1181 GEN1042-MIGG2A, AN FC-INERT MOUSE-HUMAN CHIMERIC VARIANT OF GEN1042 (DUOBODY®-CD40X4–1BB), EXHIBITS *IN VIVO* ANTITUMOR ACTIVITY AND PERIPHERAL IMMUNE MODULATION

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Background GEN1042 (DuoBody®-CD40x4–1BB) is an investigational, novel, bispecific antibody that combines targeting and conditional activation of CD40 and 4–1BB on immune cells. We recently reported preclinical characterization and encouraging clinical activity of GEN1042 in solid tumors.[1 2] Here, we investigated *in vivo* biological activity and mechanism of action of GEN1042 using the mouse-human chimeric, Fc-inert, surrogate antibody GEN1042-mIgG2a in immunocompetent human CD40/human 4–1BB double knock-in (hCD40/h4–1BB dKI) mice.

Methods Biological activity of GEN1042-mIgG2a, compared to GEN1042, was evaluated *in vitro* using cell-based reporter assays and human T-cell proliferation assays. hCD40/h4–1BB dKI mice implanted subcutaneously with syngeneic colorectal MC38 tumors were treated systemically with biweekly doses of GEN1042-mIgG2a or isotype control after tumor establishment, and pharmacokinetics, tumor growth and survival were investigated. In a parallel study, dose-dependent effects on circulating immune cells and plasma cytokines were investigated. Pilot studies were performed to investigate combination of GEN1042-mIgG2a with PD-1 blockade and a platinum-based chemotherapy doublet.

Results Comparable biological activity of GEN1042 and GEN1042-mIgG2a was confirmed *in vitro*. Biweekly dosing of 1 and 10 mg/kg GEN1042-mIgG2a resulted in largely maintained plasma concentrations within predicted levels in tumor-bearing dKI mice. Treatment with 1 or 10 mg/kg GEN1042-mIgG2a delayed tumor growth with observed significance on Day 12 after the start of treatment ($p=0.0015$ and $p=0.0232$, respectively) and 1 mg/kg GEN1042-mIgG2a significantly improved progression-free survival compared to control ($p=0.001$). Antitumor activity at 1 mg/kg GEN1042-mIgG2a was associated with favorable peripheral immune modulation, including an increased pool of memory T cells, upregulation of T-cell activation markers, induction of 4–1BB and CD86 on B cells, and changes in plasma cytokine concentrations. Preliminary data for a combination of 1 mg/kg GEN1042-mIgG2a with PD-1 blockade and a platinum-based chemotherapy doublet indicate enhancement of survival by treatment with this combination over GEN1042-mIgG2a alone in this model, resulting in complete tumor regressions in 3 out of 10 mice.

Conclusions GEN1042-mIgG2a, a mouse-human chimeric surrogate for GEN1042, incited dose-dependent *in vivo* antitumor activity in immunocompetent MC38 tumor-bearing hCD40/h4–1BB dKI mice and generated a peripheral immune profile consistent with its hypothesized mechanism of action. Establishment of this model has enabled ongoing preclinical exploration of the hypothesis that combining GEN1042 with PD-1 blockade and a platinum-based chemotherapy doublet will potentiate antitumor activity through complementary immune modulatory effects. These data support ongoing clinical studies evaluating the combination of GEN1042 with pembrolizumab and chemotherapy in patients with advanced solid tumors (NCT04083599, NCT05491317).

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Ethics Approval Animal experiments were performed according to the guidelines of the Institutional Animal Care and Use Committee (IACUC) and in accordance with the regulations of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).

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