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IO Simulator: A quantitative systems pharmacology (QSP) platform for immuno-oncology (IO) drug development.

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Background and Objective

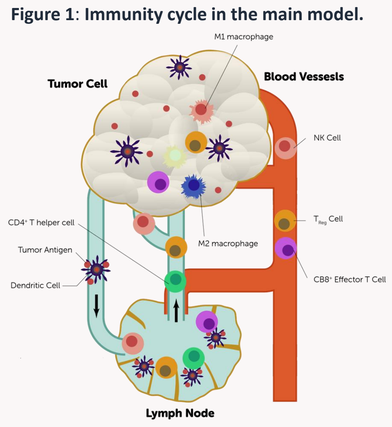
- Immunotherapies (e.g., checkpoint inhibitors) show variable response rates due to tumor-immune complexity and patient heterogeneity.
- QSP models provide mechanistic platforms for outcome prediction, dosing optimization, and biomarker identification.
- Certara's Immuno-Oncology Simulator models the full Cancer Immunity Cycle, supporting solid tumor response prediction, combination optimization, and biomarker discovery.
- Here, we demonstrate a case study conducted on IO simulator for nivolumab and ipilimumab monotherapy and their combination in melanoma.

Methods

IO simulator:

- Compartmental model: blood, lymph node, tumor microenvironment (T cells, APCs, NKs, macrophages, cytokines, tumor heterogeneity).
- Incorporates anti-CD40, anti-PD1/PD-L1, anti-CTLA4, bispecifics, ADCs, small molecules, chemotherapies.
- Parametrization via simultaneous calibration to tumor dynamics in monotherapy arms (distinct MOAs) for mechanistic consistency.

Figure 1: Immunity cycle in the main model.



- In this case study, multiple virtual populations were calibrated to **monotherapy nivolumab and ipilimumab SLD data** (Larkin J et al.,2015) and **leukocyte infiltrations** in melanoma in immune landscape of cancer database.
- Each virtual subject represents a distinct, biologically plausible parameterization of tumor-immune interactions and drug response.
- Among the monotherapy-calibrated virtual populations, we selected a virtual population that simultaneously reproduced both monotherapy and clinically observed **nivolumab + ipilimumab combination** outcomes, without additional tuning.

Results

- Virtual trial population successfully calibrated for monotherapies and leukocyte distribution (Figure 2).

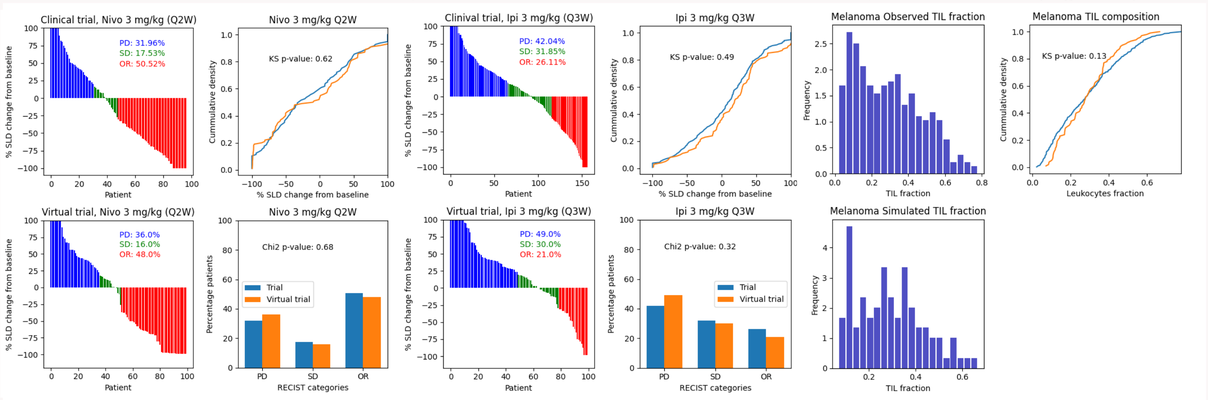


Figure 2: **Calibration results from IO simulator**. Calibration pipeline generates biologically plausible virtual patient database, then selects small calibrated virtual population matching clinical distributions.

- The calibrated virtual population quantitatively reproduced the observed SLD distribution for nivolumab + ipilimumab combination therapy (KS $p \geq 0.05$; χ^2 $p \geq 0.05$), supporting the model's ability to prospectively predict combination response from monotherapy-calibrated mechanisms (Figure 3).

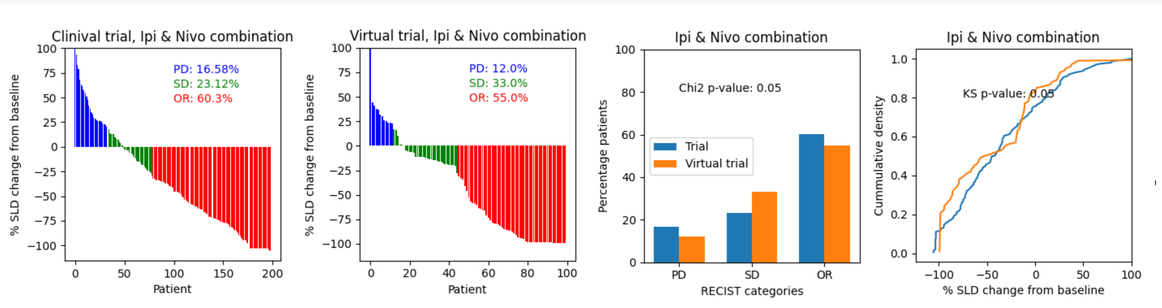


Figure 3: **Combination predictions from IO simulator**. Selected virtual population that simultaneously reproduced both monotherapy and clinically observed combination outcomes.

- Figure 4 shows distinct MOA fingerprints across compartments. Anti-CTLA4 (ipilimumab) drives rapid **CD8+ expansion in blood** due to **lymph node activation** followed by **tumor infiltration**. Anti-PD1 (nivolumab) shows **tumor-compartment specific effects** with less systemic activation.
- These compartment and MOA specific dynamics emerging from monotherapy SLD calibration alone enable **prospective prediction of combination responses** (Figure 3 and Figure 4-bottom row). The model captures **anti-CTLA4 peripheral priming** vs **anti-PD1 tumor direct effects**, validating mechanistic fidelity across the full Cancer Immunity Cycle.

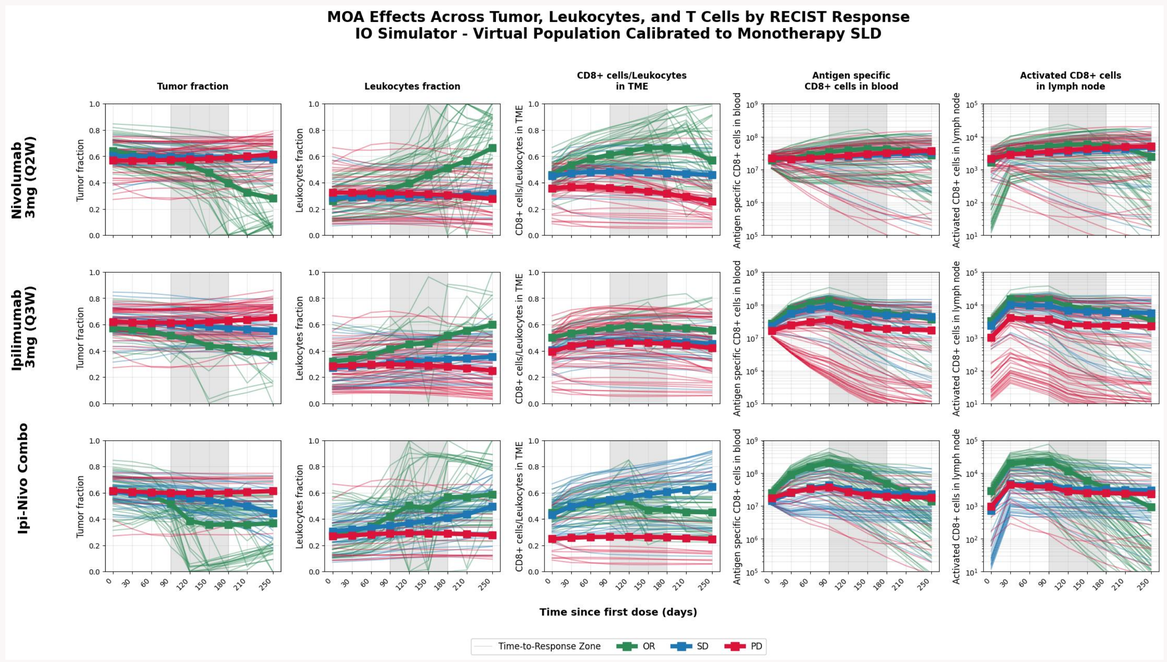


Figure 4. MOA-Specific Dynamics Across Compartments. Model simulated time courses of tumor fraction, leukocyte fraction, CD8+/leukocytes ratio in tumor, CD8+ cells in blood, and activated CD8+ cells in lymph node, calibrated solely to monotherapy SLD data and melanoma leukocyte fraction distribution . Line colors by clinical response: Green (OR), Blue (SD), Red (PD).

- Beyond reproducing clinical SLD distributions, the monotherapy-calibrated virtual population reveals **baseline biomarkers that stratify anti-tumor response across MOAs** (Figure 5).
- **High CD8 fraction predicts better responses across MOAs**. High baseline tumor CD8+ infiltration predicts improved outcomes for immune checkpoint inhibitors across multiple tumor types (HR=0.52 OS/PFS, OR=4.08 ORR; Li et al., 2021; high CD8+ activation also prognostic.)
- **Tumor volume effect is MOA specific.** Smaller baseline tumor volume/burden favors anti-PD1 response (Metabolic Tumor Volume (MTV) prognostic in NSCLC PD1; lower MTV produces better outcomes). Larger tumors enhance anti-CTLA4 efficacy via stronger lymph node priming signals, consistent with CTLA4 blockade requiring robust antigen-driven T cell activation in tumor draining lymph nodes (Shrikant et al., 1999; Walker & Sansom, 2015).

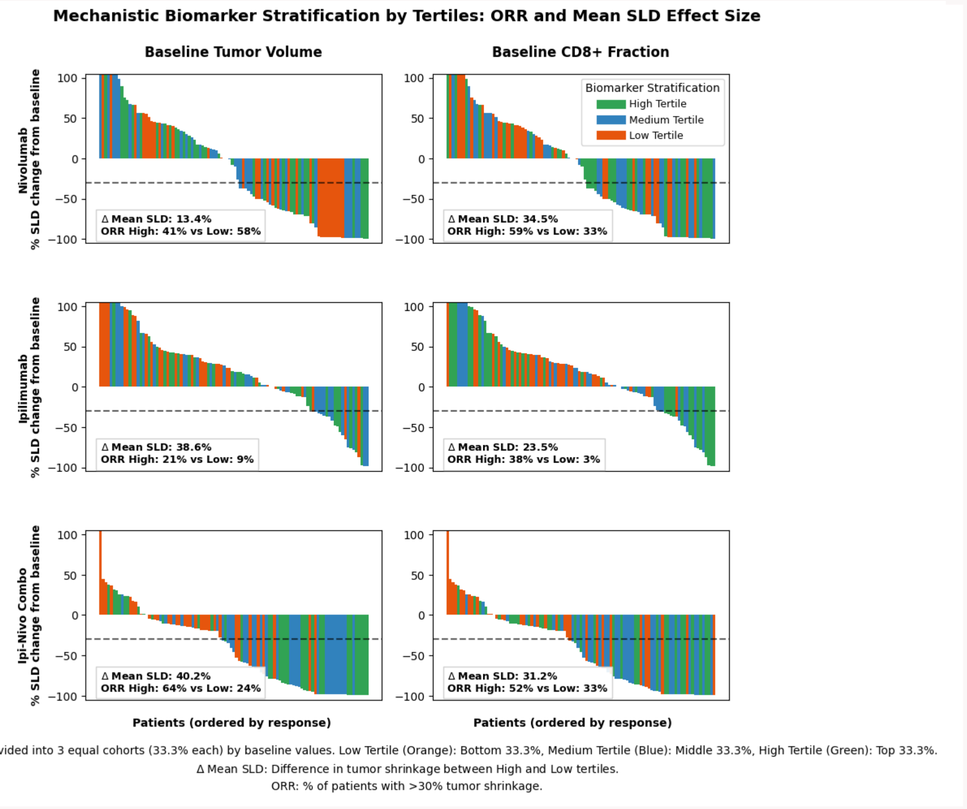


Figure 5. Baseline Biomarkers Stratify SLD Response. Waterfall plots of % SLD change from baseline, colored by biomarker tertiles: baseline tumor volume (left) and tumor CD8+/leukocyte fraction (right).

Conclusions

- Certara IO Simulator quantitatively reproduced nivolumab and ipilimumab monotherapy responses and prospectively predicted combination efficacy without re-tuning.
- **Monotherapy-calibrated virtual populations captured MOA specific immune dynamics**, distinguishing anti-CTLA4 lymph node priming from anti-PD1 tumor localized effects.
- **Baseline biomarkers stratified response**, with tumor $CD8^+$ infiltration predictive across MOAs and tumor volume showing MOA dependent effects.
- **These results highlight IO simulator as a powerful tool for combination design, biomarker discovery, and translational decision making.**

References

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