APPLICATION OF IO SIMULATOR IN IMMUNO-ONCOLOGY COMBINATION THERAPY: A SMALL CELL LUNG CANCER CASE STUDY

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Background and Objective

- Certara's Immuno-Oncology Simulator is a mechanistic QSP platform designed to support translational prediction in immuno-oncology through integration of tumour-immune biology, pharmacology, and clinical response data. Originally conceptualized and executed in QSP Designer [1], IO Simulator is now housed in Certara IQ, an AI-enabled quantitative systems pharmacology (QSP) modelling technology.
- IO Simulator incorporates multiscale representations of the Cancer Immunity Cycle [2] and supports generation of virtual patient populations (VPop) through systematic parameterization and qualification against published preclinical and clinical datasets.
- Tarlatamab, the subject of this case study, is an approved and established a bispecific T-cell engager (BiTE)-class therapy for relapsed extensive-stage small cell lung cancer (ES-SCLC). Here, we demonstrate how IO Simulator predicts combination therapy efficacy, biomarkers, and likelihood of cytokine release syndrome (CRS), and enables patient stratification and identifies dosing regimes that may both, maximize efficacy and minimize CRS risk.

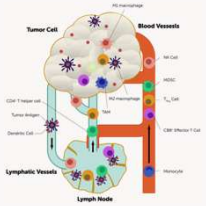


Figure 1: Schematic of the Cancer Immunity Cycle. A framework of the events underlying the anti-cancer response.

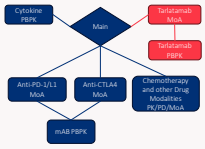


Figure 2: Modular structure of IO Simulator.

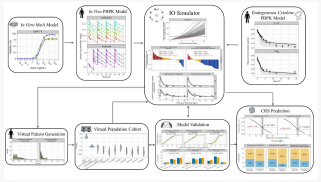


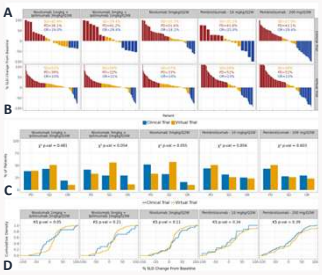
Figure 3: Overview of the calibration-qualification-prediction workflow.

Methods

- IO Simulator, a mechanistic QSP platform, was used to simulate tumour-immune interactions across tumour, lymph node, and blood compartments.
- The model integrates immune cell populations, cytokine dynamics (via Simcyp Simulator based biologics mPBPK model [3]), drug-specific PK/PD & mechanism-of-action modules within a unified virtual trial framework. VPop development was based on approach of Allen et al. [4].
- For the Tarlatamab case study, a compound-specific PK/mechanism-of-action module [5] was developed and linked to the core platform. The model incorporated DLL3/CD3 engagement, tumour target binding, T-cell–mediated killing, and cytokine release [6], with pharmacokinetics represented using a minimal PBPK framework [3].
- A small cell lung cancer (SCLC) virtual population was generated using published data on tumour volume [7], growth, DLL3 expression [8], immune infiltration, and plasma cytokines [6]. Virtual patients were calibrated to match observed tumour microenvironment characteristics and clinical response distributions for Tarlatamab, then validated against independent efficacy and cytokine biomarker datasets.
- Atezolizumab was represented using the platform's pre-implemented anti-PD-L1 module and simulated at the clinical 1200 mg Q3W regimen [9] to validate model performance in SCLC and to support virtual combination trials with Tarlatamab.
- Because cytokine release syndrome (CRS) is not yet mechanistically represented, simulated cytokine outputs were translated into CRS incidence using a statistical model based on IL-6 peak thresholds derived from published clinical data. This enabled integrated prediction of efficacy, biomarker dynamics, and safety risk for monotherapy and combination therapy scenarios.
- Further evaluation of the predictive performance and generalizability of the model was done using efficacy data from independent datasets of Nivolumab, Ipilimumab and Pembrolizumab [10].

Model Evaluation: Nivolumab–Ipilimumab-Pembrolizumab Application

- To assess model and VPop generalisability, an independent nivolumab, pembrolizumab (anti–PD-1) and ipilimumab (anti–CTLA-4) dataset, not used for model calibration, was used for evaluation. The model reproduced monotherapy and combination therapy efficacy outcomes with good agreement to observed data. These results support the model's ability to capture key tumour–immune biology and predict efficacy and biomarker responses across multiple immuno-oncology modalities



- **Figure 4: Calibration of IO Simulator and evaluation of predictive power for combination therapy.** Virtual Trial of Ipilimumab / Nivolumab/Pembrolizumab combination therapy, simulated with calibrated model, achieved good agreement with clinical data not used for calibration. (A) observed data, (B) virtual trial results and comparison of observed and simulated distributions by (C) chi-squared statistic and (D) KS statistics.

Results: Tarlatamab-Atezolizumab Case Study

- IO Simulator-based VPop with 100 patients that statistically reproduce the SCLC clinical population was generated. This calibrated VPop accurately recapitulated clinical efficacy (OR~50%,48% Tarlatamab (10mg, 100mg), ~12% Atezolizumab (1200mg)), while capturing tumour heterogeneity and cytokine dynamics. Tarlatamab–Atezolizumab combination simulations predicted 9% OR improvement vs Tarlatamab monotherapy.

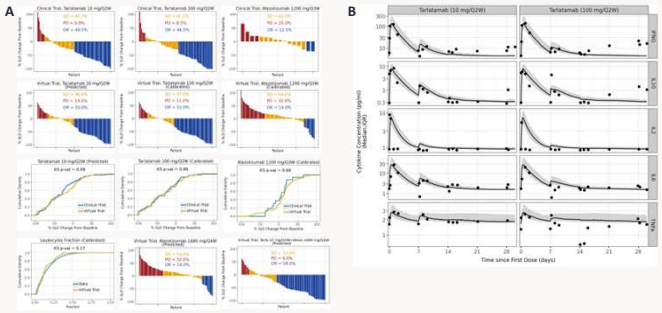


Figure 5: Calibration of IO Simulator by data on Tarlatamab therapy in SCLC and prediction of Atezolizumab and combination therapy efficacy. (A) (Top 3 rows) Calibration, prediction and goodness-of-fit for Tarlatamab (10 or 100mg/Q2W) and Atezolizumab (1200mg/Q3W) . (Bottom Row) Goodness of fit for leukocyte fraction calibration in SCLC and efficacy predictions for alternative Atezolizumab and combination Tarlatamab regimens. **(B)** Calibration of Tarlatamab cytokine biomarkers.

CRS Prediction

- Incidence-calibrated IL6 thresholds stratified patients into CRS-likely vs CRS-unlikely categories across Tarlatamab regimens: 10 mg first dose (41% observed vs 43% predicted), 10 mg second dose (30% vs 33%), 100 mg first dose (29% vs 43%), and 100 mg second dose (49% vs 17%) - indicating that predictive performance could be improved with patient-specific data of greater granularity.

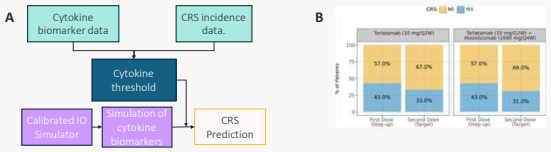


Figure 6: CRS prediction. (A) Workflow: Aggregate cytokine biomarker data and CRS incidence for Tarlatamab were used to infer a IL6 threshold that reproduced incidence. Calibrated IO Simulator was then used to simulate cytokine biomarkers and threshold inferred from clinical data was used to calculate CRS incidence. **(B)** CRS incidence was calculated for simulation for Tarlatamab with/without Atezolizumab after first and second dose.

Conclusions

- IO Simulator provides a reusable mechanistic QSP platform that enables rapid integration of new immuno-oncology therapies without rebuilding the full tumour-immune model from scratch.
- In the Tarlatamab case study, the platform successfully linked drug exposure, tumour-immune dynamics, cytokine biomarkers, and clinical response, supporting prediction of efficacy across monotherapy and combination settings.
- The model also enabled therapeutic window assessment by translating simulated cytokine profiles into CRS risk estimates, showing how efficacy and safety can be evaluated together in virtual trials.
- These results demonstrate that platform QSP models can deliver scientifically robust, decision-relevant predictions to guide dose selection, combination strategy, and patient-focused development in immuno-oncology.

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