Biologists observed with the combination therapy. Observations, an enhancement in lesion response was noted due to absolute lymphocyte counts, trends in tumor cytokines, an interplay of multiple immune cell types, cancer cells, and soluble factors. This facilitates comparison of the simulated outcomes with clinical results and serves as a sub-model within a broader framework to explore additional therapeutic mechanisms, propose new combination strategies, and prioritize putative mechanisms for inclusion. Preclinical and clinical studies were used to inform the platform design. For example, an objective response at 1-year has been reported in over 50% of melanoma patients treated with nivolumab plus 3 mg/kg ipilimumab [3]. Mounting clinical evidence suggests combinations of immuno-oncology agents relieve checkpoint-mediated immunosuppression of T cells and facilitate anti-tumor responses [1].

In addition to the core platform development team, subject-matter experts contributed in an ad-hoc fashion to prioritize putative mechanisms for inclusion. Preclinical and clinical studies were used to inform the platform design. The model was constructed in accordance with Rosato's Model Qualification Method [5] to ensure fit for purpose.

A cross-function team of drug development scientists defined the QSP model scope and modeling objectives. A QSP model was established for simulating the cancer-immunity cycle within a tumor lesion and the effects of immunotherapeutics. The model serves as a starting point for a broader simulation of the cancer-immunity cycle and the development of new therapeutic strategies. The model is capable of simulating a wide range of tumor characteristics and includes mechanisms of action and action therapeutic regimens.

RESULTS: Response to nivolumab

The platform will be expanded to include a draining lymph node and associated immune processes. The simulated outcomes are shown in comparison to published trends and serve as a mechanistic framework to support translational research and development in immuno-oncology.

REFERENCES


ACKNOWLEDGMENTS

The authors thank Bristol-Myers Squibb for providing financial support. Bristol-Myers Squibb, Princeton, NJ

Figure 5: Exploration of ipilimumab phenotype in an ipilimumab inadequate-response phenotype VP

(A) The VP exhibits a decrease in lesion volume with simulated nivolumab therapy.
(B) The cellular composition of the simulated lesion changes with therapy. Increases are observed in NK, CD8+, and Treg cells.
(C) Relatice changes in simulated cytokines are shown. The increase of IFNγ in the lesion is consistent with observations of IFNγ gene expression changes in patients with renal cell carcinoma [12], study CA209009.
(D) The density of cells in the simulated, shrinking lesion is shown while a large relative increase in the density of Treg cells, there remain 100-fold more CD8+ T cells.

Figure 7: Exploration of combination response in the ipilimumab inadequate-response phenotype VP

A comparison of the response to alternate dosing strategies in the same VP is shown. The combination therapy employs a co-stimulatory checkpoint of a concurrent regimen trial [2]. Note the simulated increase in Treg cell response to combination therapy at the same concentrations.

Figure 8: Expansion of the cancer-immunity cycle simulation and development of VP cohorts

(A) The platform will be expanded to include a draining lymph node and associated immune processes.
(B) VP cohorts will be established [14] to investigate the impact of variation in immuno-oncology pathways on treatment response.

Figure 2: Diagram depicting biological species and their dynamics

Production and clearance of blood cell populations

Additional blood biomarkers

Plasma proteins and therapeutics

Binding to blood targets

Molecular transport

Recruitment to lesion

NK and CD8-mediated cancer cell killing

Solute species production

Drug binding and mechanism

Polarization

Exhaustion

Additional markers

RESULTS: Response to ipilimumab

(A) Patient data are shown for comparison (CA184004, CA284002). Previously published [7] pharmacokinetic parameters were used for the VP.
(B) The simulations account for nivolumab PK and affinity as well as CTLA-4 expression and interaction.
(C) Circulating absolute lymphocyte counts are of interest as they are pharmacodynamic markers and putative biomarkers of ipilimumab efficacy [8]. Changes were specified as 30 cells/µL/wk with ipilimumab (CA184004).
(D) Subfractions of circulating T cells were specified based on data from melanoma patients [9].
(E) Occupancy of CTLA-4 with B7 and CD28 in B7 in the VP's simulated lesion are shown.
(F) Antibody-dependent cell-mediated cytotoxicity is simulated. The simulated concentrations of Tregs and CD8+ T cells are shown.

RESULTS: Response to nivolumab

(A) The pVp exhibits a decrease in lesion volume with simulated nivolumab therapy.
(B) The cellular composition of the simulated lesion changes with therapy. Increases are observed in NK, CD8+, and Treg cells.
(C) Relative changes in simulated cytokines are shown. The increase of IFNγ in the lesion is consistent with observations of IFNγ gene expression changes in patients with renal cell carcinoma [12], study CA209009.
(D) The density of cells in the simulated, shrinking lesion is shown while a large relative increase in the density of Treg cells, there remain 100-fold more CD8+ T cells.