

Cell-Level Pharmacodynamics-Mediated Drug Disposition Model for GI-102 (CD80/IL2v3) in Patients with Advanced or Metastatic Solid Tumors

INTRODUCTION

- GI-102 (CD80/IL2v3) is a novel immunocytokine designed to direct interleukin-2 variant (IL-2v3) to immune cells and tumor cells.
- Proliferation and activation of cytotoxic T (T_c) cells and natural killer (NK) are enhanced through selective binding affinity to IL-2Rβγ and cis-binding of CD80 to PD-L1, and the effects of IL-2 on regulatory T cells (T_{reg}) are minimized.
- GII-102-P101 (KEYNOTE-G08) (phase 1/2) study is currently ongoing in patients with advanced or metastatic solid tumors to evaluate the optimal dose(s), anti-tumor activity, safety, and tolerability of GI-102 [1].
- The aim of modeling and simulation was to 1) assess relationship between drug exposure, target receptor occupancy, and pharmacodynamic (PD) effect, and 2) provide supportive information for determining the optimal dose range(s).

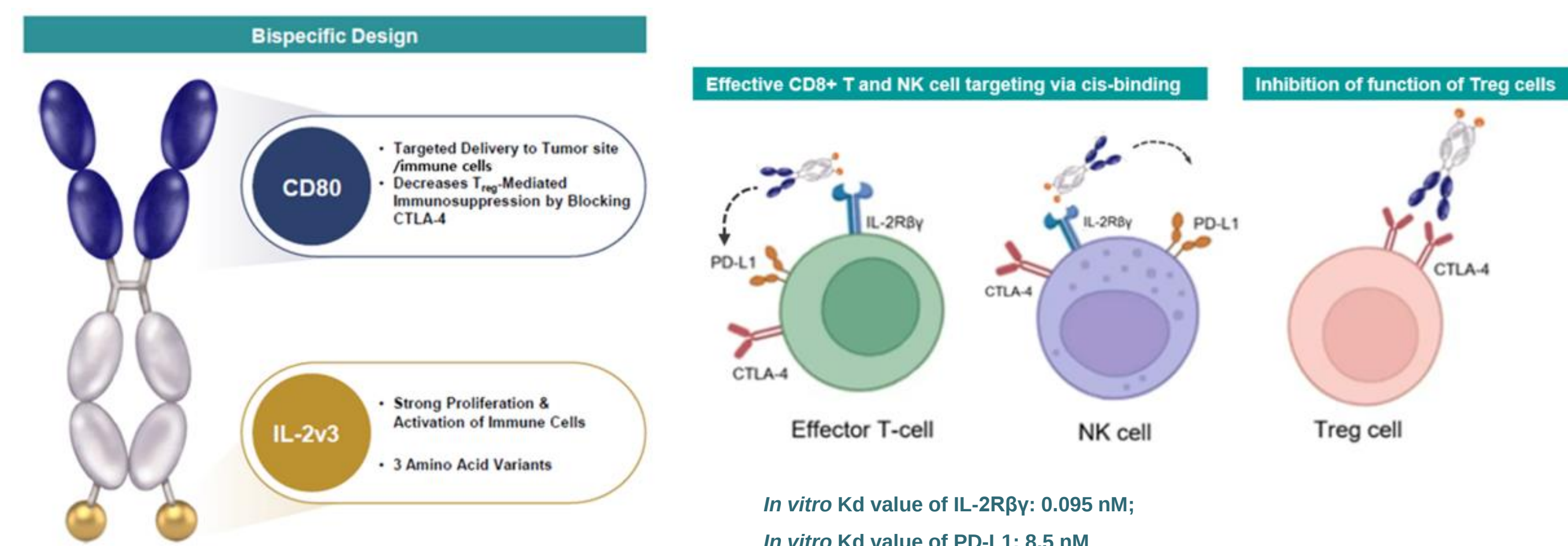


Figure 1. GI-102 structure and mechanism of action

METHODS

- The model was constructed by simultaneously fitting the available drug concentrations data (number of observations, n=966) along with total lymphocyte (n=620), T_c cell (n=368) and NK cell (n=368) counts data from a dose escalation phase of the GII-102-P101 study that included 41 patients administered with GI-102 via intravenous infusion every three weeks (Q3W), at doses ranging from 0.06 to 0.45 mg/kg. The dose escalation phase of the study was ongoing at the time of analysis.
- The PK model was based on the target-mediated drug disposition principle where GI-102 binds to IL-2Rβγ and undergoes target-mediated elimination as well as nonspecific elimination. The model incorporated time-varying PD-mediated disposition, as the increased proliferation of lymphocytes stimulated by the drug-receptor complexes affects the target receptors pool, subsequently influencing drug distribution and elimination. Additionally, a cell-level component was incorporated into the model by describing turnover and binding of the 1000 IL-2Rβγ expressed on a single cell [2,3].

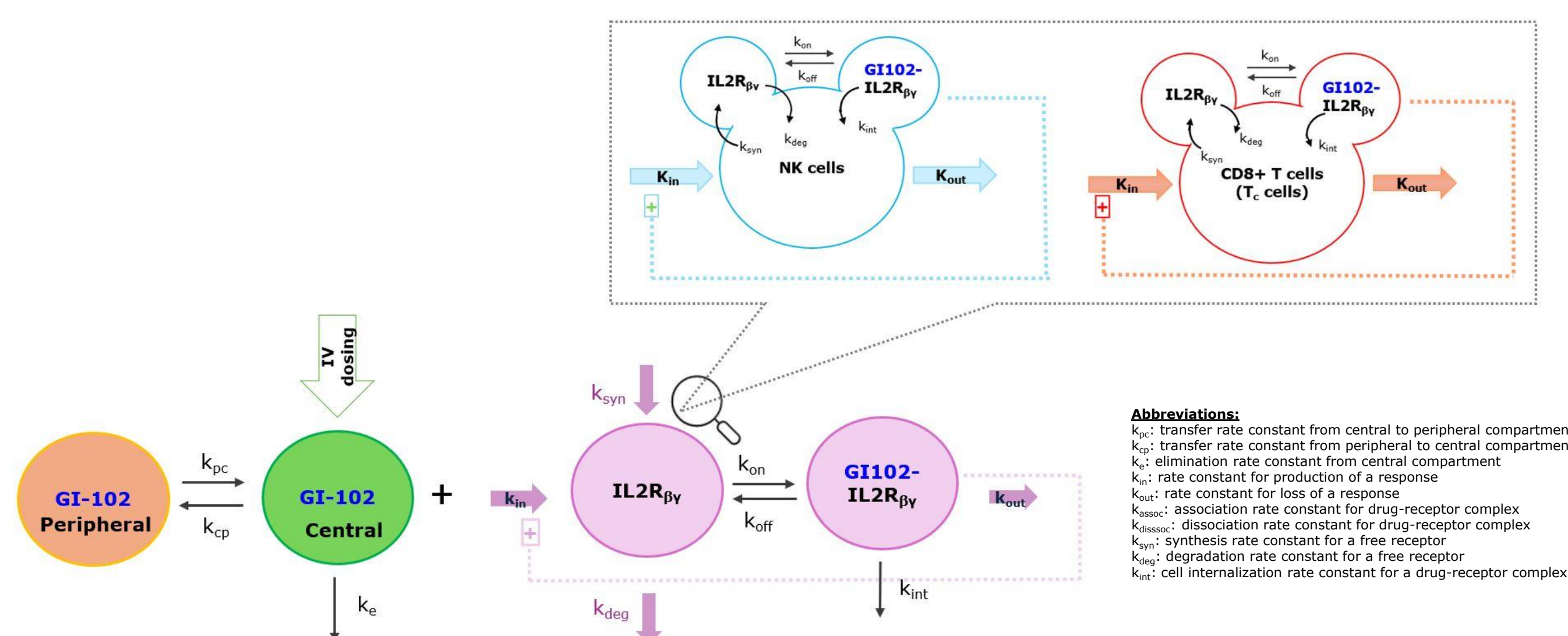


Figure 2. Schematic diagram for GI-102 Cell-level Pharmacodynamics-Mediated Drug Disposition Model (PDMDD) model

- The time delay between the drug concentrations and the increase in cell counts, driven by the stimulation of cell production by GI-102, was described by indirect response model combined with an operational model of agonism (OMA).

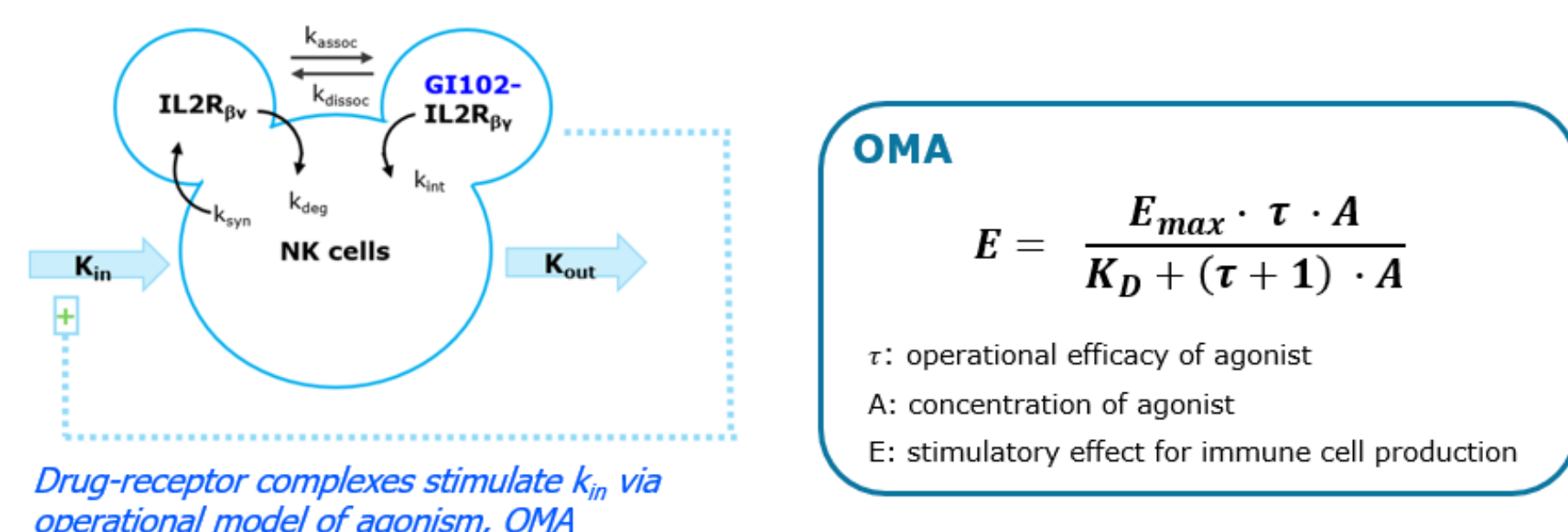


Figure 3. Schematic diagram for Indirect response PD model with operational model of agonism

- In line with the proposed mechanism of action, it was assumed in the model that the increase in total lymphocytes with GI-102 treatment is attributed to the sum of increases in three simplified subsets: T_c cells, NK cells, and other cells.
- The margination and diapedesis of lymphocytes into tissues immediately following treatment with GI-102 were described empirically.
- A mixture model was applied to account for the bimodal distribution of the observed cell counts among patients.
- An interim PK-PD model was constructed mainly based on graphical assessments.
- Modeling and simulation was conducted using NONMEM® version 7.5.0, and data processing and plotting were performed with R v4.3.3 [4,5].

REFERENCES

- Lee J, et al. A first-in-human, phase 1/2a study of GI-102 (CD80-IL2v3) in patients with advanced or metastatic solid tumors: Initial results from dose escalation. J Clin Oncol. 2024;42:2598
- Krzyzanski Wojciech, et al. A cell-level model of pharmacodynamics-mediated drug disposition. J Pharmacokinet Pharmacodyn. 2016 Sep, 43:513-527.
- Hofer T, et al. Competition for IL-2 between regulatory and effector T cells to chisel immune responses. Frontiers in immunology. 2012 Sep, 3:268
- Robert J, Bauer. NONMEM Tutorial Part I: Description of Commands and Options, With Simple Examples of Population Analysis. CPT Pharmacometrics Syst. Pharmacol. (2019) 8, 525–537.
- R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria, 2018. <https://www.R-project.org/>

RESULTS

- The developed interim model was deemed adequate for predicting central tendency of PK/PD data but may slightly underpredict total lymphocytes and NK cell count.

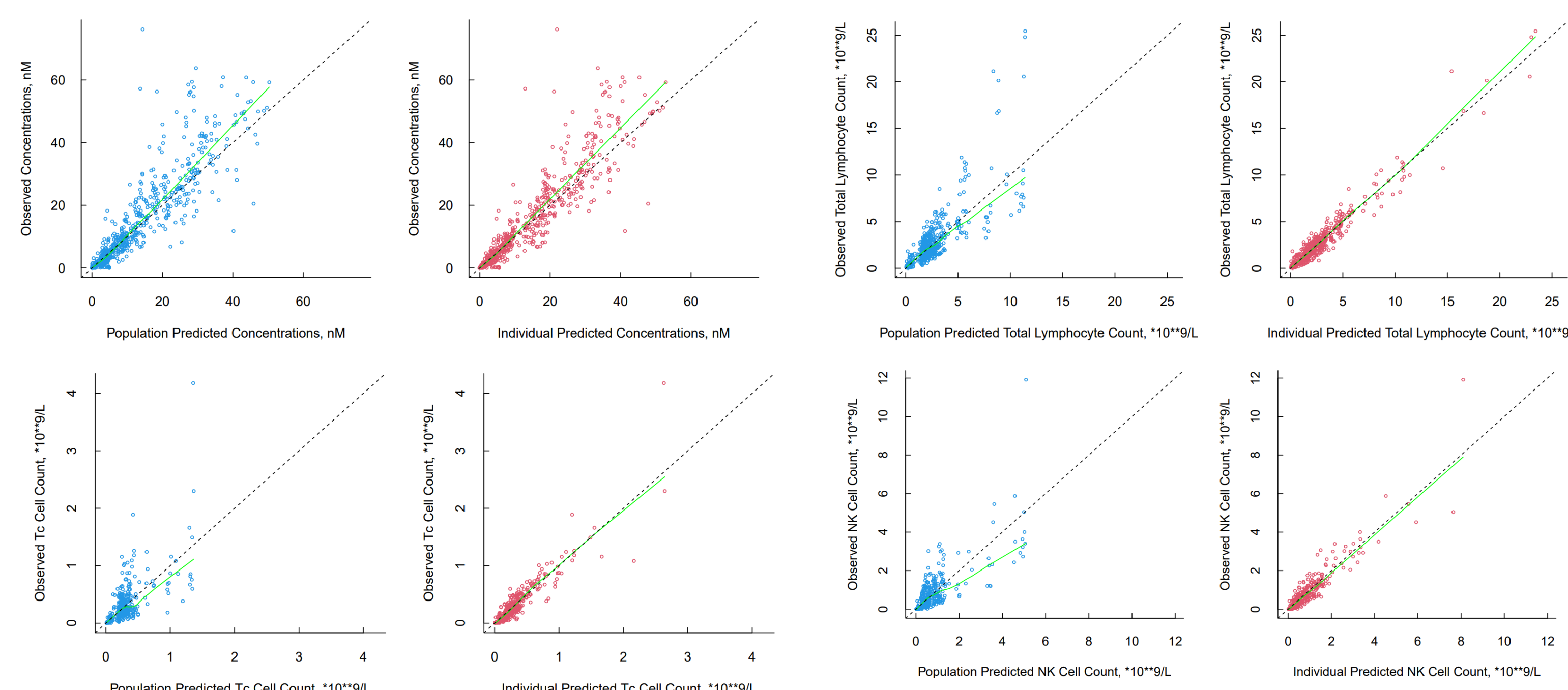


Figure 4. Basic goodness-of-fit plots for GI-102 concentration, total lymphocyte count, T_c and NK cell counts

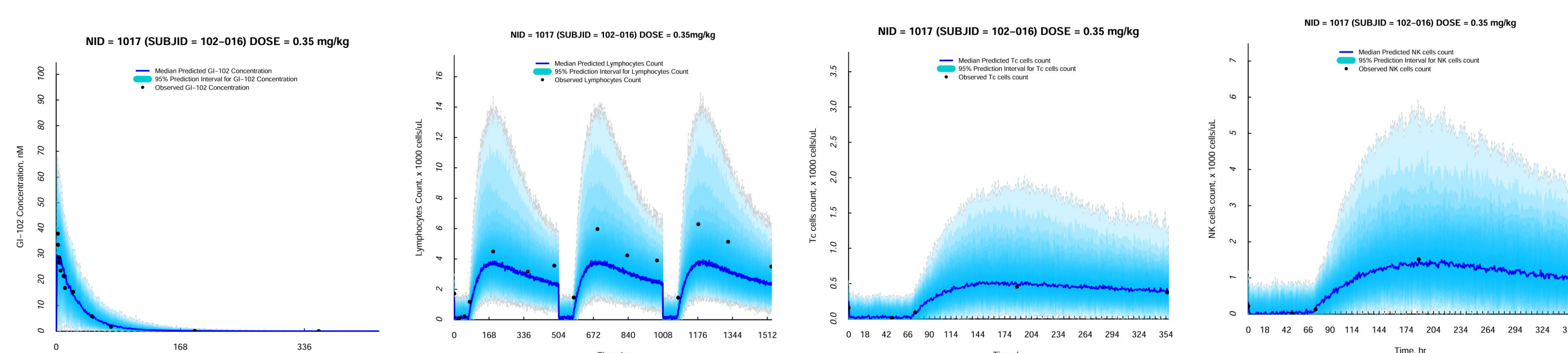


Figure 5. Individual scatter visual predictive check for GI-102 concentration, total lymphocyte count, T_c and NK cell counts (Subject receiving 0.35 mg/kg dose shown as a representative example)

Simulation scenario: IV infusion over 1 hour, Q3W, with diapedesis

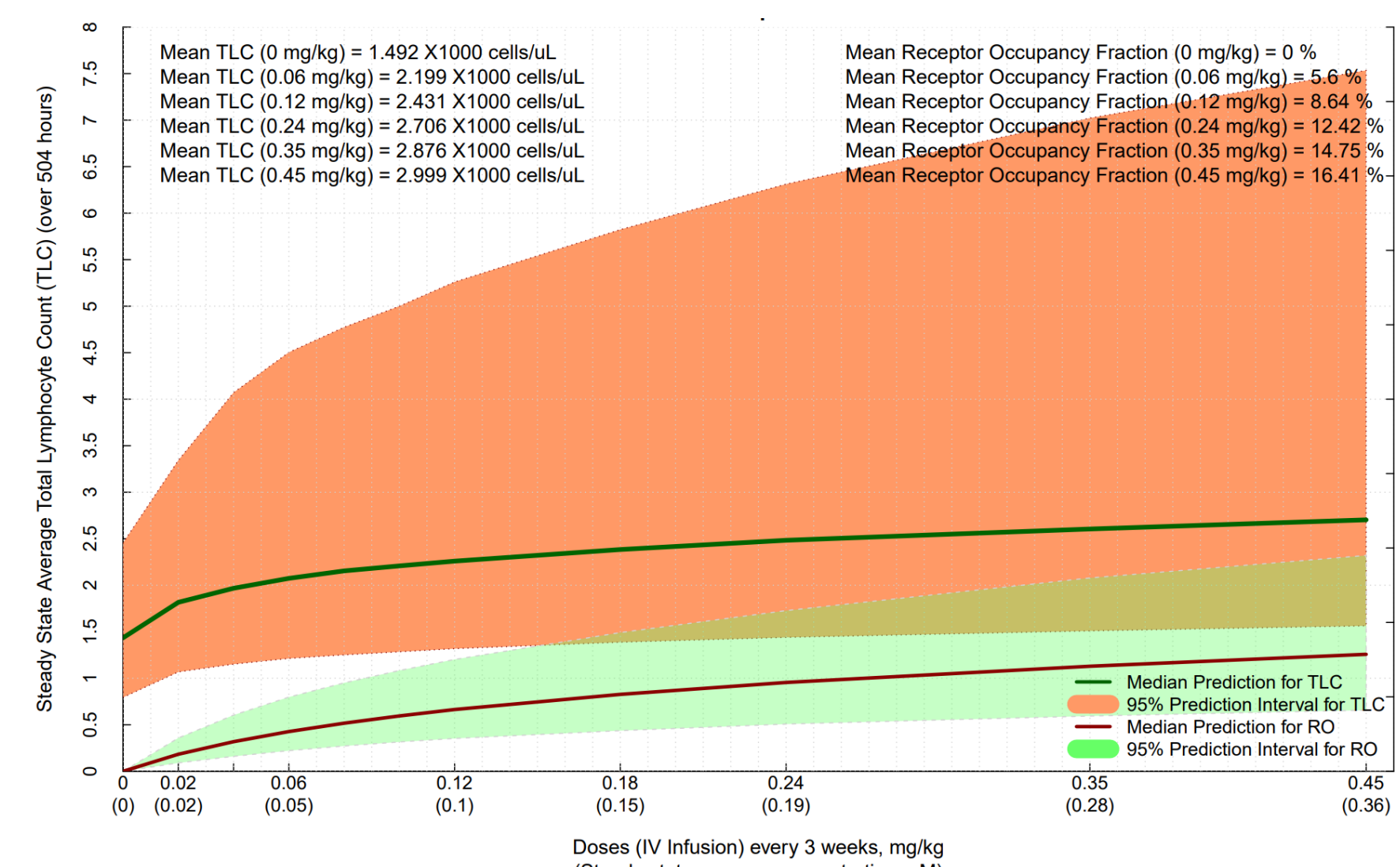


Figure 6. Simulated exposure-steady-state average total lymphocyte count (TLC) and fraction of IL-2Rβγ at various doses

- Clear exposure-response relationship was shown: Steep rise in cell counts at lower doses followed by a gradual, dose-dependent increase at higher doses
- The higher dose range (e.g., 0.24-0.45 mg/kg) showed a significant increase in total lymphocytes, with a mean predicted level reaching ~2900 cells/μL at 0.35 mg/kg.
- The average predicted maximum total lymphocyte count-to-baseline ratio was ≥ 3 starting at the 0.24 mg/kg dose level. This aligned with clinical findings, where significant increase in progression-free survival was associated with a > 3-fold lymphocyte expansion from baseline [1].

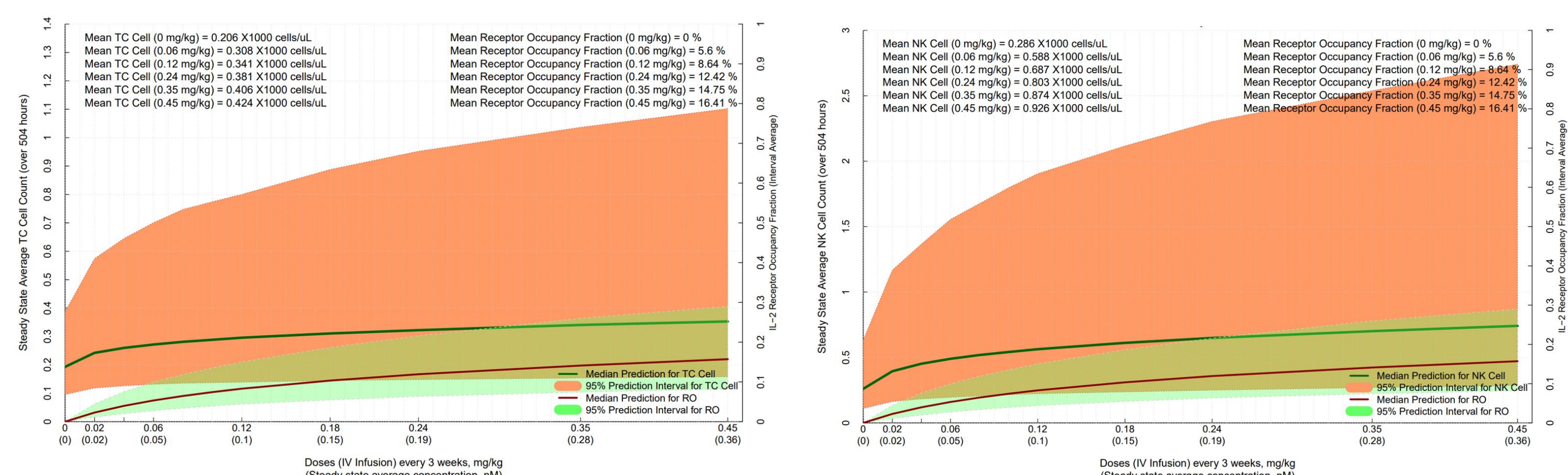


Figure 7. Simulated exposure-steady-state average Tc cell count (image on left) and NK cell count (image on right) and the corresponding fraction of IL-2Rβγ at various doses

- Proliferation of T_c and NK cells were observed at all tested doses with less than half of all receptors being occupied.
- The maximum stimulatory effect for stimulation of T_c cell and NK cell proliferation from the indirect response PD model was 1.5303 and 5.8668, respectively, for most of the population (subpop 1), and 5.2534 and 25.599 for the rest of subpopulation (subpop 2). The EC₅₀ value for the stimulation of T_c and NK cell counts proliferation was 0.0812 nmol/L and 0.0883 nmol/L, respectively, for subpop 1, and 0.0478 nmol/L and 0.0661 nmol/L for subpop2. These values were lower than K_D of 0.0949 nmol/L.

CONCLUSION

- A cell-level PDMDD model and an indirect response model in combination with OMA provided insights into the relationship between GI-102 exposure, IL-2Rβγ occupancy and increase in immune cell counts.
- While further research is necessary to update the model with complete dose escalation data, the current analysis provides preliminary prediction of the drug's PD effect at the tested doses, serving as a reference for determining the optimal dose range.