863 IN VITRO AND IN VIVO STUDIES ESTABLISH DUOBODY®-CD3XB7H4 AS A NOVEL DRUG CANDIDATE FOR THE TREATMENT OF SOLID CANCERS

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Background The immune checkpoint protein B7H4 is expressed on malignant cells in various solid cancers, whereas its expression is highly restricted in normal tissue. B7H4 is therefore an attractive target for a CD3 bispecific antibody (bsAb) therapeutic. Moreover, its expression is reported to be inversely correlated with PD-L1. Here, we describe the preclinical characterization of two B7H4-targeting CD3 bsAbs with different CD3 affinities, supporting the selection of our clinical lead, DuoBody-CD3xB7H4 (GEN1047).

Methods B7H4 protein expression in patient-derived samples was determined by immunohistochemistry. Controlled Fab-arm exchange of an Fc-silenced B7H4 antibody with two Fc-silenced CD3ϵ-binding antibodies generated two CD3xB7H4 bsAbs that differ in CD3 binding affinity by approximately 30-fold. In vitro T-cell mediated cytotoxicity, T-cell activation, and cytokine release were assayed using cocultures of B7H4-expressing tumor cells and healthy donor T cells. Nonclinical safety (NCS) of the two CD3xB7H4 bsAbs was assessed in cynomolgus monkeys, and antitumor activity of the clinical lead in vivo was tested in a patient-derived xenograft (PDX) screen in mice with a humanized immune system (HIS).

Results B7H4 protein expression was confirmed in tumor biopsies from multiple indications, including breast, ovarian and lung cancer. Both bsAbs induced target-specific and dose-dependent tumor cell kill in vitro. Maximal kill and T-cell activation were comparable for both variants, although the potency of the high CD3 affinity bsAb was higher. However, production of inflammatory cytokines at comparable effective concentrations (IC90) was lower for the low CD3 affinity bsAb. Single dose NCS studies in cynomolgus monkeys showed that both CD3xB7H4 bsAbs were well-tolerated. A dose-dependent increase in plasma cytokines IL-6 and MCP-1 2 hours after dosing was observed only with the high CD3 affinity bsAb. Based on these findings, the low CD3 affinity bsAb was selected for follow-up studies and named DuoBody-CD3xB7H4 (GEN1047). DuoBody-CD3xB7H4 demonstrated antitumor activity in vivo in a PDX screen in HIS mice. Repeated dosing of DuoBody-CD3xB7H4 in cynomolgus monkeys confirmed an acceptable safety profile up to the maximal dose tested (30 mg/kg).

Conclusions These studies describe the preclinical development of DuoBody-CD3xB7H4, a bsAb that induces T-cell mediated cytotoxicity of B7H4-positive tumor cells, which may provide an alternative therapeutic modality in the immune-oncology space for patients with solid cancers.

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). NCS studies were conducted at Citoxlab (Evreux, France) and Charles River Laboratories (Tranent, UK) in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Council of Europe).

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