AstraZeneca
IMED Biotech Unit

Models in support of oncology drug combinations and dosing

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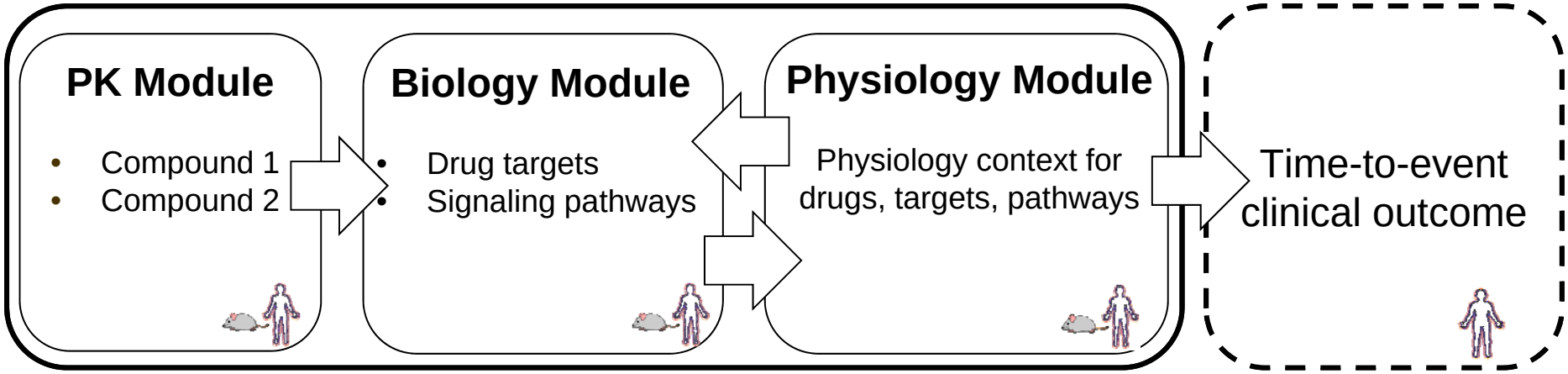
Outline

- **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.**

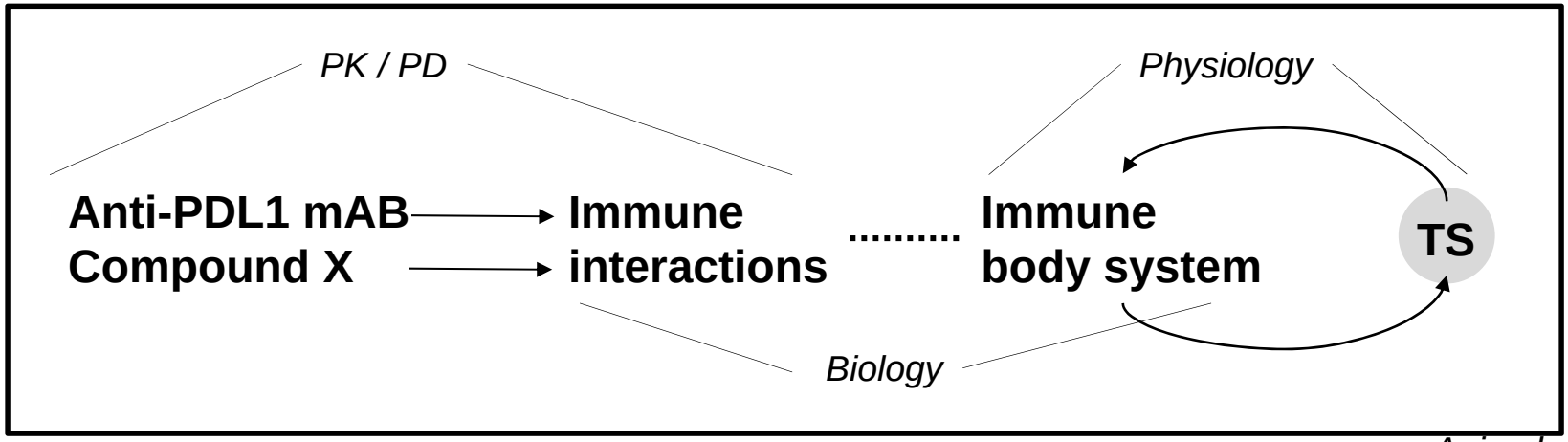
Drug-disease modeling integrates drug PK/PD, physiology and clinical data to predict clinical outcomes



QSP modeling in animal → *QSP in human*

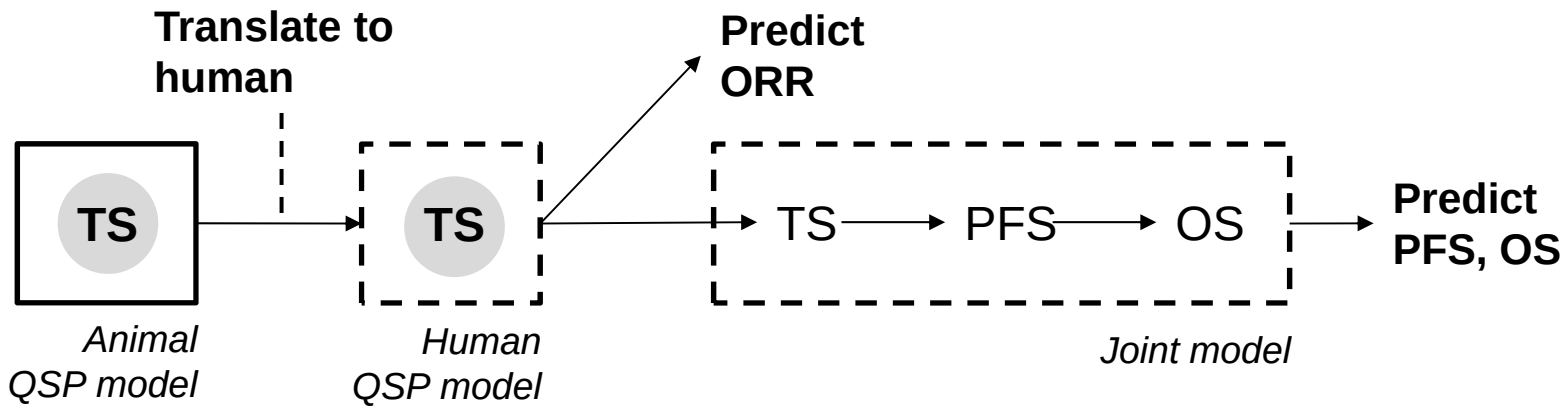
Joint modeling

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



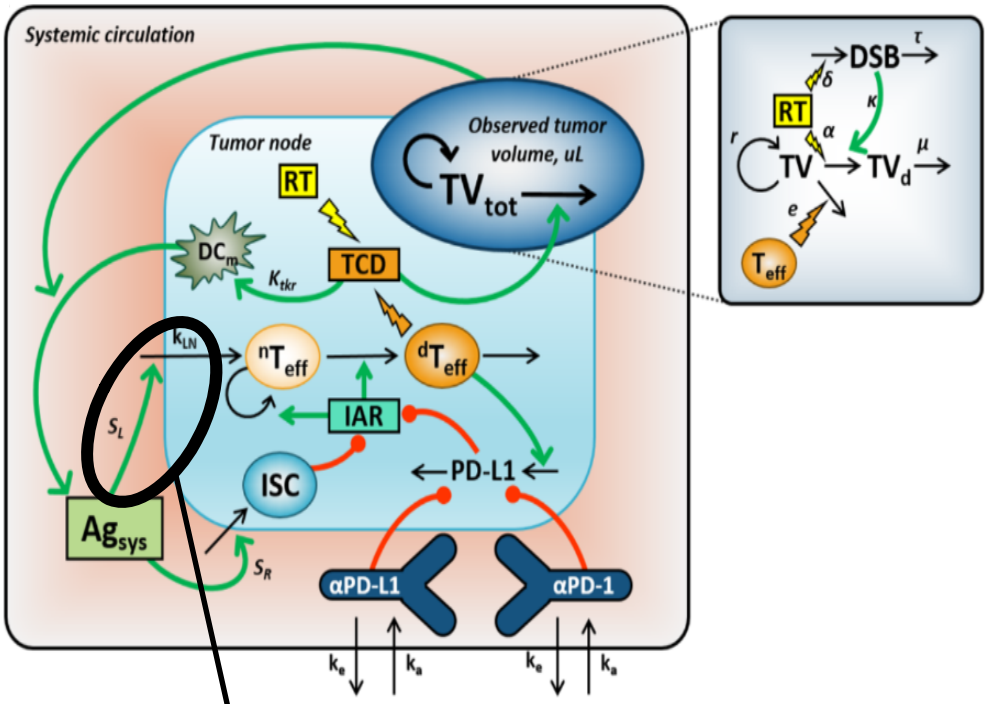
TS – tumor size
mAB – monoclonal antibody

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



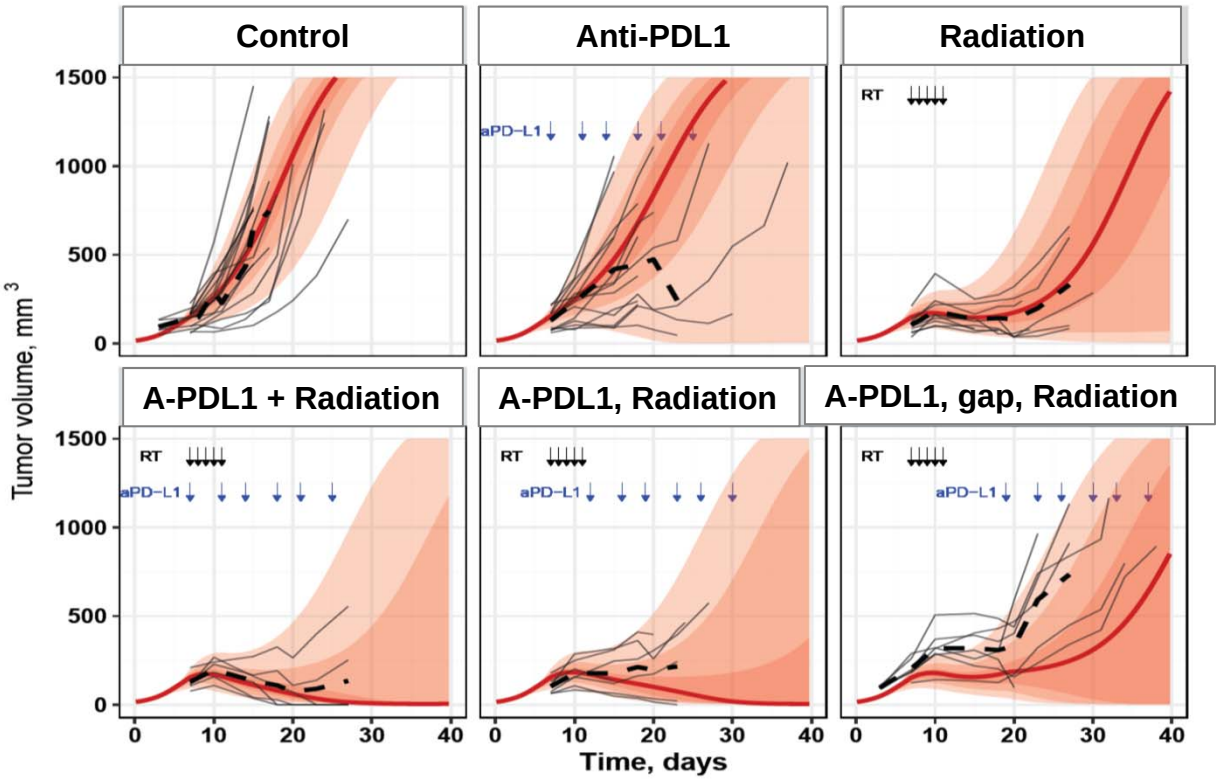
Infiltration of T cells into tumor

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

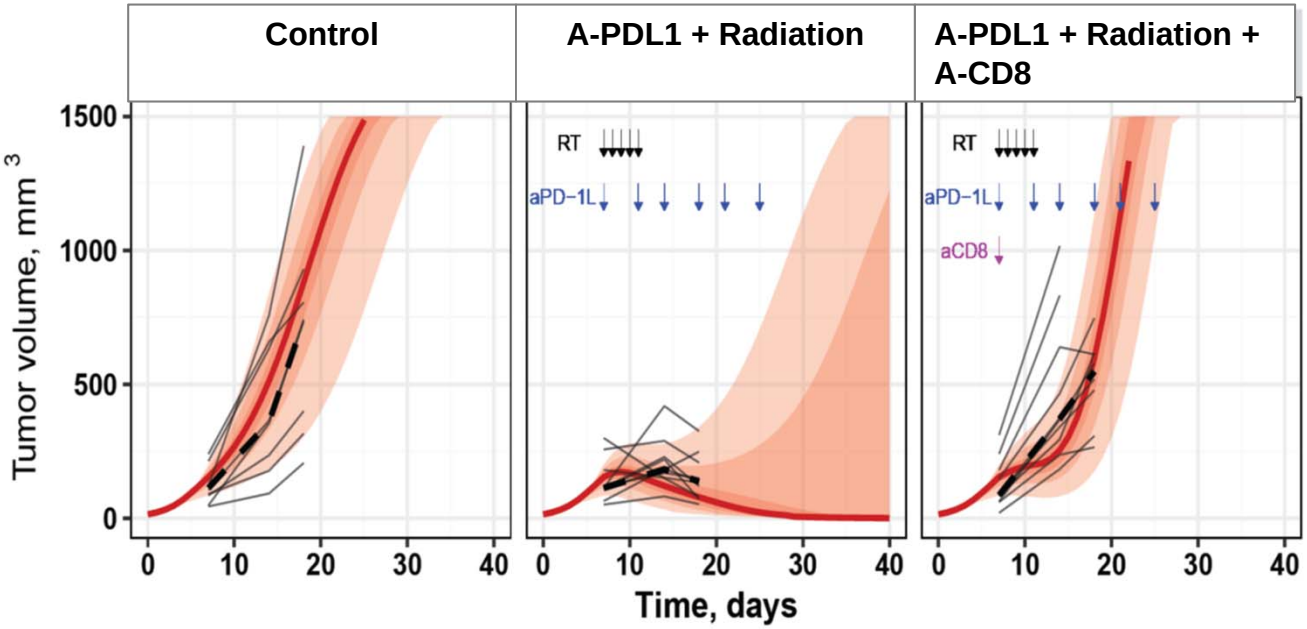


Black dashes + solid lines: data median + individual responses

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

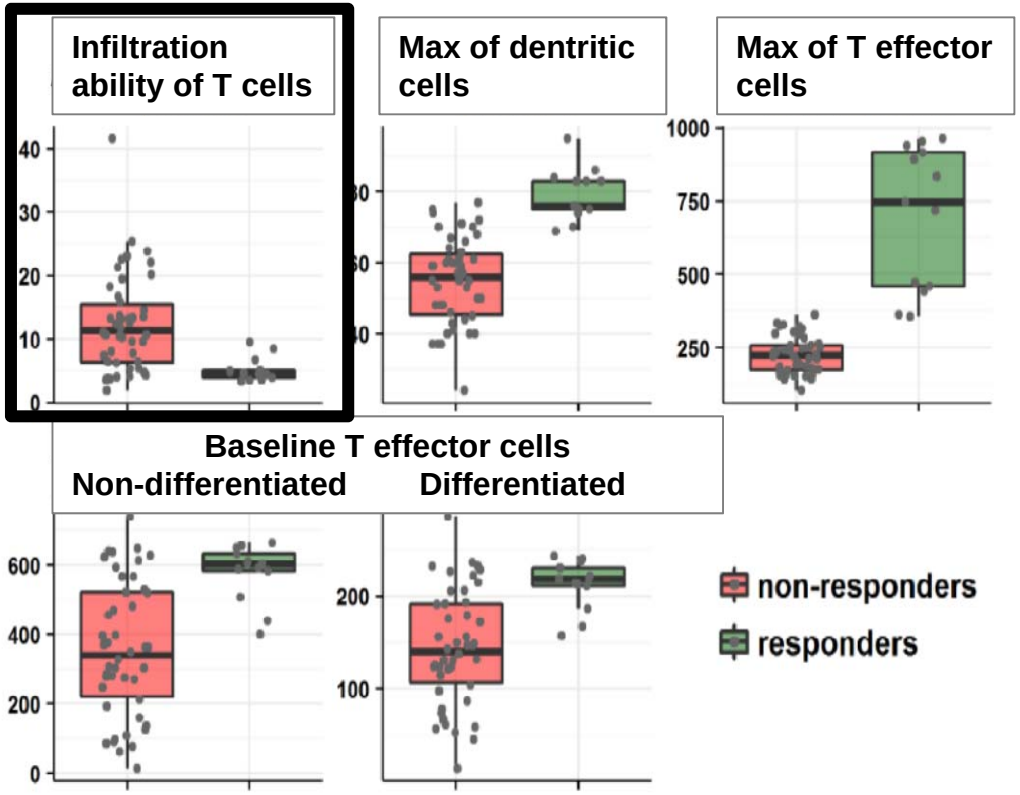


Black dashes + solid lines**:** data median + individual responses

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

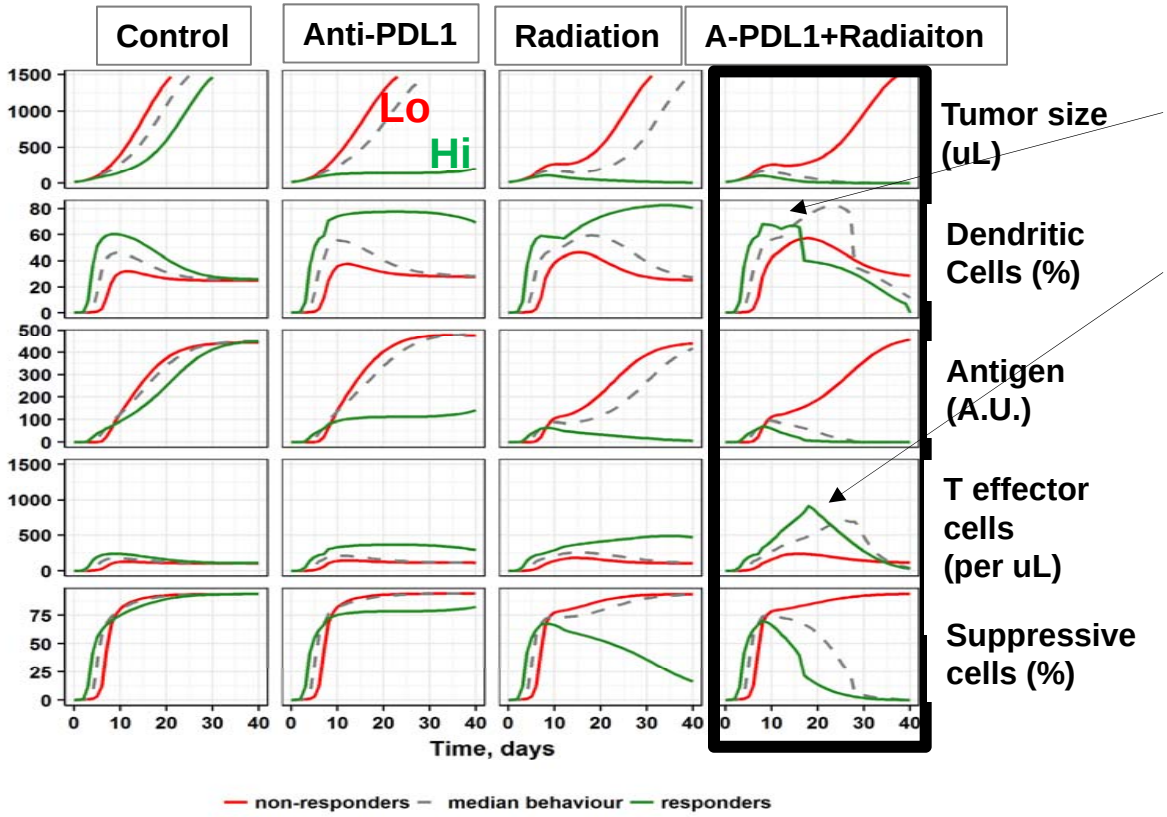


Intensive and rapid infiltration of T cells into tumor tissue corresponds to complete responders.

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 immuno-suppressive resistance in the tumor, resulting in response

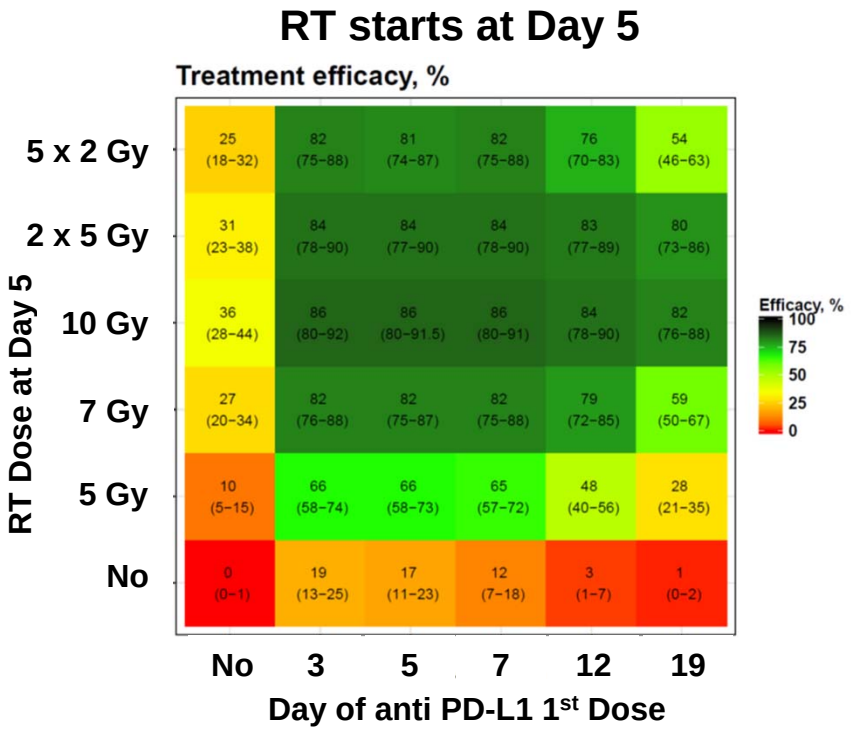


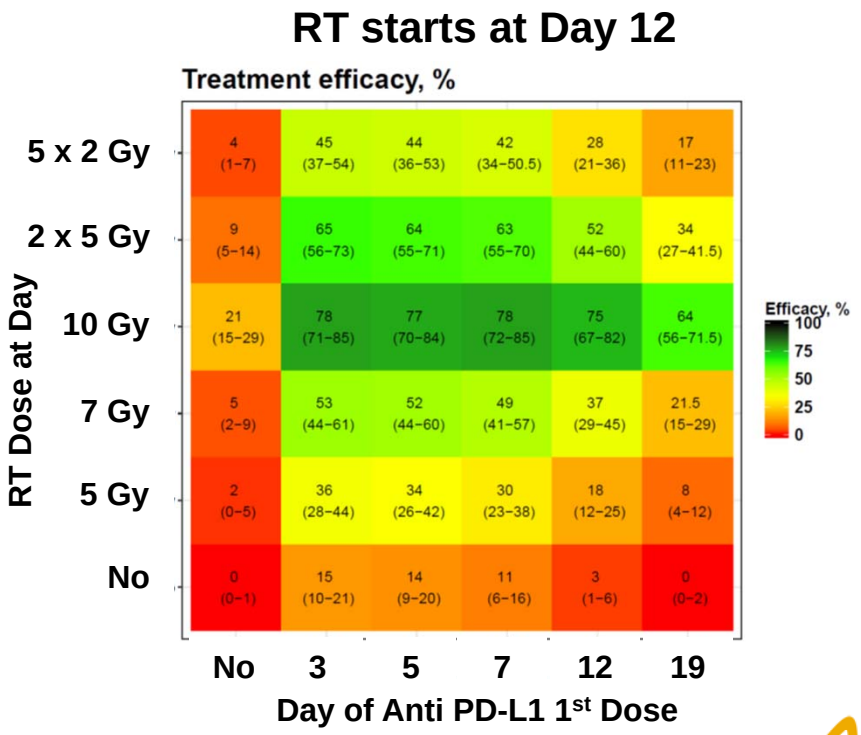
1. High levels of dendritic cell initiate T cell infiltration

2. Early, effective T cell infiltration separates responders

Hi – high infiltration ability of T cells
Lo – low infiltration ability of T cells

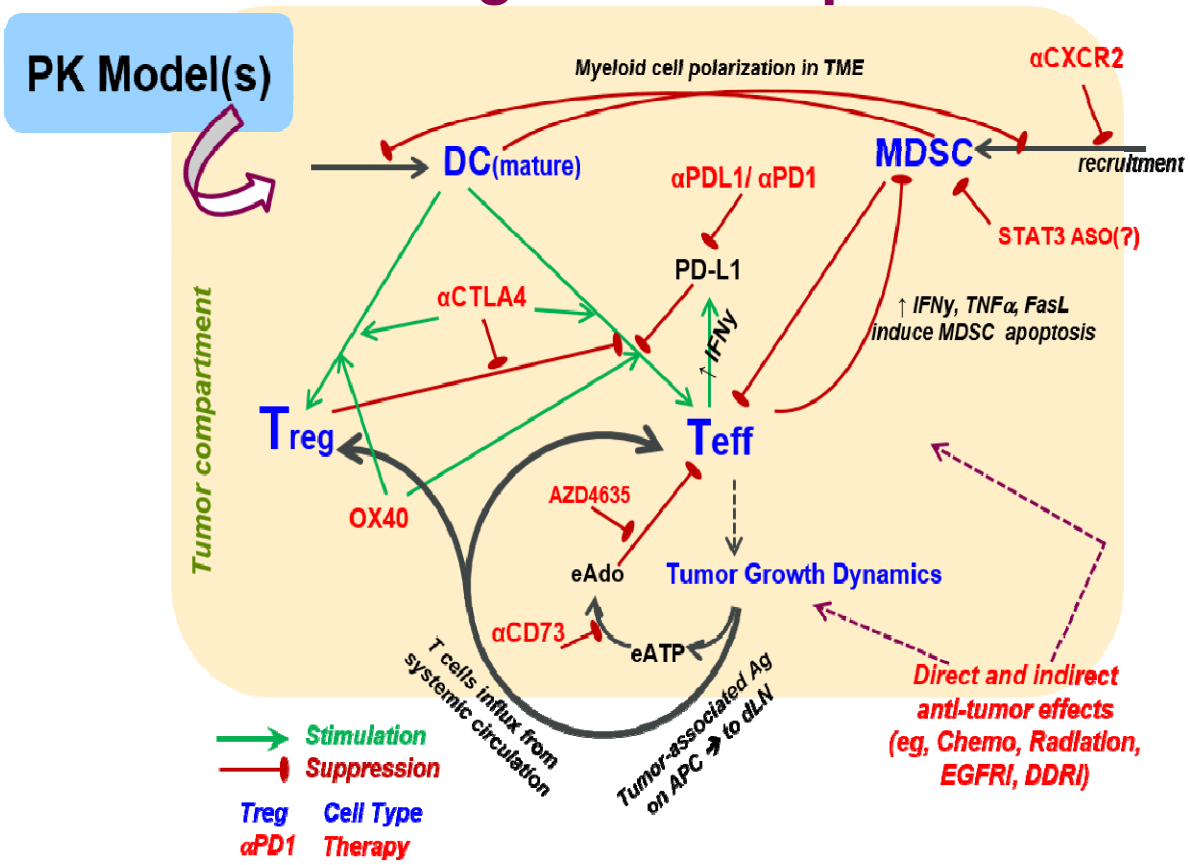
Efficacy of anti-PDL1 and radiation combo depends on relative timing and is lower in more established tumors





RT – radiation
Efficacy = % complete responder mice

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

Teff	Treg	MDSC	Treatment	Efficacy, %
+	+/-	++	aPD-L1	34
			aCXCR2	18
			OX40L	14
			aPD-L1 + aCXCR2	94
			aPD-L1 + OX40L	91
+	++	+	aPD-L1	0
			aCTLA-4	0
			aPD-L1 + aCTLA-4	98
			aCTLA-4 + OX40L	6
			aPD-L1 + OX40L	4
			aPD-L1 + aCXCR2	0

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.**