Models in support of oncology drug combinations and dosing

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Outline

• AstraZeneca drug-disease modeling approach in oncology integrates PK/PD and pathophysiology from animal and human and clinical data to predict clinical outcomes.

• A quantitative systems pharmacology model of mouse treated with radiation and anti-PDL1 was qualified to describe immune-tumor interactions and predict tumor response to immunooncology combinations.
Drug-disease modeling integrates drug PK/PD, physiology and clinical data to predict clinical outcomes

PK Module
- Compound 1
- Compound 2

Biology Module
- Drug targets
- Signaling pathways

Physiology Module
- Physiology context for drugs, targets, pathways

Time-to-event clinical outcome

QSP modeling in animal $\rightarrow$ QSP in human

Joint modeling
Quantitative systems pharmacology modeling enables the research of dose, schedule, sequencing of immunotherapy combinations.

Anti-PDL1 mAB → Immune interactions → Immune body system → TS

PK / PD

Physiology

Biology

Animal QSP model

TS – tumor size
mAB – monoclonal antibody
Joint modeling of tumor size dynamics and survival is used to predict survival outcomes for novel combinations.

- **TS** – tumor size
- **ORR** – overall response rate
- **PFS** – progression-free survival
- **OS** – overall survival
Quantitative systems pharmacology model of anti-PDL1 monoclonal antibody and radiation in mouse

Model captures anti-PDL1 effect, key immune cells interactions, and tumor size dynamics.

8 / 25 parameters fitted to data, 17 / 25 parameters estimated from literature and biological constraints.

Ability of T cells to infiltrate tumor tissue was modeled as a distribution across mouse subjects.
The mouse model of immune system/tumor size described the training anti-PDL1 and radiation data well.

- **Control**
- **Anti-PDL1**
- **Radiation**
- **A-PDL1 + Radiation**
- **A-PDL1, Radiation**
- **A-PDL1, gap, Radiation**

Black dashes + solid lines: data median + individual responses

**Solid red**: model-predicted median

**Red-shaded areas (light to dark)**: 90%, 60% and 30% prediction intervals
The mouse model of immune system/tumor size was qualified to describe immune interactions by predicting external anti-CD8 data.

**Diagram Description**

- **Control**
- **A-PDL1 + Radiation**
- **A-PDL1 + Radiation + A-CD8**

- **Tumor volume, mm³**
- **Time, days**

- Black dashes + solid lines: data median + individual responses
- **Solid red**: model-predicted median
- Red-shaded areas (light to dark): 90%, 60% and 30% prediction intervals
The mouse model of immune system/tumor size explained how tumor infiltration by T cells drives tumor response

Intensive and rapid infiltration of T cells into tumor tissue corresponds to complete responders.

Responders have higher maximal mature dendritic cells and intratumor T-effector cells.

Baseline T-effector cells are higher in responders.
Early, effective T cell infiltration overcomes immunosuppressive resistance in the tumor, resulting in response

1. High levels of dendritic cell initiate T cell infiltration

2. Early, effective T cell infiltration separates responders

Hi – high infiltration ability of T cells
Lo – low infiltration ability of T cells
Efficacy of anti-PDL1 and radiation combo depends on relative timing and is lower in more established tumors.
A general mouse model of immune system/tumor size describes the effect targeted therapies
The mouse model of immune system/tumor size predicted proportion of complete mice responders for combinations

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Efficacy = % complete responder mice
Summary

• We developed and qualified a QSP model for predicting tumor effect of dose, schedule and sequencing of immunotherapies in mouse using radiation and anti-PDL1 as a “system probe”.

• We used an extended QSP model to prioritize combinations of immunotherapies and direct anti-tumor therapies by response predictions in mouse.

• An immune system / tumor size model translated to human, together with a joint model of tumor size dynamics and survival will be used to prioritize combinations for first-in-man trials at AstraZeneca.