DOSE SELECTION FOR DUOBODY®-PD-L1×4-1BB (GEN1046) USING A SEMIMECHANISTIC PHARMACOKINETICS/PHARMACODYNAMICS MODEL THAT LEVERAGES PRECLINICAL AND CLINICAL DATA

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Background DuoBody-PD-L1×4-1BB (GEN1046) is a class-defining bispecific antibody, designed to elicit an anti-tumor immune response by simultaneous and complementary blockade of PD-L1 on tumor cells and conditional stimulation of 4-1BB on T-cells and NK cells. Optimizing target engagement for a bispecific antibody is challenging, as it involves binding with two targets, and predicting trimer levels in tumors based on affinity of individual arms and target expression. Here we describe a semimechanistic, physiologically based pharmacokinetic/pharmacodynamic (PK/PD) model that predicts a dosing regimen for DuoBody-PD-L1×4-1BB, which results in the formation of maximum levels of a therapeutically active 4-1BB-bispecific antibody-PD-L1 trimolecular complex (trimer), and optimal PD-L1 receptor occupancy (RO).

Methods An integrated semimechanistic PK/PD model that describes the distribution of DuoBody-PD-L1×4-1BB into central and peripheral compartments and partitioning into tumor/lymph nodes was developed. The model used PK/PD data and physiological parameters from the literature for parameterizations of PD-L1 and 4-1BB expression levels and T-cell trafficking. The model incorporates dynamic binding of DuoBody-PD-L1×4-1BB to its targets to predict trimer formation and RO for PD-L1 in tumors. Model parameters were calibrated to match in vitro PD studies, such as analyses of T-cell proliferation and cytokine release, as well as clinical PK data. Sensitivity to model assumptions were assessed by varying PK/PD parameters, and assessing their impact on trimer formation and PD-L1 RO. The model was subsequently used to explore in vivo trimer levels and PD-L1 RO in tumors at various dosing regimens.

Results The model was able to adequately describe the PK of DuoBody-PD-L1×4-1BB in the central compartment. Simulations showed a bell-shaped response for average trimer levels in tumors that peaked at 100 mg every 3 weeks (Q3W), with doses >100 mg resulting in reduced trimer formation. Average PD-L1 receptor occupancy at the 100 mg dose was predicted to be approximately 70% over 21 days and increased at higher doses. Based on these model predictions, and available safety, anti-tumor activity, and PD data from the ongoing GCT1046-01 trial (NCT03917381), 100 mg Q3W was chosen as the expansion dose for further evaluation in Part 2 of the study.

Conclusions This semimechanistic PK/PD model provides a novel approach for dose selection of bispecific antibodies such as DuoBody-PD-L1×4-1BB, by using preclinical and clinical PK/PD data to predict formation of optimal trimer levels and PD-L1 receptor occupancy.

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Trial Registration Written informed consent, in accordance with principles that originated in the Declaration of Helsinki 2013, current ICH guidelines including ICH-GCP E6(R2),

applicable regulatory requirements, and sponsor policy, was provided by the patients.

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