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Objectives: Flotetuzumab (MGD006 or S80880) is a bispecific DART molecule that recognizes CD3 and CD123 membrane proteins, redirecting T-cells to kill CD123-expressing cells [1]. A mechanistic population pharmacokinetic/pharmacodynamic (PK/PD) model was developed to characterize its exposure-response relationships and the impact of its immunogenicity in cynomolgus monkeys.

Methods: 32 monkeys received multiple escalating doses via intravenous infusion continuously for 4-days weekly. Free plasma flotetuzumab concentrations, anti-drug antibody (ADA) development, and T-cell and CD123-cell counts were integrated into the model, which included sequential binding of flotetuzumab to CD3 and CD123 receptors (K_D 9.2 and 0.27 nM) [2]. 8 monkeys receiving 7-day continuous infusions were used to externally assess model performance. Modeling and simulations were performed with MONOLIX and Berkeley-Madonna.

Results: A two-compartment model with linear and ADA-mediated elimination described the PK profiles well (mean clearance 0.707 L/hr). Flotetuzumab-CD3 binding resulted in dose-dependent T-cell trafficking, captured by an indirect response model (IC_50 1.18×10^{-3} pmol/L), which was suppressed in ADA presence. Formation of the tri-molecular complex led to T-cell activation, captured with a virtual compartment (stimulation factor 2.1×10^6 cells/pmol). Activated T-cells acquired self-proliferation capacity (mean duration 411 hr) and drove the peripheral depletion of CD123-cells (second-order rate constant 2.1 hr^{-1}). CD123-cell depletion could persist after ADA-mediated drug elimination. Model predictions of 7-day infusion treatments were consistent with observations.

Conclusions: A mechanistic PK/PD model was developed in which T-cell activation and expansion was used as a key driver of flotetuzumab pharmacological activity. It should be noted that no ADA has been observed in 16 patients treated with flotetuzumab and analyzed for such response as part of the ongoing clinical study.