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Trial Registration NCT04083599

Ethics Approval This trial is undertaken following full approval of the final protocol, amendments, informed consent form, applicable recruiting materials, and subject compensation programs by the Independent Ethics Committee/Institutional Review Board.

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