Development and application of a quantitative systems pharmacology model of tumor receptor occupancy to support extending dosing intervals for nivolumab across indications

FDA-MCERSI Workshop on Creating a Roadmap to Quantitative Systems Pharmacology Informed Rare Disease Drug Development

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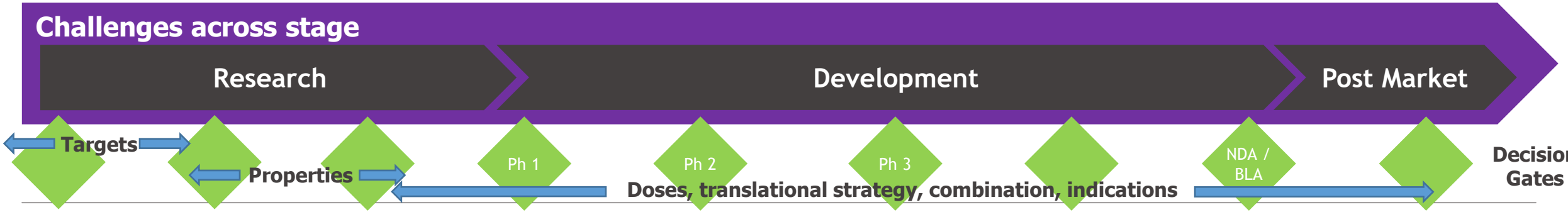
Bristol Myers Squibb™

Agenda

- Background on mechanistic modeling as applied at BMS
- Background on the model-informed drug development (MIDD) strategy to enable new dosing regimens for nivolumab
- Tumor receptor occupancy modeling for nivolumab
  - Development of approach
  - Mechanistic insights and key results
- Considerations for reporting model results
- Conclusion

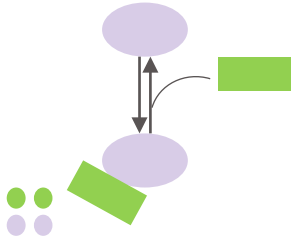
Challenges mechanistic modeling can help with

- Target verification: is a disease sensitive to targets of interest? If appropriate platform model is available it can help.
- Drug properties: are PK, affinity, safety, ADME, tissue delivery, internalization properties appropriate? Model can help identify property targets and address lead versus backup or modality questions.
- Translational strategy: can I develop a rational in vitro to in vivo translation, what are mechanistic drivers, when do I sample biomarkers, and what does a good target population look like?
- Dose range for FIH: can I remove unnecessary low dose levels, assess informative dose range, or identity an anticipated maximum dose for testing
- Dose for Ph2 and establishing POC: update with emerging PK, trial design trial with improved dose levels, evaluate combinations, test patient groups, and assess biomarkers
- Confirmatory and understanding for Ph3: update model with data to improve prediction accuracy for new trial design, suggest new patient populations, justify/confirm optimal results, clarify contribution of components
- Post Market: new indications, new combinations, and more convenient dosing regimens



Mechanistic modeling strategies are fit-for-purpose

Pathway Models

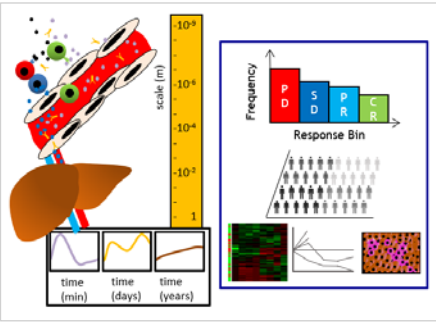


Mechanistic PK Models

Receptor Occupancy Models

Mechanistic PK-PD Models

Platform and Disease Models



Mechanistic Model Scope (Breadth, Data, and Complexity)

Modeling approach considers:

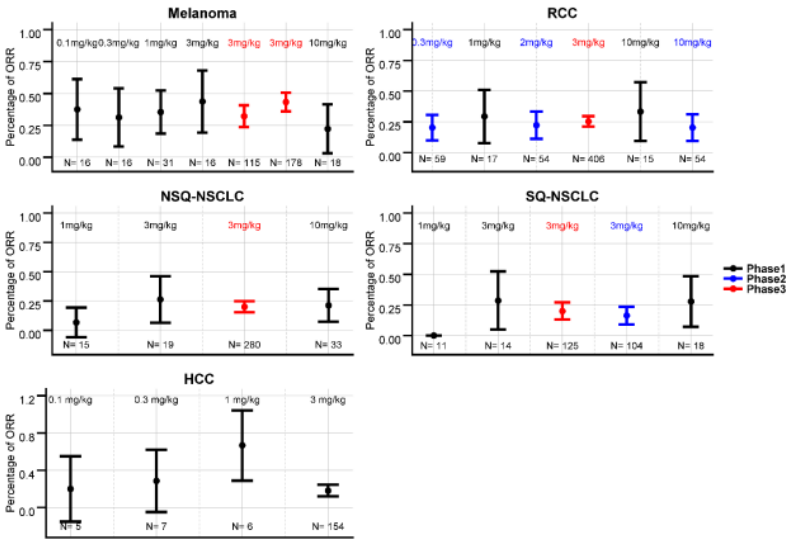
- Timelines
- Scientific questions
- Available information and data

Context: receptor occupancy was one component of multiple strategies to support 240 mg Q2W and especially 480 mg Q4W

- Motivation
  - Flat dosing for simpler dose preparation
  - Q4W extended dosing frequency provides a convenient treatment option for patients and health care professionals (Q4W vs. Q2W)
- Many clinical data were available for other regimens, MIDD critical for establishing safety-benefit of 480 mg Q4W
- Comparison of exposures was done via modeling
  - Well-established PK model
  - Comparison of key PK outputs (Cmax1, Cmin1, Cavg1, Cmaxss, Cminss, Cavgss, Cavgd28, Cmind28)
  - Comparison of key regimens: 3 mg/kg Q2W, 240 mg Q2W, 480 mg Q4W
- Safety-bridging evaluation was done via modeling
  - Assessment of pharmacokinetic exposures for 480 mg Q4W and benchmarking against 10 mg/kg Q2W
  - E-R safety analyses to predict probability
- Efficacy-bridging was done via modeling
  - E-R analysis, especially for tumors with rich data
  - RO modeling to enable extrapolation across more tumor types: base case, best case, worst case

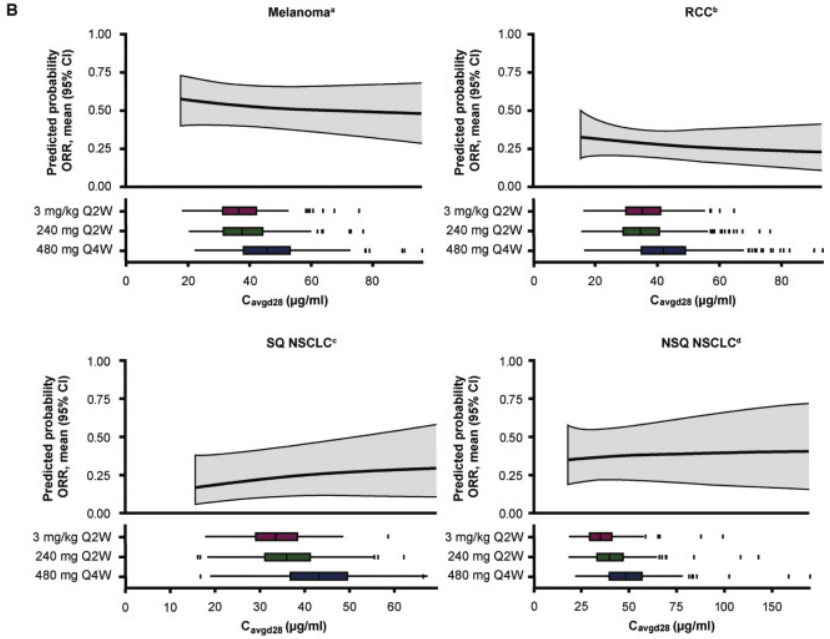
Zhao X, Shen J, Ivaturi V, et al (2020) Model-based evaluation of the efficacy and safety of nivolumab once every 4 weeks across multiple tumor types. Annals of Oncology 31:302–309. https://doi.org/10.1016/j.annonc.2019.10.015

Context: modeling approaches were applied to supplement gaps in clinical data



CENTER FOR DRUG EVALUATION AND RESEARCH. 2018. 125554Origs048. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/125554Orig1s048.pdf

Bi Y, Liu J, Furmanski B, et al (2019) Model-informed drug development approach supporting approval of the 4-week (Q4W) dosing schedule for nivolumab (Opdivo) across multiple indications: a regulatory perspective. Annals of Oncology 30:644–651. https://doi.org/10.1093/annonc/mdz037



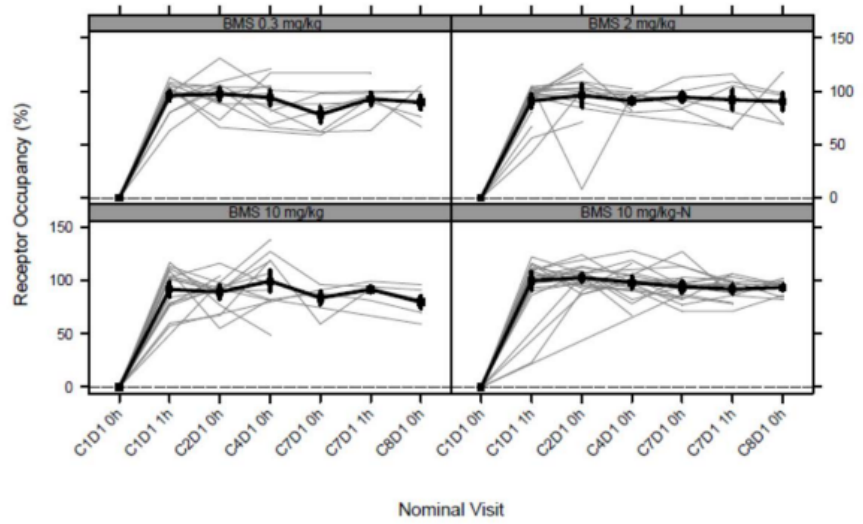
Zhao X, Shen J, Ivaturi V, et al (2020) Model-based evaluation of the efficacy and safety of nivolumab once every 4 weeks across multiple tumor types. Annals of Oncology 31:302–309. https://doi.org/10.1016/j.annonc.2019.10.015

- Similar average exposure predicted at 480 mg Q4W compared to 3 mg/kg Q2W at SS based on modeling and simulation
  - Differences in Cmin1 and Cmin28 (not shown)
- Flat exposure-response relationships for melanoma and RCC
- Trend toward a higher ORR with increased nivolumab exposure in SQ NSCLC
- Differences suspected in some tumor types between 1 mg/kg Q2W and 3 mg/kg Q2W dosing
- Predicted ORR was similar within the exposure range of 3 mg/kg Q2W and flat dosing of 480 mg Q4W
- Mechanistic modeling could provide (1):
  - Additional confidence exposures, especially early exposure, for 480 mg are acceptable

Peripheral RO was known to be saturated despite differential response observations

In the nivolumab metastatic RCC study CA209009, RO was assessed using fresh whole blood specimens. RO of peripheral CD3+ T cells (and CD4+ or CD8+ subsets) was measured at baseline and at six timepoints following initiation of nivolumab treatment (Dose 1-1H, Dose 2-0H, Dose 4-0H, Dose 7-0H, Dose 7-1H, Dose 8-0H). Kinetics of RO were similar across all dose cohorts (0.3 mg/kg, 2 mg/kg, 10 mg/kg, 10 mg/kg-treatment naive) (Figure 6) Receptor occupancy of >90% was achieved at one hour post nivolumab treatment at all dose levels, and remained near this level through Dose 8 Day 1.

Figure 6: Time course of PD-1 occupancy by nivolumab by dose level – Study CA209009



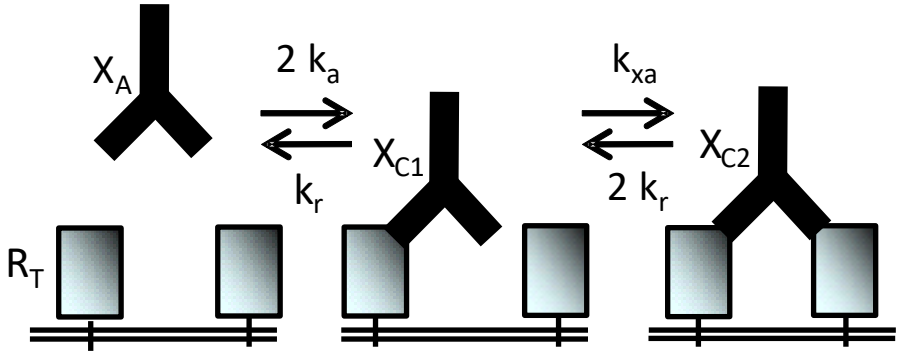
European Medicines Agency 2015. 682492. https://www.ema.europa.eu/en/documents/variation-report/opdivo-h-c-3985-ii-0001-epar-assessment-report-variation_en.pdf

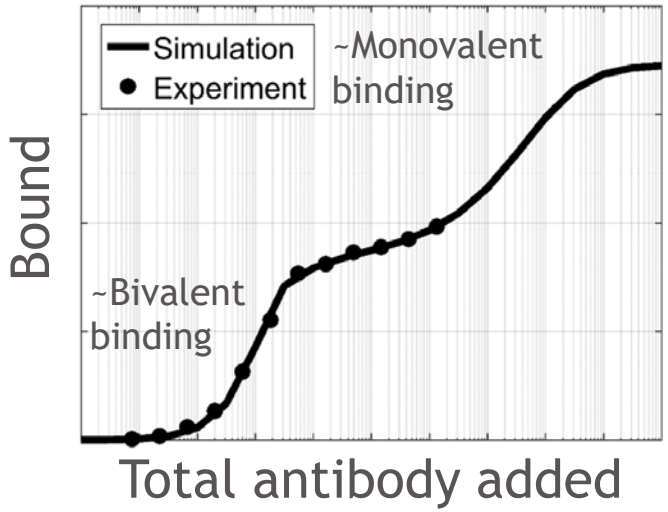
- Various measures of peripheral RO with nivolumab have been published
- CA209009 was a study that used fresh whole blood and reported ~100% RO
- Peripheral RO was largely saturated even at low doses (0.3 mg/kg Q3W)
- Saturated peripheral RO at low doses coupled with observations of differential response at 1 mg/kg Q2W suggested:
  - Heterogeneity in tumor types, with NSCLC representing a tumor requiring higher exposure
  - The blood is not a good tissue to establish proof-of-mechanism and engagement at the site
- Mechanistic modeling also could provide (2):
  - Rationale for why site of action may deviate from blood and prediction of tissue engagement

Tumor RO analysis: building blocks & workflow

Datasets	In vitro measures for nivolumab (new)	Pharmacokinetic (prior)	Literature research (prior)
Base models	Mini-models for nivolumab parameter estimation (new)	PopPK (prior, BMS)	Tumor transport, PD-1/ligand pathway (integrated from information in literature)
Integration, checks, sensitivities for tumor RO	• Combined, integrative model • Check peripheral receptor occupancy predictions with data • Multivariable sensitivity analysis of tumor RO at day 28 following initial 480 mg dose		
Prediction given population PK distribution	"Best case:" tumor characteristics that give highest RO distribution	"Base case:" initial literature estimates	"Worst case:" characteristics that give lowest RO distributions

New in vitro datasets generated for estimating antibody avidity

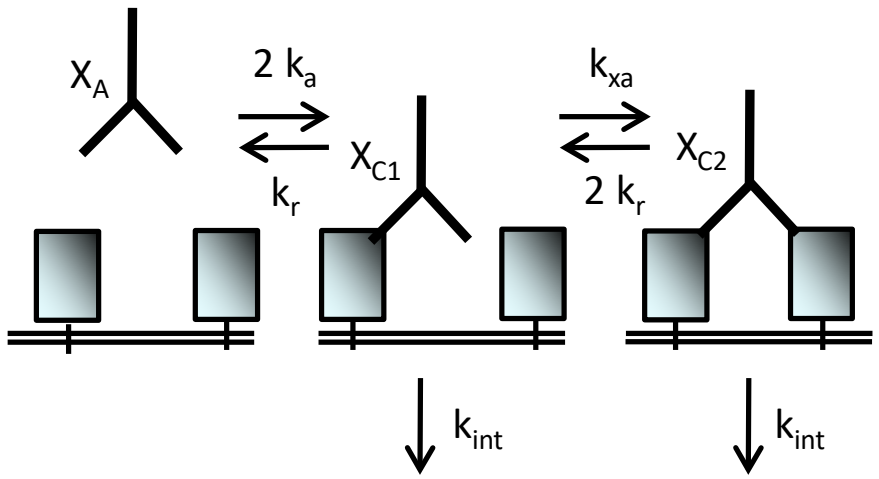


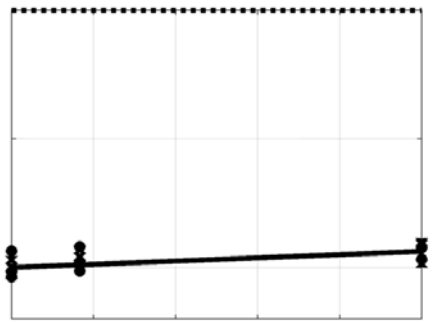


Schmidt BJ, Bee C, Han M, et al (2019) Antibodies to Modulate Surface Receptor Systems Are Often Bivalent and Must Compete in a Two-Dimensional Cell Contact Region. CPT Pharmacometrics Syst Pharmacol 8:873–877.

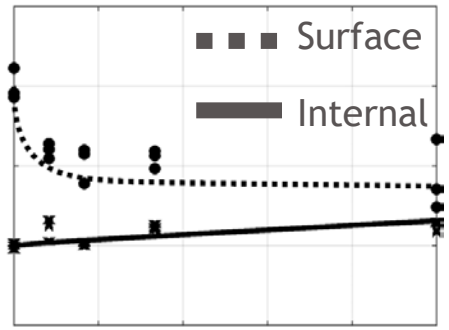
- SPR data with antibody Fab fragments informed monovalent kinetics
  - k_a
  - k_r
- A new cell binding assay was developed to assess affinity and avidity characteristics for antibodies
- The assay uses directly labeled primary antibodies and quantitative calibration beads
- Modeling and fitting the assay is critical for expression and avidity parameters
  - k_{xa}, antibody cross-linking rate parameter uses a two-dimensional reaction (area/number/time)
  - RT, expression parameter (number/area)

New in vitro datasets generated for estimating internalization





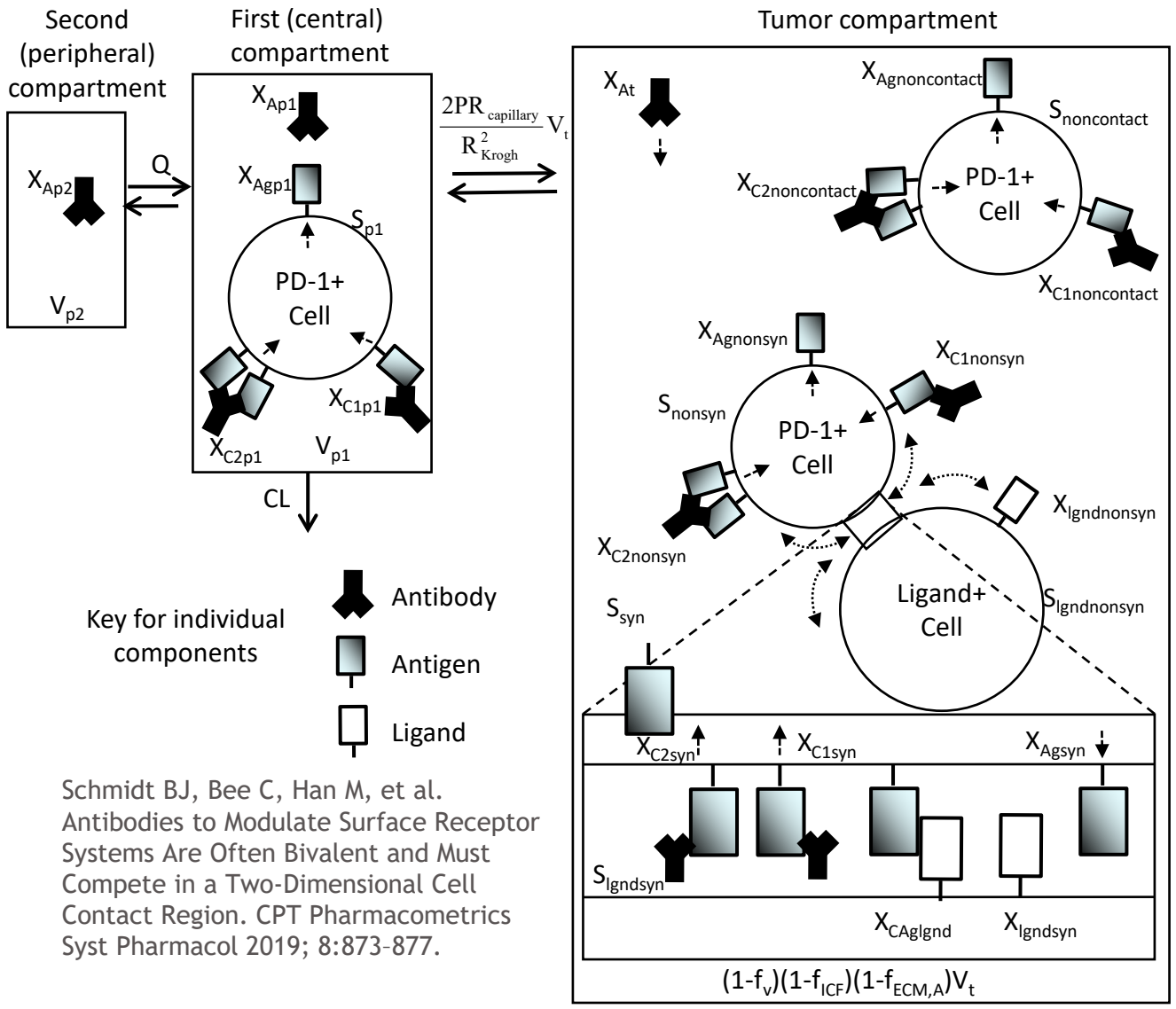
"Continuous"



"Pulse-chase"

- A fluorescence quench assay was developed to inform net internalization rates
  - "Continuous" mode
  - "Pulse-chase" mode
- Similar to avidity measurements, protocols were fit with simulations of the protocol to estimate key parameters – here net internalization rate
- Model accounts for antibodies "falling off" in pulse-chase model

RO model structure

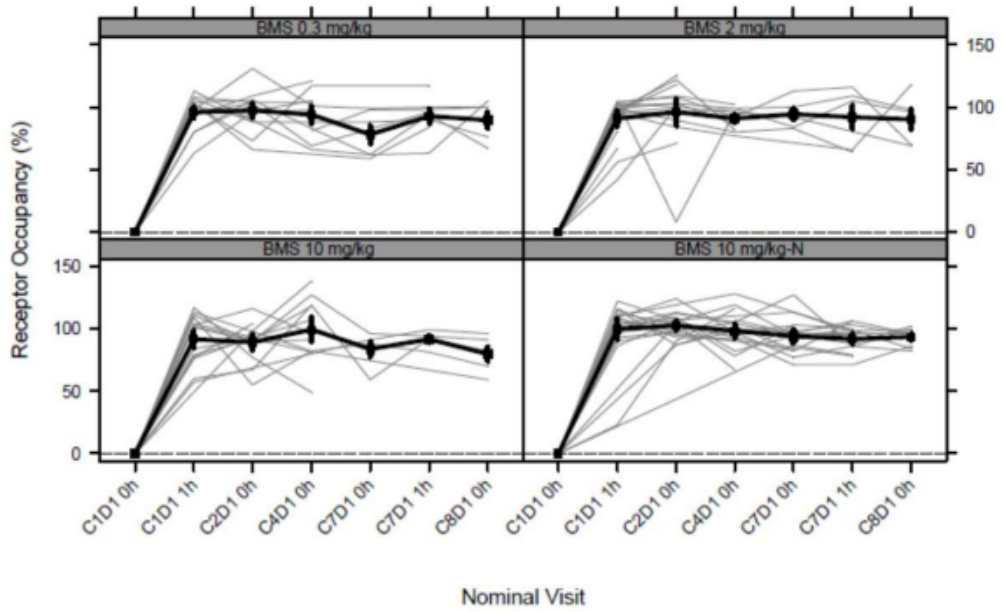


Schmidt BJ, Bee C, Han M, et al. Antibodies to Modulate Surface Receptor Systems Are Often Bivalent and Must Compete in a Two-Dimensional Cell Contact Region. CPT Pharmacometrics Syst Pharmacol 2019; 8:873–877.

- Population pharmacokinetic model
  - Two compartment model with time-varying clearance
  - Categorical covariates include tumor type
- Tumor transport model
  - Based on previously published work
    - Schmidt MM, Wittrup KD. A modeling analysis of the effects of molecular size and binding affinity on tumor targeting. Mol Cancer Ther 2009;8:2861-71
    - Thurber GM, Dane Wittrup K. A mechanistic compartmental model for total antibody uptake in tumors. J Theor Biol 2012;314:57-68.
  - Captures enhanced permeation and retention effect and impact of elevated interstitial pressure
- Cell binding model
  - Blood and tumor
  - Affinity, avidity, membrane transport, synapses with 2D confinement and ligand competition
  - General references for related pathways
    - Agrawal NGB, Linderman JJ Mathematical Modeling of Helper T Lymphocyte/Antigen-presenting Cell Interactions: Analysis of Methods for Modifying Antigen Processing and Presentation. Journal of Theor Biol 1996; 182:487–504.
    - Bromley SK, Iaboni A, Davis SJ, et al The immunological synapse and CD28-CD80 interactions. Nature Immunology 2001; 2:1159–1166.

Model check: saturation of peripheral RO captured

Figure 6: Time course of PD-1 occupancy by nivolumab by dose level – Study CA209009



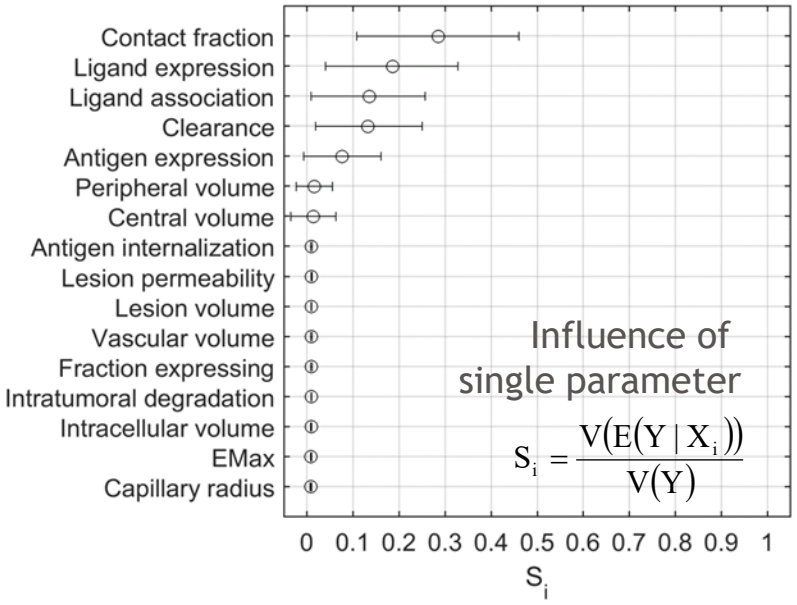
European Medicines Agency 2015. 682492. https://www.ema.europa.eu/en/documents/variation-report/opdivo-h-c-3985-ii-0001-epar-assessment-report-variation_en.pdf

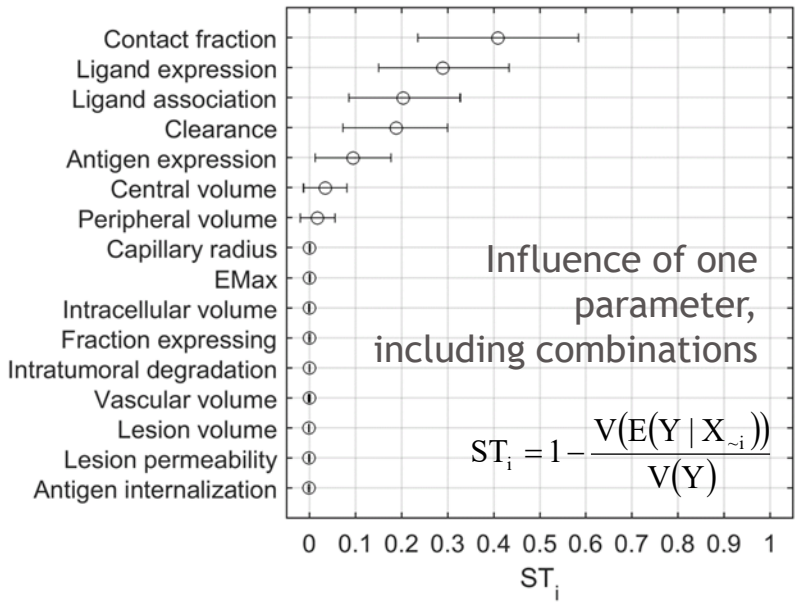
Dose (mg/kg)	Assay N	Assay RO Median (IQR)	Simulated N	Simulated RO Median (IQR)	Δ Median (Simulation - Assay)
0.3	14	0.940 (0.870 - 1.110)	2947	0.965 (0.961 - 0.969)	0.025
2	15	1.000 (0.983 - 1.088)	2947	0.987 (0.985 - 0.988)	-0.013
10	36	0.985 (0.885 - 1.055)	2947	0.995 (0.994 - 0.995)	0.010

Parameters for sensitivity analysis

Symbol	Units	Description	Rationale for range
CL	L day^{-1}	Baseline clearance	Bounds are for a 95% prediction interval created from the PPK model and a virtual patient population with matched covariate distribution from the available population of 2,497 subjects.
Emax	dimensionless	Maximal effect of the time-varying clearance	Bounds are for a 95% prediction interval, similar to CL.
Vp1	L	Volume of the first (central) compartment	Bounds are for a 95% prediction interval, similar to CL.
Vp2	L	Volume of the second (peripheral) compartment	Bounds are for a 95% prediction interval, similar to CL.
P	μm day^{-1}	Capillary permeability to antibody	A 1/3×-3× range from the reported IgG permeability.
$R_{capillary}$	μm	Radius of a tumor capillary	From studies of vessel architecture in tumor models.
f_V	dimensionless	Vascular volume fraction for the tumor	Values ranging from 0.4% to 5%, or even 10%, are reported.
f_{ICF}	dimensionless	Fraction of the non-vascular tumor volume that is intracellular	Cancer cells often comprise more than 50% of a tumor's volume, and intracellular volume fractions greater than 0.7 have been reported.
k_{int}	day^{-1}	Antigen complex internalization rate	Internalization study provides a 6-fold range of rates to explore.
R_T	molecules μm^{-2}	Total density of antigen on the cell surface	Set based on ranges observed from total receptor fits expressed on activated donor cells.
$f_{contact}$	dimensionless	Fraction of antigen-expressing cells in contact with ligand expressing cells	Potential range for fraction of PD-1+ cells in contact with ligand-expressing cells.
V_t	L	Tumor volume	Calculated from the 2.5 to 97.5 percentile for about 1,000 individual baseline tumor longest diameter measures from Study CA209003, then converted to volume assuming spherical geometry (worst case).
L_T	molecule μm^{-2}	Density of ligand on the cell surface	PD-L1 expression on DCs were reported. It is also possible some cancer may upregulate PD-L1. A high upper range for total expression, up to about 10× per cell relative to dendritic cells, was therefore explored.
k_{deg}	day^{-1}	Degradation rate of free antibody in tumor	Antigen-independent degradation and clearance rates for nivolumab or other IgG_4 antibodies in tumor have not been reported. Literature experiments with A431 cells suggested pinocytosis rates to explore.
$f_{expressors}$	dimensionless	Scaling factor for the total number of cells in the lesion expressing the antigen	Scaling factor to adjust volume fraction and number of cells in tumor that express PD-1. A scaling factor 30 was employed to span the range observed in the reports.
$k_{xa,lgnd}$	μm^2 $molecule^{-1}$ day^{-1}	Association rate of receptor-ligand complexes	$k_{xa,lgnd}$ limits were set to correspond published solution phase dissociation constant range for PD-L1 assuming a fixed dissociation rate.

Sensitivity analysis elucidates factors that may drive tumor target engagement under dosing scenarios of interest





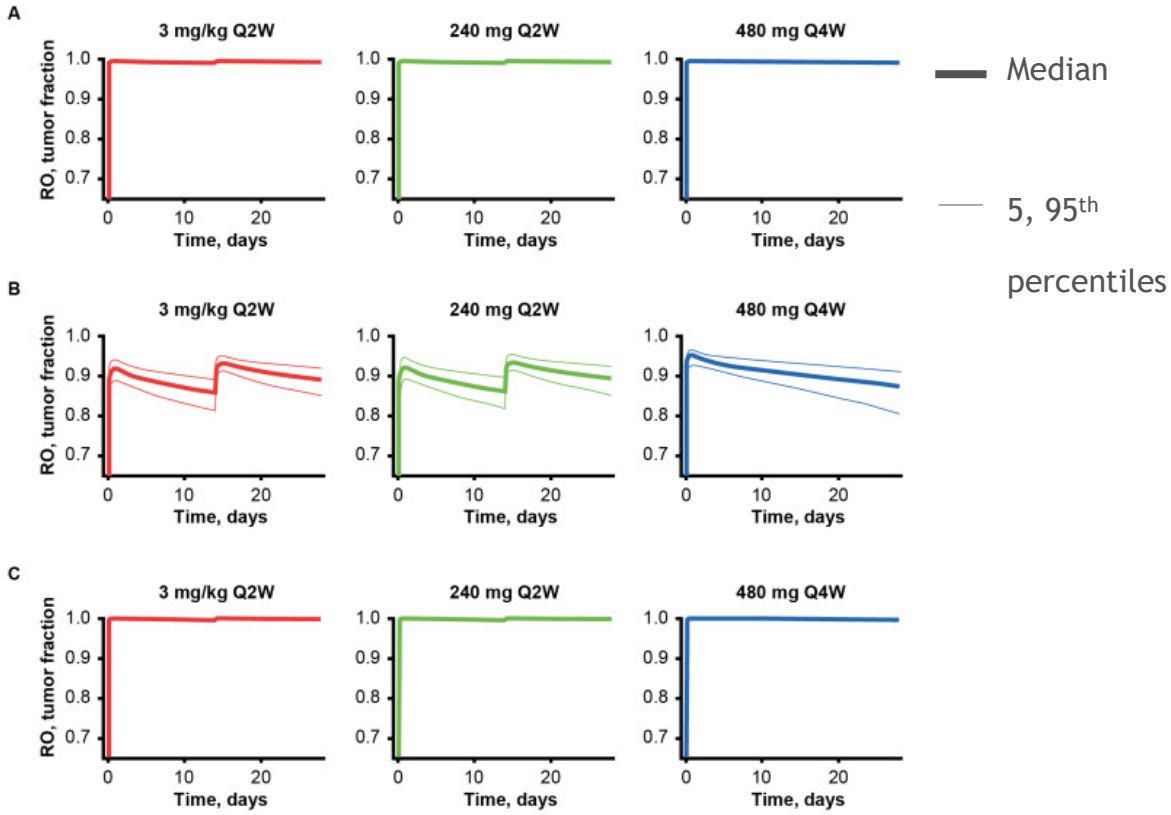
- Intratumoral RO at day 28 following a 480 mg dose of nivolumab was assessed
- Convergence of the Sobol indices was verified (not shown)
- The open circles indicate the median from bootstrapping, and the error bars indicate the 95% confidence interval
- Intratumoral RO was most sensitive to:
  - fraction of PD-1 expressing cells involved in contact with ligand expressing cells (contact fraction)
  - ligand expression
  - ligand association
  - baseline clearance
- Many physiological factors expected to vary between tumors were identified as relatively uninfluential determinants of nivolumab intratumoral RO

Simulations projected minimal differences for tumor RO for new dosing regimens (1)

Base case

Worst case

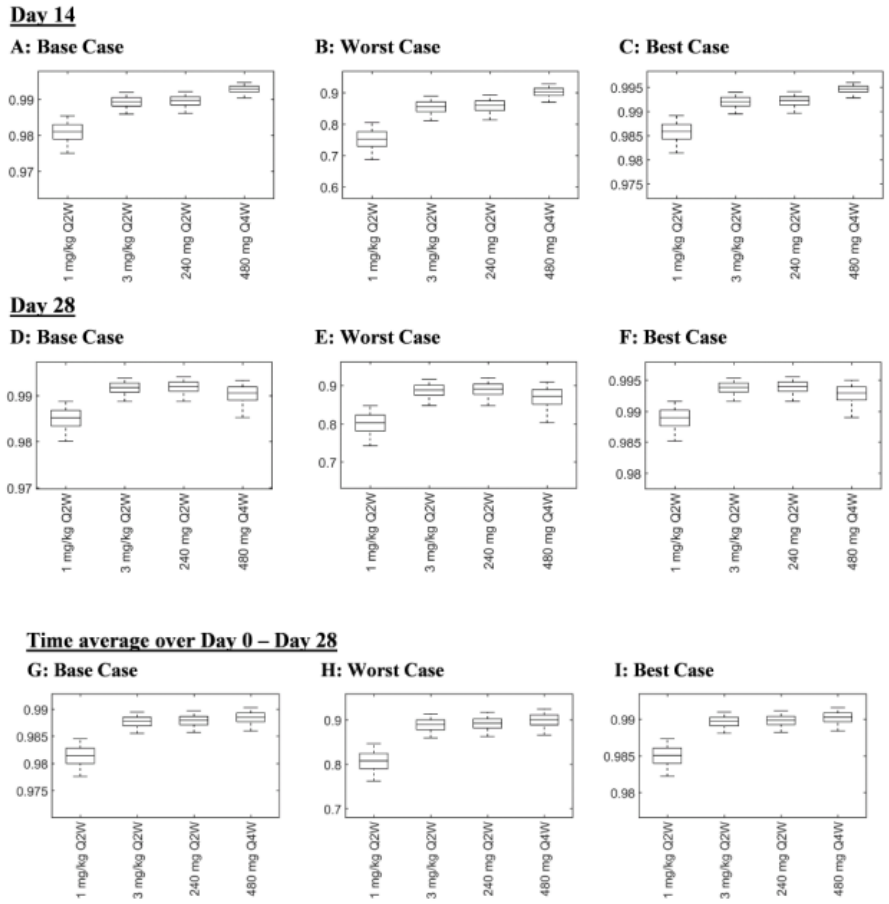
Best case



- Pharmacokinetic parameter distributions were set according to the population PK model
- Tumor parameters were varied for scenarios to give different cases if their sensitivity index exceeded 0.05
  - Contact fraction
  - Ligand expression
  - Ligand association
  - Antigen expression
- Different scenarios are representative of tumors with different biophysical characteristics
- "Worst case" scenarios were needed to drive lower RO

Zhao X, Shen J, Ivaturi V, et al (2020) Model-based evaluation of the efficacy and safety of nivolumab once every 4 weeks across multiple tumor types. Annals of Oncology 31:302–309. https://doi.org/10.1016/j.annonc.2019.10.015

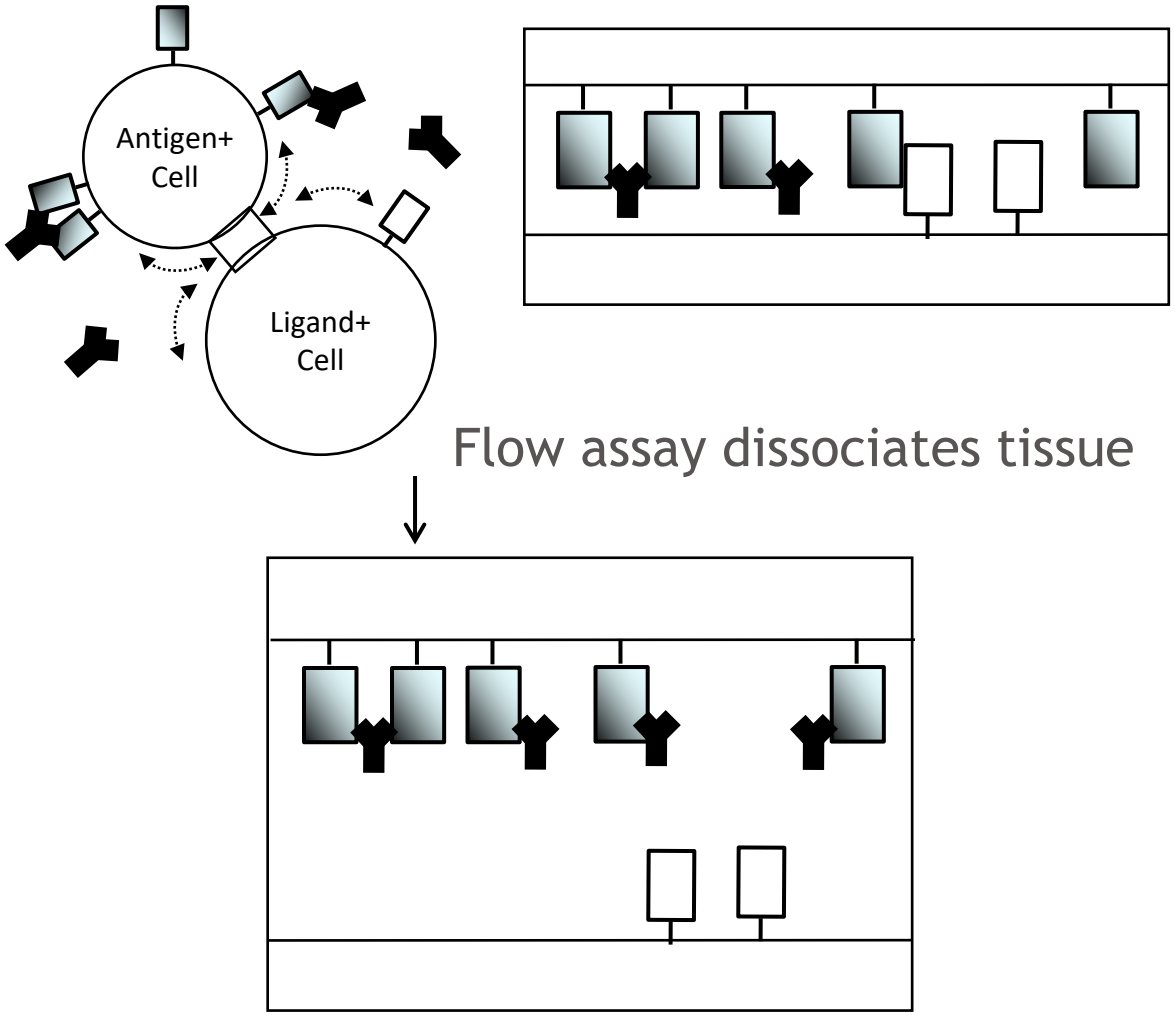
Simulations projected minimal differences for tumor RO for new dosing regimens (2)



CENTER FOR DRUG EVALUATION AND RESEARCH. 2018. 125554Origs048. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/125554Orig1s048.pdf

- "Worst case" predicts differences in tumor RO between 3 mg/kg Q2W and 1 mg/kg Q2W, shown for the first 28 days
  - -0.47% (best case)
  - -9.2% (worst case)
- Most sensitive parameters that define "worst case" are specific to tumor pathways (cell contact), peripheral RO is high
- 480 mg Q4W dosing regimen exhibits
  - Higher intratumoral RO at Day 14 than 3 mg/kg Q2W regimen
  - Marginally lower, comparably high intratumoral RO at Day 28
- High time-average intratumoral RO is maintained with 240 mg Q2W and 480 mg Q4W dosing regimen relative to 3 mg/kg Q2W across the various scenarios representing a variety of tumor types
- RO QSP model supports the 240 mg Q2W and 480 mg Q4W regimens
  - Time-average RO will be maintained over the first 28 days for a variety of scenarios with different tumor characteristics.

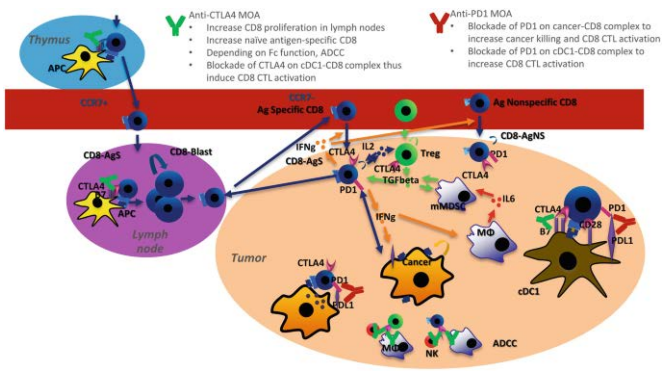
Implications of results for measuring RO and validation at the site of action



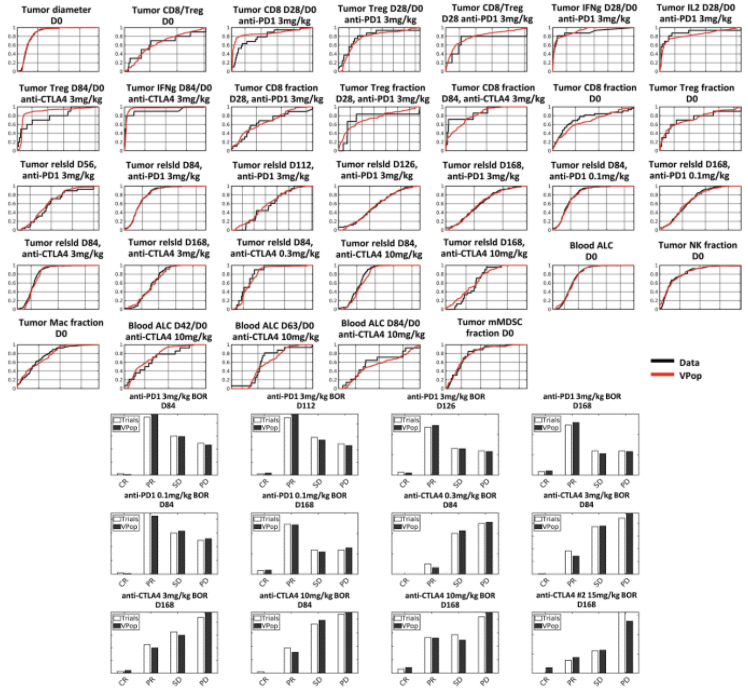
- If an antibody blocks a receptor-ligand interaction in an immune synapse (e.g. as with checkpoints)
  - Dissociating tissue would
    - Relieve competition
    - Release drug from blood (here, minor impact)
    - Make it easier for the antibody to bind receptor
  - Analysis suggests RO at site won't necessarily be reflected with methods that dissociate tissue
    - RO from flow-based assays would be higher than the tissue RO in important quantitative regimes of low net antibody internalization/degradation and higher confinement affinities
- Considerations for validation data at site of action
  - Imaging & IHC-based methods, with intact tissue (sections), have potential to address methodological challenges
  - Clinical challenge: want to capture the sensitive regions of the D/E-R curve
    - Not always practical post-market, special considerations

Data availability guide application strategy to guide decisions

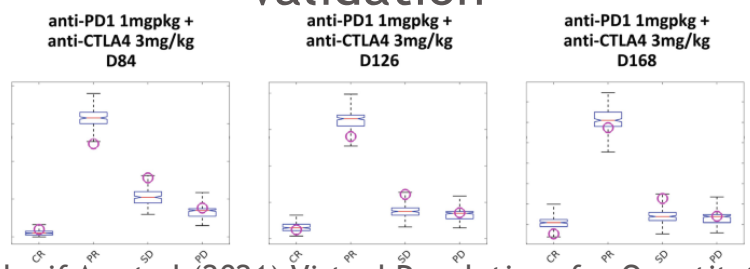
Model



Calibration



Validation



- Case highlights differences in strategies for mechanistic model application
  - Scenario based
    - Build confidence in the model
    - Don’t have direct measures of key outputs, e.g. RO at the site
    - Develop base/best/worst case scenarios to extrapolate based on mechanism
  - Targeted prediction
    - Validation data available more directly related to model output of interest
    - Might be challenging for e.g. occupancy data at site
    - Other endpoints (ORRs) can be more amenable
- Data availability can be a bigger influence than “model size” for strategy

Cheng Y, Straube R, Alnaif A, et al (2021) Virtual Populations for Quantitative Systems Pharmacology Models. In: Systems Medicine. Springer

Report format and submission considerations

- Synopsis
- Table of contents, list of tables, figures, and appendices

1. Introduction and background
    1. Background
    2. Rationale
2. Objectives
3. Methods
    1. Model development
    2. Blood RO
    3. Development of scenarios
    4. Software & hardware description
4. Results
    1. Blood RO
    2. Tumor RO: sensitivity results to guide scenarios
    3. Prediction of scenarios for regimens of interest
5. Discussion
6. Conclusions
7. Abbreviations
8. References

- Appendix: experimental data sources, mini-model fits, more details on submodel development

- No QSP report guidance at the time, PBPK report prior art to guide sections
  - CDER. Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry (Draft). 2017.
  - This report: 94 pages
- Flexibility in file formats and allowing for directory structure was critical to sending a package to enable reproducible analyses
  - Not all text files
  - Directory structure organized files
  - Version-controlled toolbox organized in folders and binary/proprietary model format (sbproj)
  - Made it easy to re-run
    - runAll.m command in MATLAB
  - Submitted zip archive on a physical disk

New report considerations for QSP in 2022, 2023

- Executive Summary
- Table of contents, list of tables, list of figures, list of appendices

1. Introduction
   - 1.1 Overview of modeling strategy
   - 1.2 Overview of model, simulation design, validation
   - 1.3 Drug implementation in model
   - 1.4 PK support
2. Materials and methods
   1. Modeling strategy (structure, drug implementation)
   2. Model parameters, simulation design, calibration, validation (pk, parameters, simulation pipeline, cohort constraints & VPop data types, training & validation sets)
   3. Hardware, software & files
3. Results
   1. Calibration approach and fit to calibration data
   2. Reproduction of validation data
   3. Model application & predictions
4. Discussion
   1. Summary of model fitting and validation
   2. Risk assessment and model impact
   3. Discussion of prediction results
5. Conclusions
6. Abbreviations
7. References

- Appendix: Model background (summary of model rationale and structure, model equations and parameters)

- PBPK report guidance used didn't suggest new elements found in new QSP community discussions
  - E.g. did not address risk, other elements
  - Resources to guide new formats being tried at BMS as on left
    - Bai JPF, Schmidt BJ, Gadkar K, et al FDA-Industry Scientific Exchange on assessing quantitative systems pharmacology models in clinical drug development: a meeting report, summary of challenges/gaps, and future perspective. 2021. The AAPS Journal 23:10. https://doi.org/10.1208/s12248-021-00585-x
    - Check what reviewers are looking for: CENTER FOR DRUG EVALUATION AND RESEARCH. 2022. 761261Orig1s000. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000IntegratedR.pdf
    - CDRH. 2021. Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions. Draft Guidance
- Maintaining flexibility in future file formats would be helpful
  - Binary and flexible formats, directories
  - Flexible zip archives

Conclusions

- Mechanistic modeling can be applied to address a variety of questions along the research and development pipeline
- MIDD was critical for the approval of nivolumab Q4W 480 mg across tumor types
- Mechanistic modeling was employed to:
  - Develop additional confidence in the new dosing regimen
  - Enable a pan-tumor assessment and extrapolation across cancers by accounting for critical biophysical differences, encapsulating rare and more common tumors
  - Explain potential differences between the periphery and tumor tissue
- Mechanistic modeling is not limited to early research and translation
- Mechanistic modeling has the potential to play a larger role in drug development, including post market and BLAs

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Questions?

- Follow-up
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- BMS QSP&PBPK team is hiring
  - Multiple experience levels
  - QSP roles, PBPK roles
  - Multiple QSP Associate Director level roles to expand group's role in preclinical space
    - Prior pharmaceutical industry QSP experience
    - Manage a pre-clinical book of work, great growth opportunity