

Application of Quantitative Systems Pharmacology (QSP) Approach to Guide Development of a Bispecific CD40-EpCAM Antibody, KK2269

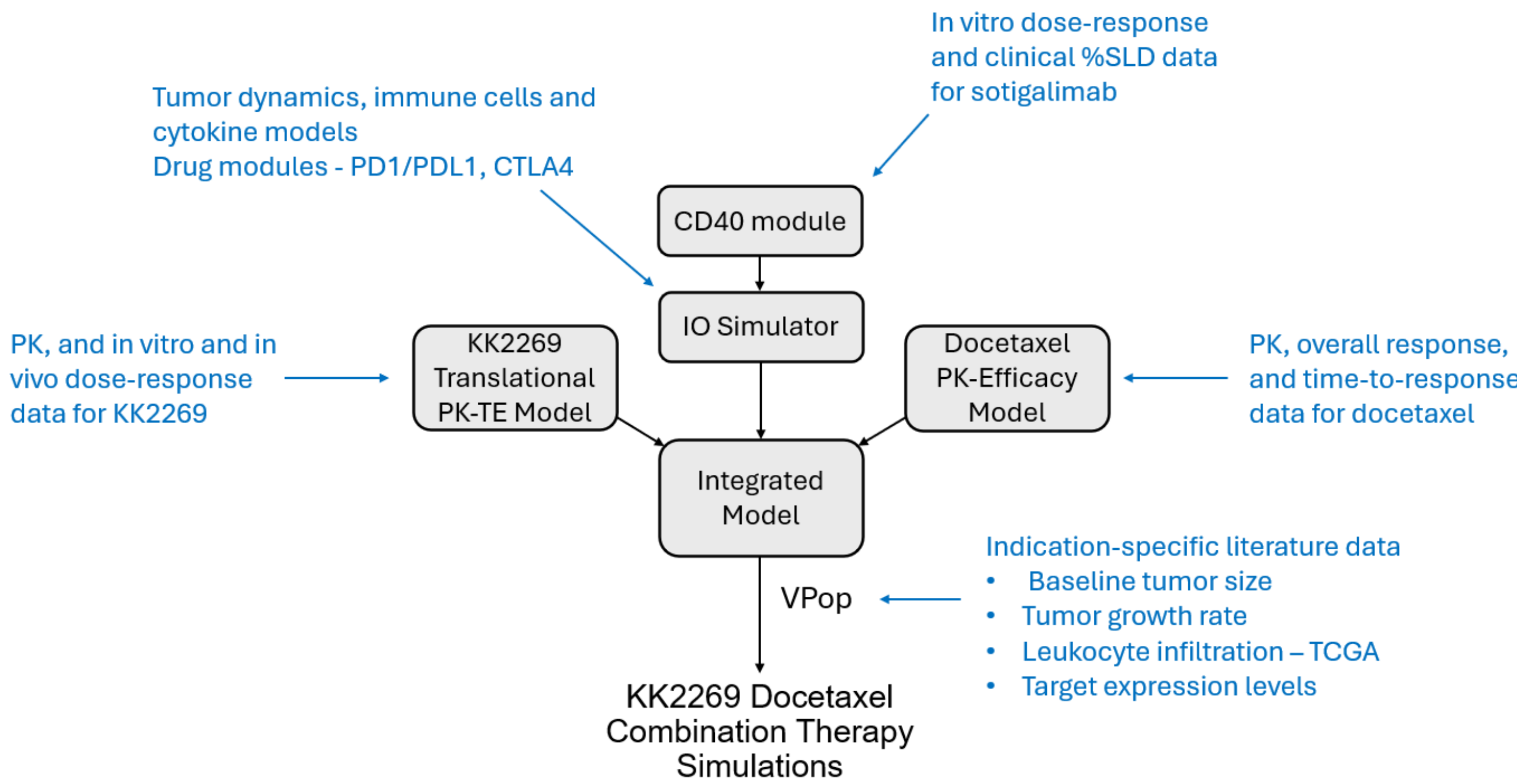
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Background and Objective

- KK2269 is a novel bispecific antibody binding CD40 and epithelial cell adhesion molecule (EpCAM) for targeting solid tumors.
- KK2269 has a dual receptor-dependent mechanism that increases selectivity in anti-tumor activities and reduces off-target effects observed for systemic/monoclonal CD40 agonists. The key objectives of this work were,
 - To develop a modular IO model including effects of CD40 agonism and docetaxel chemotherapy to support combination therapy development in solid tumor indication¹.
 - To predict KK2269 and docetaxel combination therapy following different dosing regimens using virtual trials in solid tumor indications

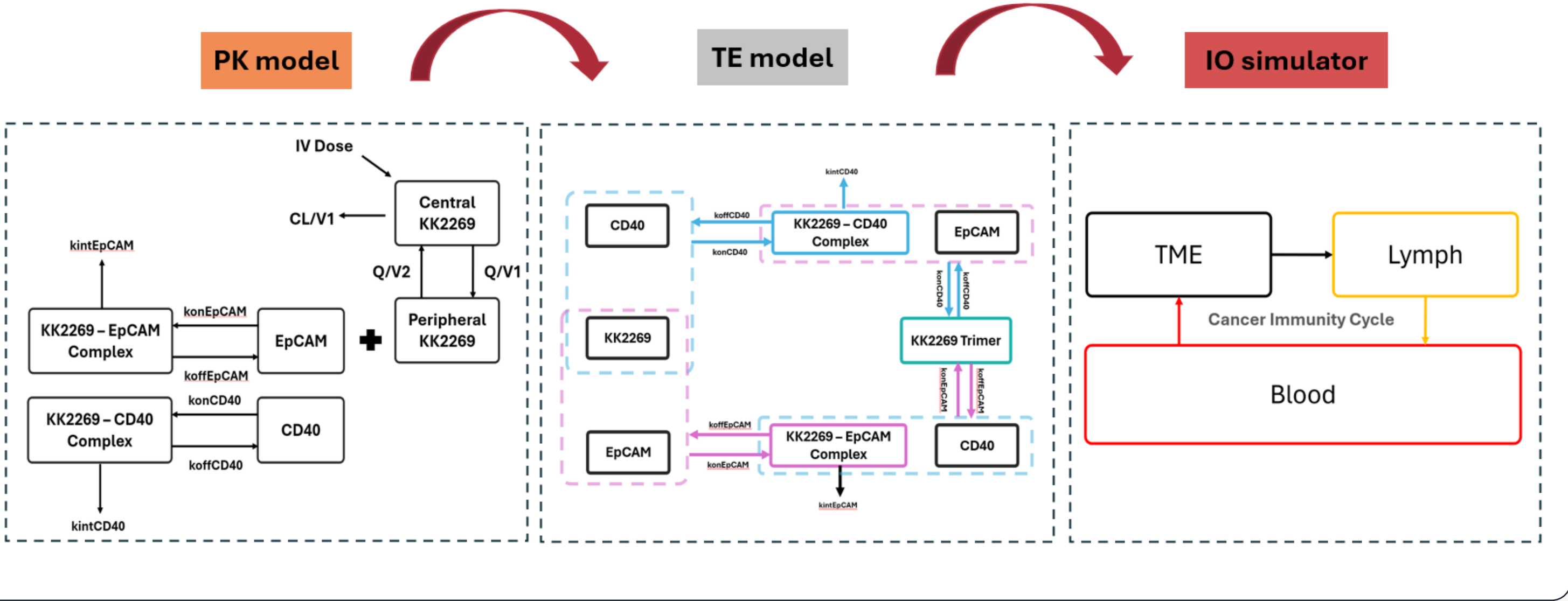
Figure 1. Workflow for KK2269 docetaxel combination therapy simulations.



Methods

- IO Simulator² is extended as a drug companion model.
- The models developed, integrated and simulated with QSP Designer³ platform.
- Previously developed KK2269 translational PK-TE model⁴ was integrated with the IO Simulator².
- Mechanisms of CD40-mediated immune activation was integrated in the IO Simulator using published in vitro⁵ and clinical trial data⁶ from anti-CD40 antibody, sotigalimab.
- Mechanism of docetaxel chemotherapy induced tumor killing was incorporated in the model using published docetaxel monotherapy data.
- We created virtual population based on literature data. We leveraged immune landscape of cancer database to incorporate leukocyte infiltrations in different solid tumors.
- The integrated model was used to perform KK2269 docetaxel combination therapy virtual trial simulations.
- KK2269 PK-TE model is linked to the IO Simulator, enabling simulation of immune dynamics through the inclusion of the CD40 pathway (Fig. 2).

Figure 2. Key mechanism of actions in the model.



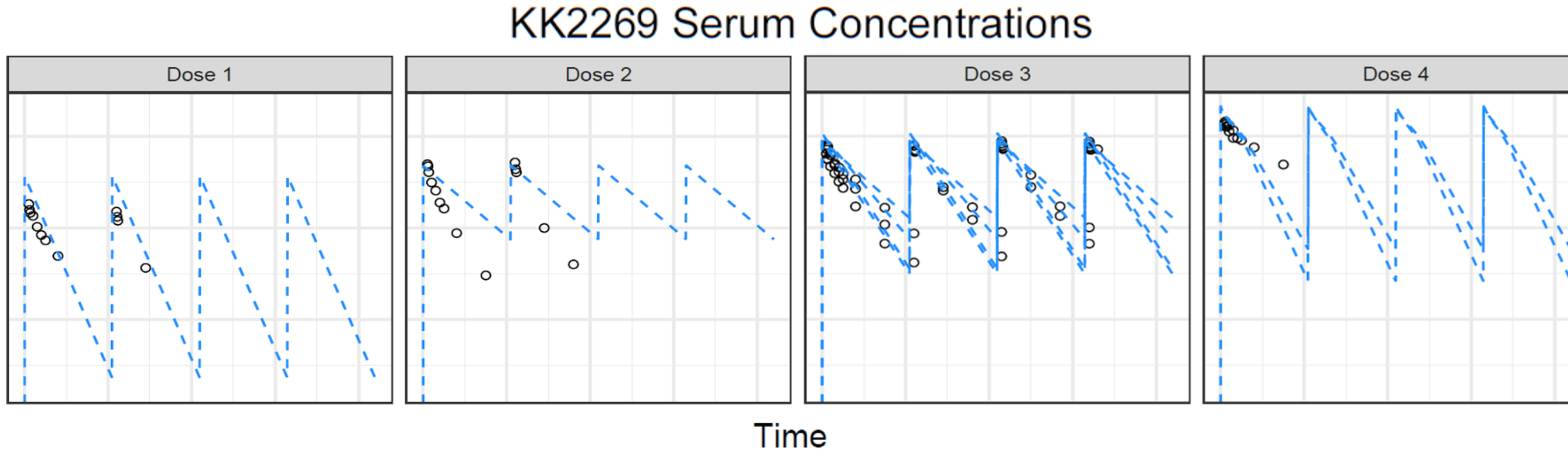
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Results

- The predictions for KK2269 from the translational PK model aligned reasonably well with the preliminary clinical PK data (Fig. 3).

Figure 3. PK of the translational model vs observations.



- The CD40 pathway within the IO Simulator has been significantly refined using sotigalimab in vitro dose-response data, offering detailed depiction of CD40-mediated immune activation.
- We first generated plausible patients⁷, next we calibrated virtual population using distributions of clinical waterfall plot and the distribution of tumor-infiltrating leukocytes at baseline (TCGA data⁸).
- The model predicted sotigalimab monotherapy efficacy outcomes were consistent with the published clinical observations⁶ (Fig. 5).
- The simulations of docetaxel monotherapy aligned well with the observed time-to-response kinetics (Fig. 6) and clinical outcomes data^{9,10}. (Fig. 4,6).

Figure 4. DTX monotherapy results for observed⁹ vs predictions for NCT03624309.

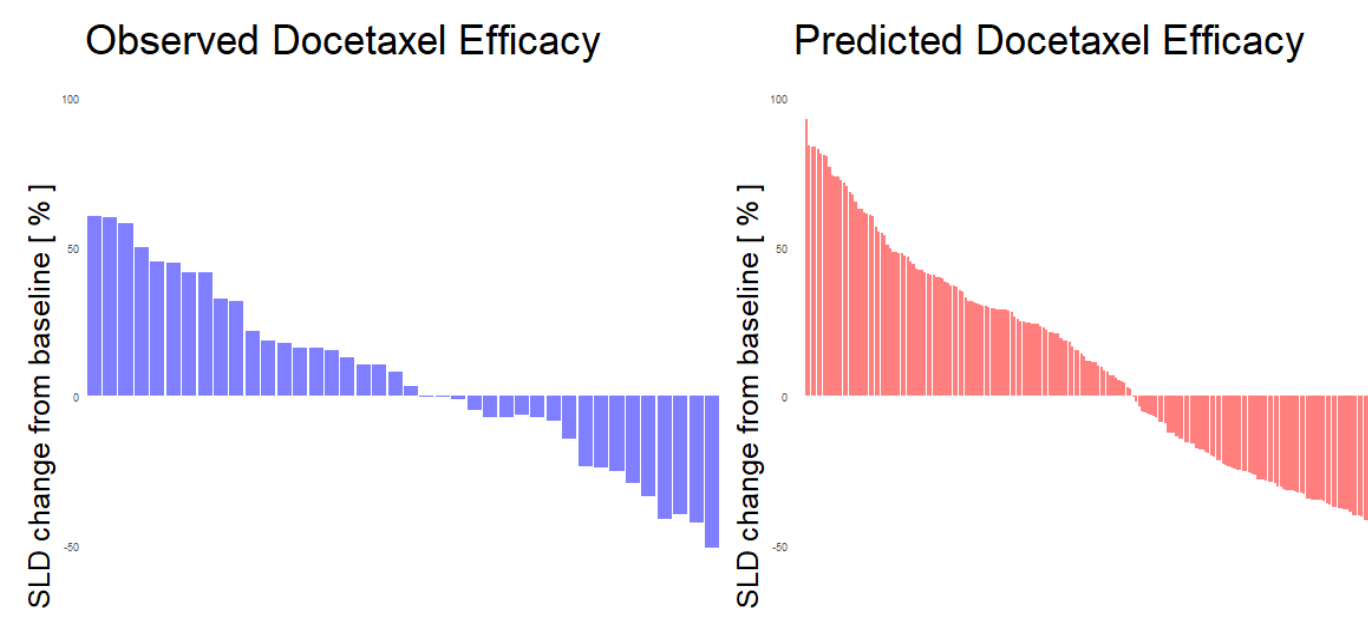


Figure 5. Sotigalimab monotherapy results for observed⁶ vs predictions.

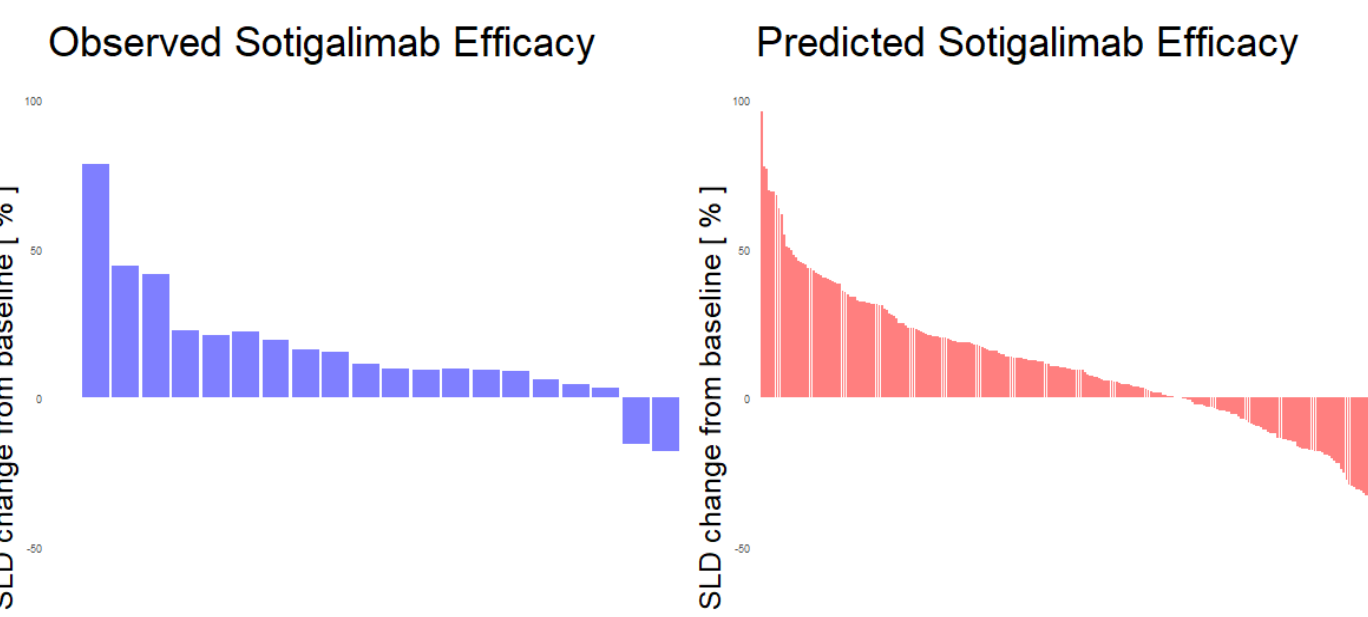
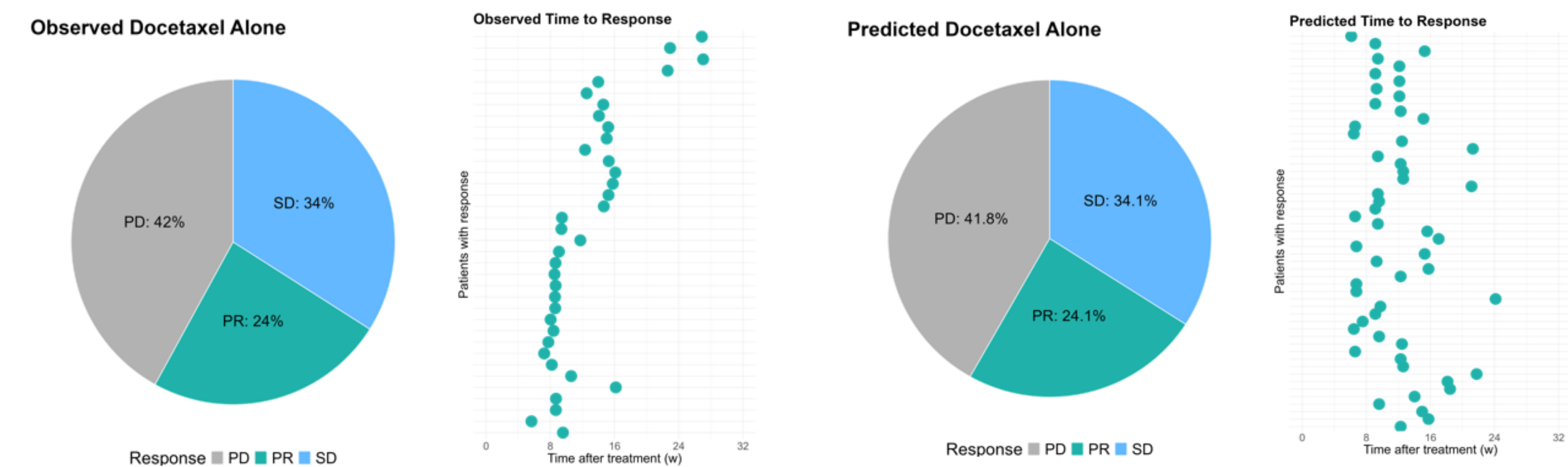
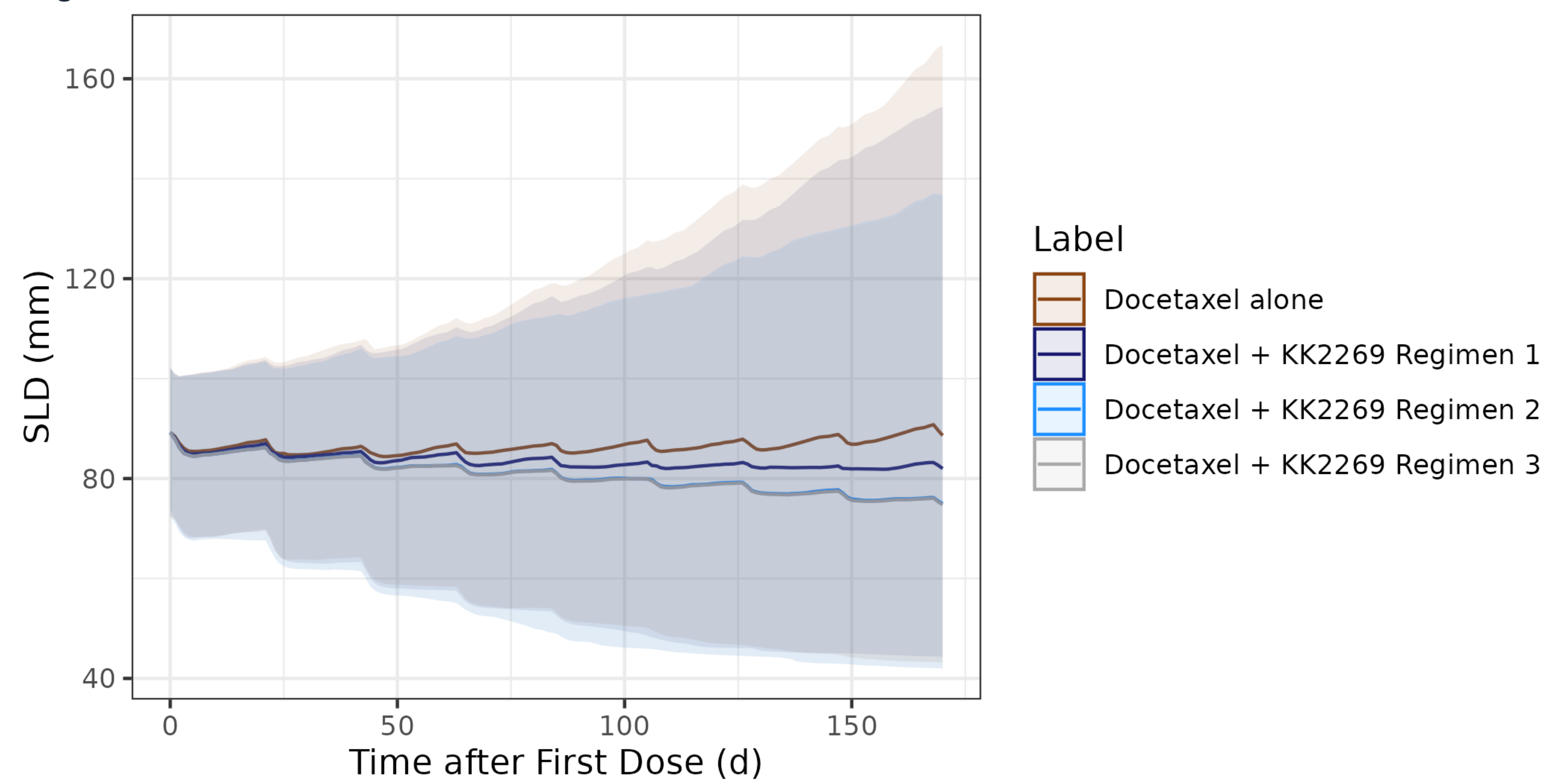


Figure 6. DTX monotherapy response categories according to RECIST1.1 guidelines¹¹ clinical vs predictions including the time to response kinetics comparison for NCT01673867.



- The integrated model allowed virtual clinical trial simulations comparing docetaxel monotherapy and three different dosing regimen of KK2269 and docetaxel combination therapy (Fig. 7).

Figure 7. Docetaxel alone vs combination with KK2269 predictions for SLD (mm) profiles for 3 different dosing regimens.



Conclusions

- We present an integrated mechanistic model describing cancer immunity cycle, PK, the CD40 activation pathway, and chemotherapy effects and use a learn-and-confirm cycle to iteratively calibrate it as new data emerge across stages of drug development.
- The model predicted the response to KK2269 and docetaxel combination therapy. With incorporation of additional combination therapy data, the model can support further optimization of dosing strategies.

