(W-005) Utilizing PBPK/RO model for description of GEN1042 (BNT312) PK and prediction of trimer level to guide dose selection

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Objectives: GEN1042 (BNT312; DuoBody®-CD40x4-1BB) is an investigational bispecific antibody that combines targeting and conditional activation CD40 and 4-1BB on immune cells for stimulation of tumor-specific immune responses. GEN1042 is designed to induce CD40 and 4-1BB agonist activity by forming ternary complexes (trimers) necessary to mediate immune modulation of peripheral APC and T cells. Since quantifying these trimers is challenging in vivo, we used a model-based approach for evaluating trimers in tumors and lymph nodes (LN). The aims of this study were to describe PK of GEN1042 and to predict trimer levels of GEN1042 crosslinked to CD40 and 4-1BB in tumors and LN to guide GEN1042 dose selection.

Methods: A minimal PBPK/RO model was developed on the basis of a model published in [1]. The model describes:

(1) Six physiological compartments: plasma, LN, the interstitial space in normal tissues and tumor and the endosomal space within the capillary barrier in normal tissues and tumor

(2) Distribution of GEN1042:

- FcRn-dependent transport by endothelial cells (ECs) & competition with endogenous IgG;
- Trans-endothelial transport: convection (normal tissues) & diffusion (tumor);
- Lymphatic drainage from tissue/tumor.

(3) Elimination:

- ECs are considered as a primary site of mAb degradation (uptake by endothelial cells);
- Elimination via binding with target receptor and subsequent internalization from cell surface (TMDD).

(4) Binding of antibody with target receptor(s):

- first binding in 3D, second in 2D;
- formation of trimeric complex in the immunological synapse between cells;

- number of cells expressing this receptor and receptor expression.
- RO was implemented in accordance with [2].

To take into account the effect of GEN1042-induced IFN-γ and TNF-α increase on expression of CD40 by ECs, an empirical dependence of CD40 synthesis on the dose of GEN1042 was implemented in the model and its parameters were fitted against PK data after single administration of GEN1042.

Results: The PK of GEN1042 was well captured in the PBPK/RO model. The nonlinear PK profile of GEN1042 can be explained by drug elimination via interactions with CD40 expressed by ECs (TMDD effect).

Furthermore, the AUC for percentage of trimer levels on CD8+ T cells or antigen-presenting cells (APCs) in tumors (macrophages and myeloid dendritic cells [mDCs]) or LN (B cells or mDCs) at different dose levels was simulated. Maximum trimer engagement (>90% of the maximum) of 4-1BB on T cells and CD40 on APCs in tumors was observed at approximately 100 to 250 mg and from 50 to 250 mg, respectively. While predictions show peak trimer formation at a dose range of 100–250 mg, trimer engagement was observed at a broad dose range of 30–400 mg Q3W in tumors and LN.

Conclusions: The developed PBPK/RO model can adequately describe nonlinear PK of GEN1042 and predict levels of GEN1042 trimers crosslinked to CD40 and 4-1BB in tumors and LN to guide GEN1042 dose selection.

Citations: [1] Shchelokov D, Demin O. Jr, Cancer Res, 2020, 80, 2233

[2] Shchelokov D, Demin O. Jr, MAbs, 2023, 15(1):2156317