DEVELOPMENT AND APPLICATION OF PHYSIOLOGICALLY BASED PHARMACOKINETIC – PHARMACODYNAMIC (PBPK-PD) MODEL FOR DOSE OPTIMIZATION OF TAK-102: GPC3 TARGETED CAR-T ARMORED WITH IL-7 AND CCL-19


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Background TAK-102 is a GPC3 targeted CAR-T armored with IL-7 and CCL-19. The program is currently in Phase-1 dose escalation stage enrolling patients with GPC3 expressing solid tumors. Cohort 1 (DL = 10 Million CAR-T cells/body) and cohort 2 (DL = 100 Million CAR-T cells/body) enrollment is now complete. A PBPK-PD model was developed to characterize cellular kinetic (CK) data in peripheral blood by flow cytometry, a ddPCR assay and longitudinal total tumor volume data of enrolled patients. The developed model was further leveraged to explore the impact of GPC3 expression, initial tumor burden and CAR-T cell dose level on observed CK in patients.

Methods Firstly, a kinetic-pharmacodynamic (K-PD) model was developed to describe the recovery kinetics of host T-lymphocytes after lymphodepletion. Then, a fully human PBPK-PD model for TAK-102, compartmentalized into blood and relevant tissues, was developed where each tissue was further divided into vascular and extra-vascular sub-compartments. The tumor extra-vascular space consists of both GPC3 expressing and GPC3 non-expressing tumor cells. Target engagement was described by the formation of CAR-target complexes upon interaction between CAR-T and GPC3 expressing tumor cells in the model. These CAR-target complexes induce tumor volume depletion and expansion of total (bound and unbound) CAR-T cells. Effect of host T-lymphocytes on expansion of CAR-T cells (lymphodepletion mediated reduction of host T-lymphocytes would pose less competition for CAR-T cells to expand) was implemented in the model. The developed model was simulated to investigate the effect of initial tumor burden, GPC3 expression and CAR-T cell dose on CK.

Results The K-PD model was able to describe the host T-lymphocytes recovery kinetics post lymphodepleting chemotherapy (Fludarabine with Cyclophosphamide). The PBPK-PD model was able to capture the multiphasic cellular kinetic behaviour of CAR-T cells along with tumor kinetics. Lack of sensitivity of CAR-T expansion towards increasing dose levels (200 million-1 billion) was observed in model simulations. Steady increase in expansion was observed with increasing initial tumor burden (100 ML-1000 ML), keeping the dose and GPC3 expression fixed. Similar correlation between cellular expansion and GPC3 expression (1%-30%) was observed keeping the dose and initial tumor burden fixed.

Conclusions The developed model was able to describe the observed data, while accounting for tumor heterogeneity of CAR-T cells, impact of lymphodepletion regimen on CAR-T expansion and target-mediated expansion of effector CAR-T cells. Using model simulations, CAR-T expansion was found to be driven by initial tumor burden and GPC3 expression.

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