Prediction of clinical outcomes in a heterogenous NSCLC virtual patient population: a Quantitative Systems Pharmacology (QSP) approach.

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BACKGROUND

- Non-small cell lung cancer (NSCLC) is a major cause of mortality in the United States[1]. Immune checkpoint inhibitors (ICIs) show promise for advanced or metastatic NSCLC[2,3].
- Treatment outcomes vary based on disease traits and the immune microenvironment. Identification of effective combination therapies is inefficient and time consuming[2,3].
- We developed a QSP model to predict the efficacy of novel ICI combinations in NSCLC patients with varying PD-L1 expression, tumor histology, and immune environments.

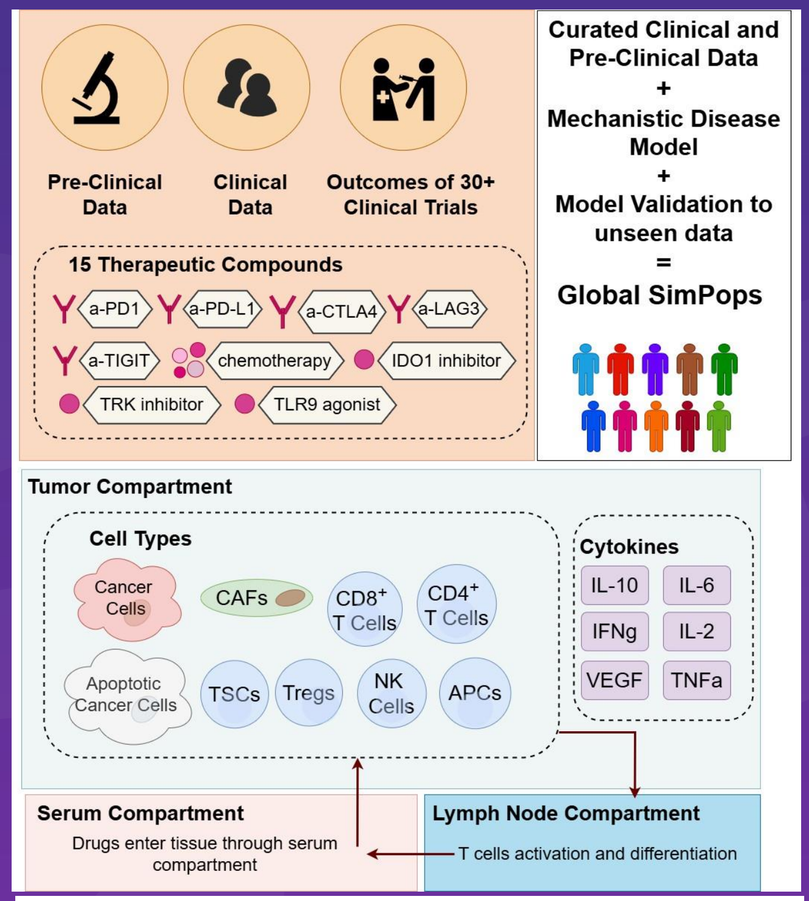
METHODS

- We identified key immune cell types and cytokines in NSCLC pathogenesis and immune response. We combined this knowledge with Simulations Plus' library of solid tumor processes and developed a mechanistic NSCLC model in the Thales™ platform.
- We included majority of late-phase clinical trials spanning ICIs, chemotherapies and other therapeutic modalities to constrain a virtual population representative of advanced/metastatic NSCLC. The model represents distinct tumor sub-types, immune environments, and inter-patient differences.
- BOR, ORR, and PFS response data from **30+ clinical trials across 15 therapeutics were recapitulated within a single virtual population**, capturing clinical efficacy and inter-patient heterogeneity.

RESULTS

- The optimized SimPops® successfully predicted clinical outcomes for new therapeutic regimens, demonstrating real-world applicability.
- The SimPops® capture disease heterogeneity and predicts clinical outcomes for patient populations subset by squamous vs. non-squamous histology and baseline PD-L1 expression.

Global NSCLC SimPops® accurately predicted clinical outcomes of new immune checkpoint combination therapies and captured subgroup differences by histology and PDL1 expression.



IFNg: Interferon gamma; TNFa: Tumor Necrosis Factor alpha; CAFs: Cancer associated fibroblasts; NK Cells: Natural Killer cells; APCs: Antigen presenting cells (grouped together for simplicity); TSCs: Tumor supporting cells (pro-tumor immune cells are grouped together for simplicity); Tregs: Regulatory T cells

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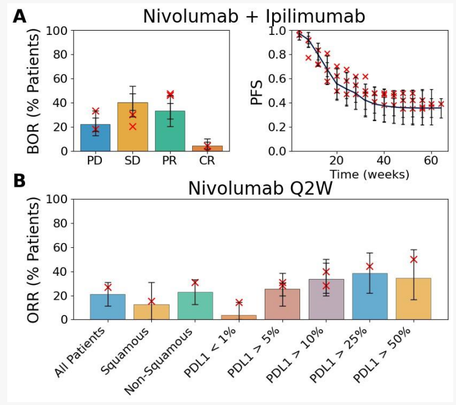
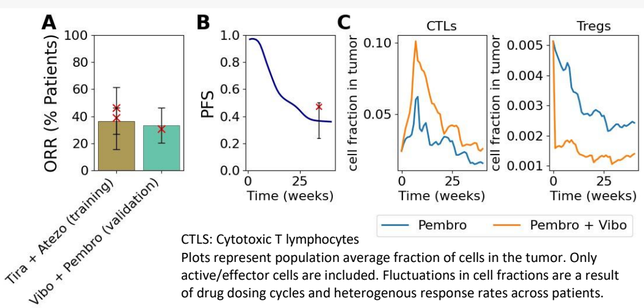
Figure 1: Model accurately predicts efficacy of unseen nivolumab (aPD1) and ipilimumab (aCTLA4) combination therapy and nivolumab Q2W monotherapy. The SimPops captures response by tumor histology and % baseline PDL1 expression. The model was trained with regimens of nivolumab + chemo and ipilimumab + pembrolizumab; shown here are data for other nivolumab regimens held out for validation. Figures show predictions of (A) BOR and PFS for nivolumab and ipilimumab combination (B) ORR of nivolumab monotherapy for patient subgroups by histology and baseline PDL1 expression. Clinical trials: NCT02477826, NCT01454102, NCT02041533



- Bars: model prediction
- Error bars: 90% confidence interval of model prediction.
- Markers: published clinical data.
- BOR: Best Overall Response (RECIST)
- PD: Progressive Disease
- SD: Stable Disease
- PR: Partial Response
- CR: Complete Response
- PFS: Progression free survival

Figure 2: Model accurately predicts efficacy of unseen aTIGIT drug vibostolimab (vibo) with pembrolizumab (aPD1, pembro) and provides mechanistic insights into tumor immune response. The model was trained on clinical data from aTIGIT tiragolumab and aPDL1 atezolizumab. The SimPops predicted ORR and PFS response for vibo+ pembro combination. Comparison of immune response between pembro alone or in combination with vibo revealed that lower abundance of Tregs after the combination regimen leads to higher CTLs compared to monotherapy. (A) ORR fit for tiragolumab and prediction for vibo + pembro (B) PFS prediction for vibo + pembro (C) Dynamics of CTLs and Tregs after pembro or vibo + pembro. Clinical trials: NCT02794571, NCT03563716, NCT02964013



CTLS: Cytotoxic T lymphocytes
Plots represent population average fraction of cells in the tumor. Only active/effector cells are included. Fluctuations in cell fractions are a result of drug dosing cycles and heterogenous response rates across patients.

CONCLUSION

Our NSCLC QSP model can test new drug regimens and accelerate drug development. It can be readily extended to other NSCLC patient populations.

References:
1. American Cancer Society. Cancer Facts
2. & Figures 2025
3. Desai et al Can Treatment Revs (2023)
4. Mountzios, G. et al Nat Rev Clin Oncol (2023)

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