A QUANTITATIVE SYSTEMS PHARMACOLOGY MODEL OF HEAD AND NECK SQUAMOUS CELL CARCINOMA: A TOOL FOR EVALUATING TREATMENT OUTCOMES FOR COMBINATION THERAPIES

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Background Head and neck squamous cell carcinoma (HNSCC) is one of the most frequent cancers worldwide. Different approaches are applied to treat the cancer. Recently, several therapies were approved for treatment of head and neck cancers, and some are at the clinical trial stage.1-4 The aim of this study was to develop a comprehensive quantitative systems pharmacology (QSP) model of HNSCC that captures key cellular and molecular processes and allows to explore combination therapies.

Methods QSP model of HNSCC includes sub-modules describing:
- cell life cycles of CD4, CD8, Tregs, NK and B cells, mDC, monocytes and macrophages, different subpopulations of tumor cells (insensitive to chemotherapies and cetuximab)
- cell and cytokine distribution between blood, tumor, lymph nodes and peripheral tissues
- antigen presentation and cytotoxicity
- interaction of surface molecules in immunological synapses (e.g. PD1-PDL1)
- pharmacokinetics (PK) of various chemotherapies (carboplatin/cisplatin, pemetrexed, 5-fluorouracil), targeted therapy (cetuximab), and checkpoint inhibitors (pembrolizumab, atezolizumab)
- Effect of chemotherapies on both tumor cells and immune cells
- Direct effect of cetuximab on tumor cell growth (mediated by its binding to EGFR) and its ADCC effect (mediated by activation of NK cells via formation of trimer between EGFR located on tumor cell, cetuximab and Fcg3A receptor on NK cells)

The model of a reference Virtual Patient (VP) was parameterized on the wide range of in vitro and in vivo data available from the public domain. VP population was generated to simultaneously describe clinical data (RECIST criteria, TrR, DoR, PFS) for Pembrol, Cetuximab, Cisplatin alone and following combinations Cisplatin+5-fluorouracil, Cetuximab+Cisplatin, Cetuximab+Cisplatin+5-fluorouracil available in public domain. VP population was generated to simultaneously describe clinical data (RECIST criteria, TrR, DoR, PFS) for Pembrol, Cetuximab, Cisplatin alone and following combinations Cisplatin+5-fluorouracil, Cetuximab+Cisplatin, Cetuximab+Cisplatin+5-fluorouracil available in public domain (figure 1).

Results The model of reference VP accurately describes baseline concentrations of cells and cytokines in patients with head and neck cancers and changes in immune cell numbers and surface molecule levels under various treatments. VP population was validated against following individual and combination therapies Cetuximab+Cisplatin/Carboplatin+Pemetrexed, Pembrolizumab+Cisplatin/Carboplatin+5-fluorouracil, Pembrolizumab+Cetuximab and Atezolizumab alone. VP population was applied to explore response to combination therapies at the level of clinically measured endpoints and biomarkers. This analysis allows us to explore correlations between responder/non-responder status and biomarker values.

Conclusions The developed QSP model can adequately describe the effects of various drug therapies, including chemotherapy and immunotherapies, and their combinations on progression and outcomes of head and neck cancers. The model can be used as a tool for evaluating treatment outcomes for standard and novel therapies.

REFERENCES
Abstract 874 Figure 1  Correspondence between simulated and clinically measured PFS for different therapies. Dosages, regimens and references to clinical data are as follows: Pembrolizumab monotherapy: 200mg Q3W, [1]; Cetuximab monotherapy: 400mg first dose, then 250mg Q1W, [2]; Cisplatin monotherapy: 100mg/m² Q3W, [3]; 5-fluorouracil + Cisplatin: 5-FU 4000mg Q3W, Cisplatin 100mg/m² Q3W, [4]; Cetuximab + Cisplatin: Cetuximab 400mg first dose, then 250mg Q1W, Cisplatin 100mg/m² Q3W, [3]; Cetuximab + Cisplatin + 5-fluorouracil: Cetuximab 400mg first dose, then 250mg Q1W, Cisplatin 100mg/m², Q3W, 5-FU 4000mg Q3W, [1].

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0874