# EVOLVING ROLE OF *MODELING & SIMULATION* IN RESEARCH, DEVELOPMENT AND APPROVAL OF MEDICINES

## AMED SYMPOSIUM

September 3rd, 2019

Tokyo, Japan

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INVENTING FOR LIFE

# Disclosures & Acknowledgements

- I am an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and shareholder of Merck & Co., Inc., Kenilworth, NJ, USA

- Ideas and concepts here from colleagues at the research laboratories of Merck & Co., Inc., Kenilworth, NJ, USA
  - IQ QSP WG
  - Brian Topp for his concepts around Virtual Patients and Tumor growth

- Examples: Published and accordingly attributed

# Modalities in Therapeutic Interventions

**A Decade Ago**

- ❑ Small Chemicals/Peptides
- ❑ Biologics – mAB
- ❑ Early Combinations
- ❑ Many areas of unmet medical need

- ➢ Establishing predictive approaches in decision-making
- ➢ Limited tailoring of medicines for patients

**Now**

- ❑ Biologics – mAB
- ❑ Bispecific/Targeted Molecules
- ❑ Combination Treatments
- ❑ Gene and Cell Based Treatments
- ❑ Vaccines as Treatments

- ➢ Mechanistic Models
- ➢ Establishing Proof of Concept
- ➢ Getting the Dose Right
- ➢ Adaptive Trials – Drug-Disease Models
- ➢ Precision Medicine

While many of the quantitative approaches can be applied, a key difference for biotherapeutics versus small molecules is the interplay with the disease state

# Framework for the Application of M&S

## *Accelerate Therapeutic Development and Differentiation*

- Bring translational, quantitative thinking as early as practical and useful for decision-making on whether each new target, molecule and development in a portfolio has the right amount of risk for development
- Influence portfolio decisions

– Develop a Quantitative framework of Causal Human Biology (Mechanistic platforms, Disease progression models, Translational PK/PD)

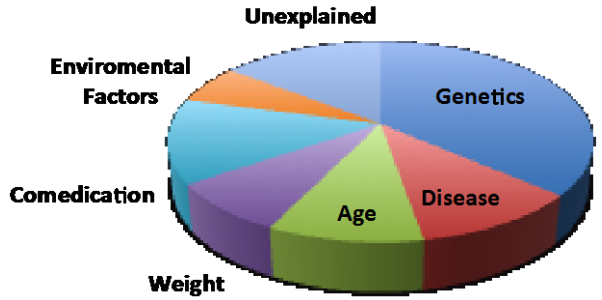
- Opportunity to influence the path to the clinic through clinical plans and study designs including model-informed fast to Clinical POC trajectories
- Balance *post-hoc* analysis to *a priori* design of clinical trials using simulation and probabilistic prediction of outcomes

➢ *Detect negative results in trials earlier and adapt (dose, study design) and learn from failed trials (target biology, wrong dose or endpoints)*

# Variability: The Challenge

## Patients vary widely in their susceptibility to disease and response to drugs

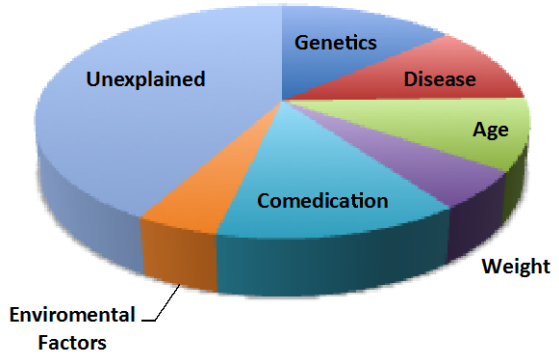
**Pharmacokinetic Variability**




**Those likely to benefit (responders) without undue harm**

**Based on condition, genomics, biomarkers etc**

**Pharmacodynamic Variability**




**Based on**
- **Age, disease, genetics,**
- **Ethnicity, co-medication etc**

**Initial dose may not be optimal.**

"….the appreciation of controllable sources of variability in drug action and potential injury to patients should be achieved prior to the marketing of new pharmaceutical products."
- JAMA, March 31, 1993
Rowland TED, FDA 2015

# Pharmacometrics : Where We Were ~Two Decades Ago

FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug Products (1998)

FDA Guidance for Industry: **Population PK** (1999)

Center for Drug Development Science workshop report on **Simulation** in Drug Development – Good Practices (1999)

PK-PD Modeling in Drug Development, Annual Rev Pharmacol Toxicol 2000; 40:67-95 (2000)

FDA Guidance for Industry: E/R Relationships – **Study Design, Data Analysis and Regulatory Applications** (2003)

Early Research and Adopters on **Physiological Based Pharmacokinetics**

Early Research in **Systems** Approach in **Pharmacology**

# Where We Are Now

- **Translational Pharmacokinetics and Pharmacodynamics – Biomarkers and Use of Pharmacodynamic Endpoints**
- **Model based Meta-Analysis**
- **Quantitative Systems Pharmacology**

"…In silico clinical trials use computer models and simulations to develop and evaluate devices and drugs. Modeling and simulation play a critical role in organizing diverse data sets and exploring alternate study designs. This enables safe and effective new therapeutics to advance more efficiently through the different stages of clinical trials. FDA's efforts in modeling and simulation are enabled through multiple collaborations with external parties that provide additional expertise and infrastructure to advance the development of these state-of-the-art technologies…" FDA Commissioner's Blog, July 2017

**Dose Adjustments in subpopulations based on Exposure Response Analysis**

**Dosing Adjustments Based of Population Pharmacokinetics and Integration of ER**

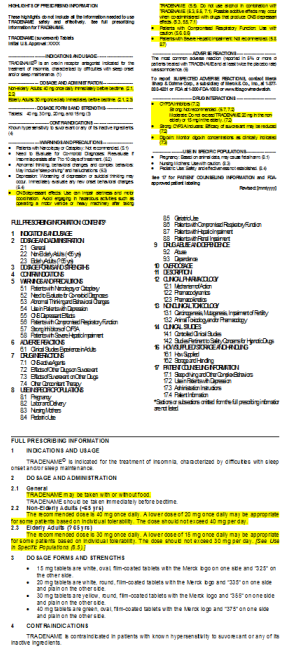
Use of Concentration –QT Analysis in Assessing Cardiovascular Safety

**World wide regulatory agencies using quantitative and predictive approaches**

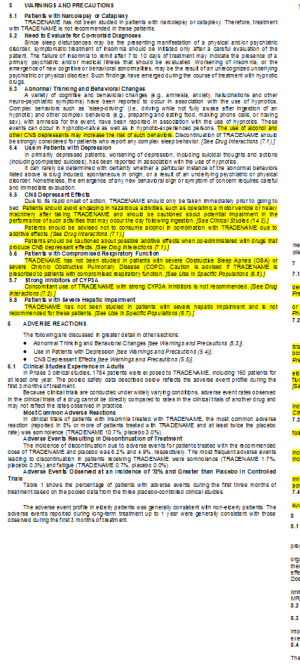
**Devices**

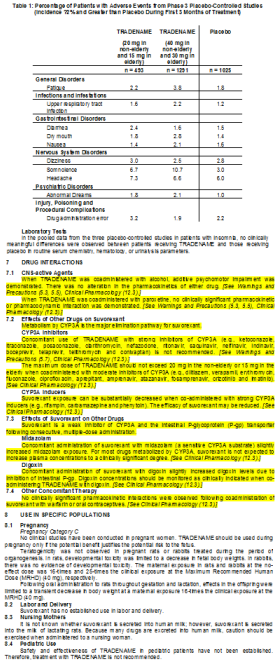
# Drug Label

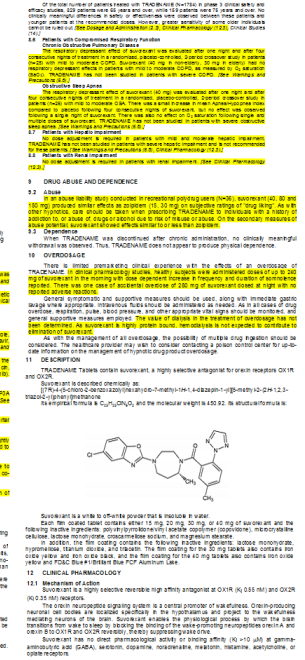
## *Example from Belsomra™ (suvorexant)*

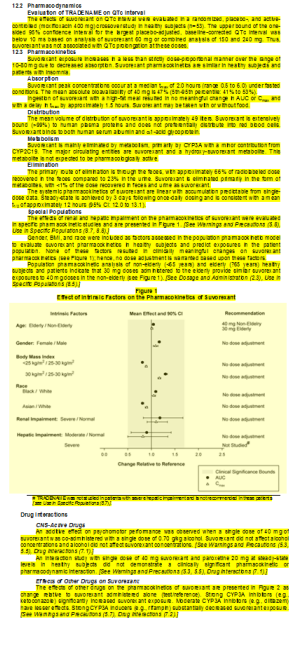


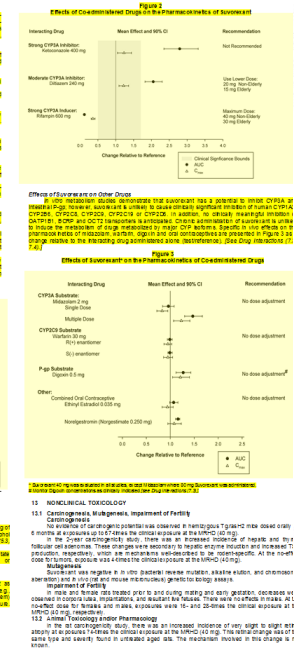


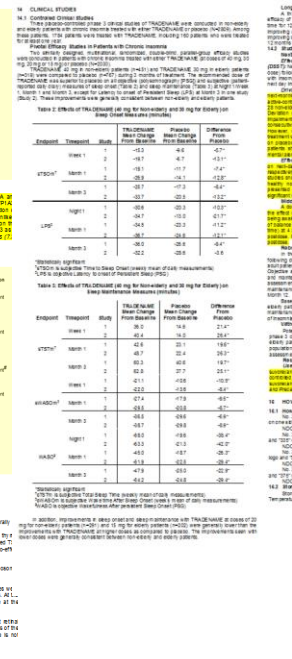


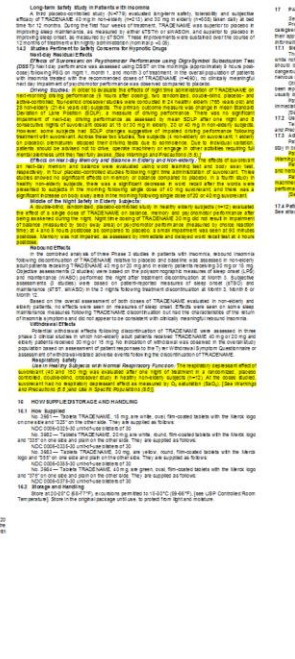






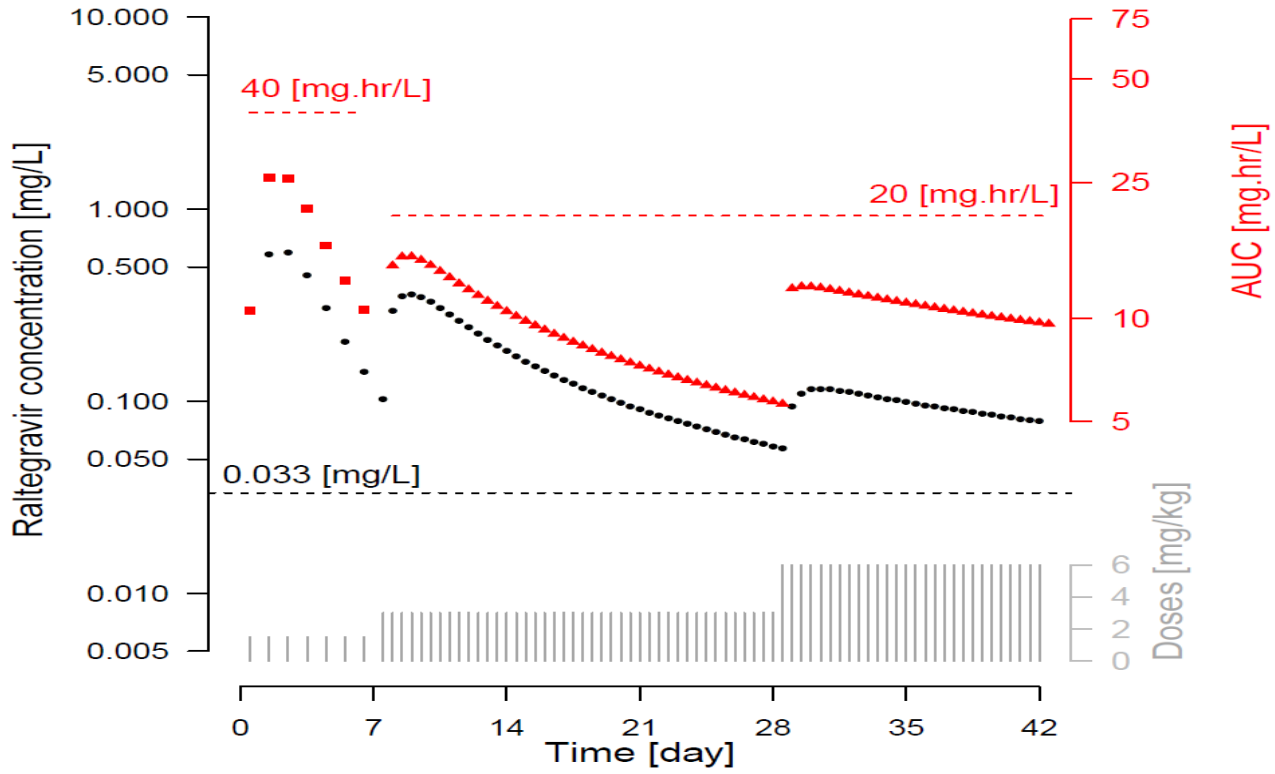






- **Contributions in:**
  - Dosage and Administration
  - Warnings and Contraindications
  - Clinical Pharmacology
  - Immunogenicity
  - Special Populations
  - Drug-Drug Interactions

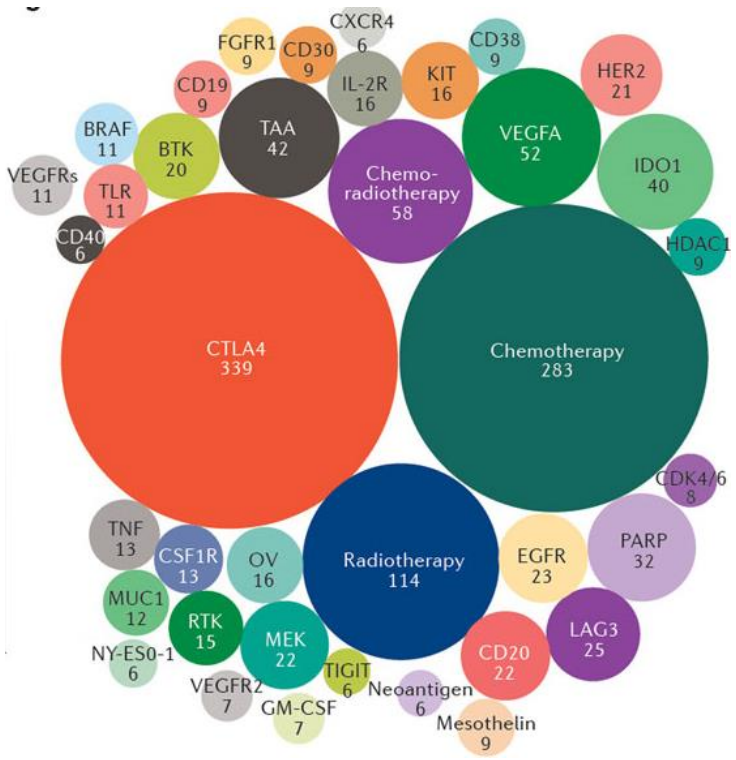
# Raltegravir Dosing in Neonates




**Placental transfer and metabolized by uridine diphosphate glucuronosyltransferase (UGT) 1A1, and could displace unconjugated bilirubin from albumin, potentially increasing neonatal risk of kernicterus, as was seen with sulfisoxazole.**

**Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1110 Study Team**

# Very Active Immune Oncology Clinical Landscape




*Nature Reviews Drug Discovery* **volume 17**, pages 854–855 (2018)

- Unprecedented competition in the field
- Expectation high for new IO drugs, however, challenging to demonstrate clinical benefit relative to the improved SoC
- Typical approach of individual studies for each new tested drug may not be efficient (time, resources)
- Speed vs certainty in results. Common to move from Phase 1 to Phase 3 directly
- Dose
  - Best Starting dose, not MABEL ?
  - How best to ascertain therapeutic range whilst patient sparing and non-exposure of patients to sub-therapeutic doses.

# Pembroluzimab (KEYTRUDA®)

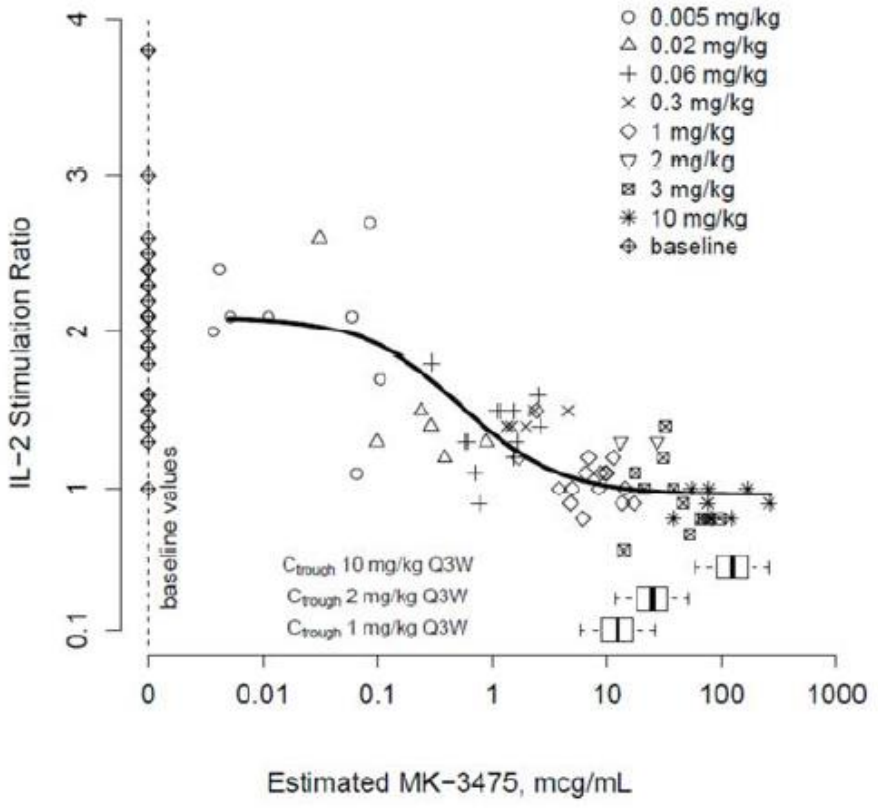
- **Potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype**

- **Blocks interaction between programmed death (PD) -1 and its ligands, PD-L1 and PD-L2**

- **Unlike many of the historical mAbs in oncology, pembroluzimab binds to immune cells, not tumor cells. Blocks interaction of PD-1 on Tcells –enhancing T cells response against tumors**
  - Global approvals in melanoma, NSCLC, HNSCC, HL, MSI-H, Bladder, metastatic squamous lung cancer, etc.

- **Enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection**

# Ex-vivo IL2 assay: Peripheral PK-PD in the Clinic to inform efficacious dose




Pembroluzimab Exposure is Associated with Complete Functional Blockade of PD-1 in the *ex vivo* IL-2 Release Assay at Doses of 1 mg/kg Q3W or Higher

J Elassaiss-Schaap, S Rossenu, A Lindauer, SP Kang, R de Greef, JR Sachs and DP de Alwis CPT:PSP, Jan 2017

THE ASCO POST

NEWS MEETINGS TOPICS VIDEOS

# Exploring the Opportunities and Challenges of Seamless Drug Development

By Caroline McNeil
February 25, 2017


ASCO post, Feb 2017, Seamless FIH Cancer Trials

One prime example of a highly effective drug developed seamlessly is pembrolizumab (Keytruda), which targets the programmed cell death ligand 1 (PD-L1). This immunotherapy showed high efficacy in its earliest trial among patients with melanoma. Rather than conclude that trial and start on a phase II trial, investigators added expansion cohorts, first to test the drug in patients with non–small cell lung cancer and then to test lower doses in both groups and also to provide training and validation sets for the PD-L1 expression test. More cohorts were added as more information was collected. Several years later, the drug was approved for advanced melanoma without a randomized, controlled trial.

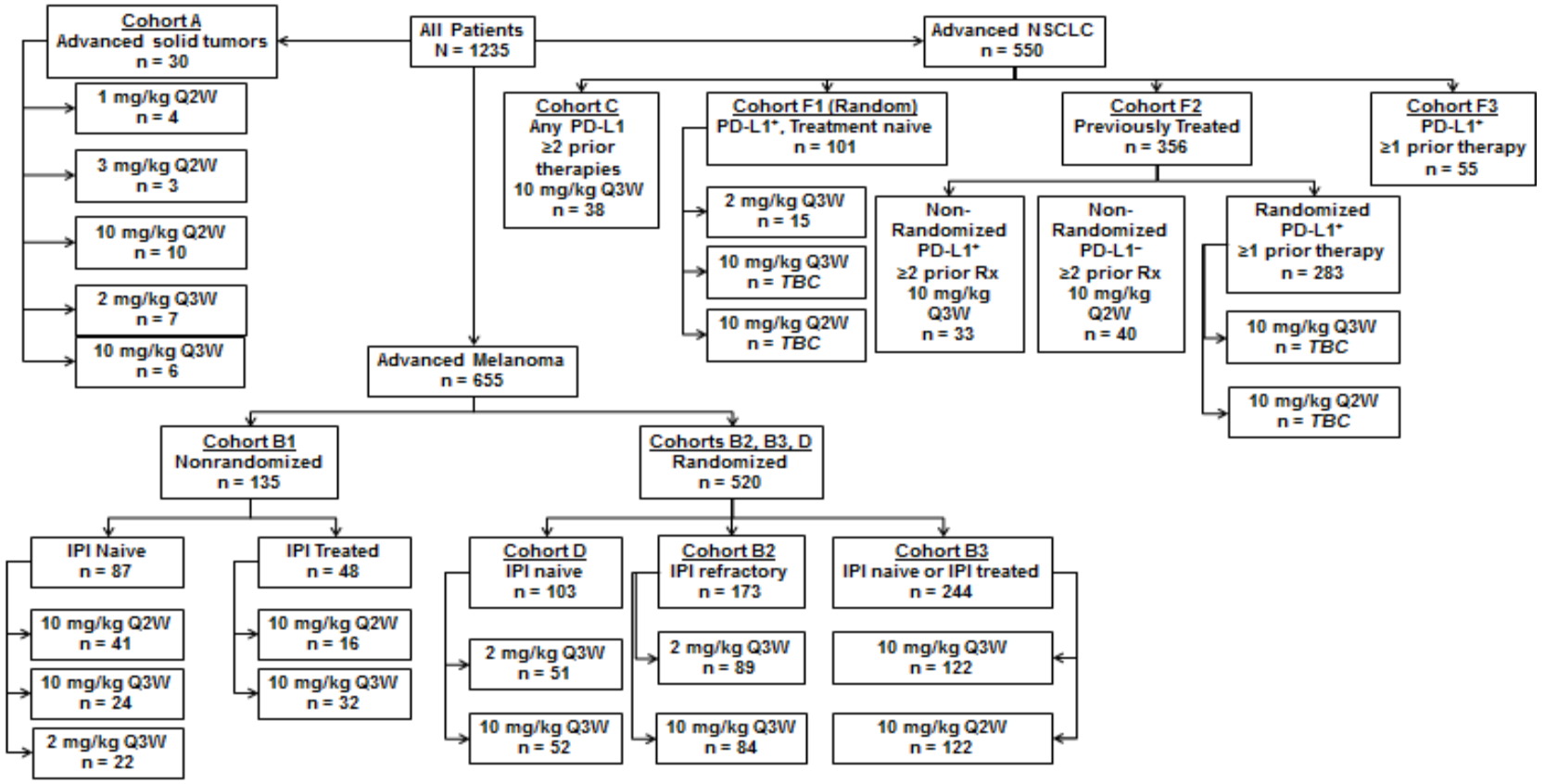
> Traditional phase I, II, and III trials cannot provide enough information, as cancer therapies are splintered into multiple subgroups and treatment categories.
>
> — *Janet Woodcock, MD*

That was in 2014. Now there are more than 40 active, first-in-human cancer trials that are using this seamless strategy, according to members of the U.S. Food and Drug Administration (FDA), writing in *The New England Journal of Medicine*.[1]

One reason for the increase in seamless trials is their usefulness in evaluating a targeted drug in many subgroups of patients. "Traditional phase I, II, and III trials cannot provide enough information, as cancer therapies are splintered into multiple subgroups and treatment categories," said **Janet Woodcock, MD**, Director of the Center for Drug Evaluation and Research at the FDA, speaking at the workshop. "I don't think clinical development right now can keep up with the rapidly evolving science."

# Keynote 01: First in Human to Registration

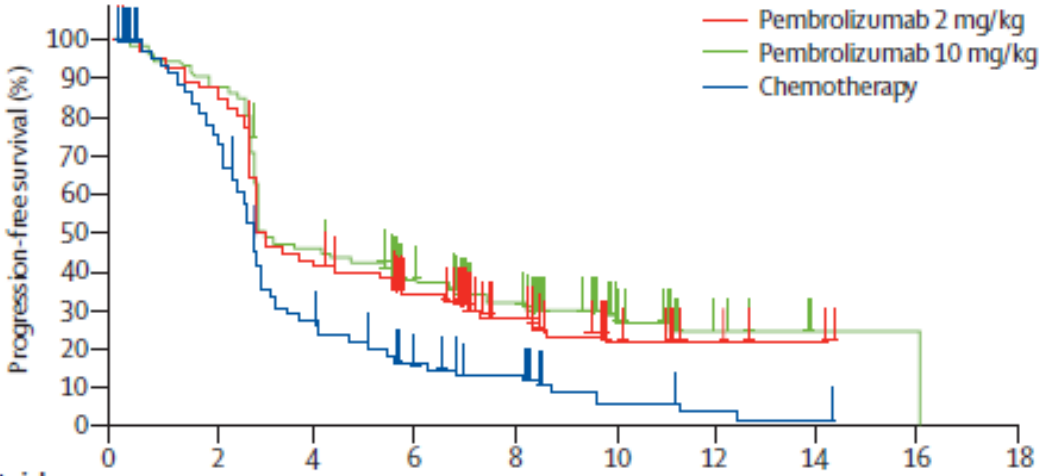
From a small Phase I, expansion to a 655-patient study in Melanoma patients




Kang, S.P., Gergich, K., Lubiniecki, G.M., de Alwis, D.P., Chen, C., Tice, M.A. and Rubin, E.H., 2017. Pembrolizumab KEYNOTE-001: an adaptive study leading to accelerated approval for two indications and a companion diagnostic. *Annals of Oncology*, *28*(6), pp.1388-1398.

# Progression Free Survival from randomized studies confirmed 2 mg/kg as an optimal dose

**Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial**




| Number at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab 2 mg/kg | 180 | 153 | 74 | 53 | 26 | 9 | 4 | 2 | 0 | 0 |
| Pembrolizumab 10 mg/kg | 181 | 158 | 82 | 55 | 39 | 15 | 5 | 1 | 1 | 0 |
| Chemotherapy | 179 | 128 | 43 | 22 | 15 | 4 | 2 | 1 | 0 | 0 |

- ❑ Increase in the use of drug –target binding models preclinically and in clinical development (measure of target engagement)
- ➢ Dosing requirements in early clinical development
- ❑ Assess fixed Dose versus Body-size-Based Dosing for Therapeutic Biologics
- ❑ Influence of Disease State in the characterization of pharmacokinetics
- ❑ Dose ranging and exposure-response analysis

Ribas et al, Lancet 2015

Pembrolizumab exposure-response assessments challenged by association of cancer cachexia and catabolic clearance. Cancer Clin. Research, 2018

# Model-Based Approaches: Mechanistic and Physiologically Based Approaches

- Physiologically based PK models that can help inform "target" concentrations

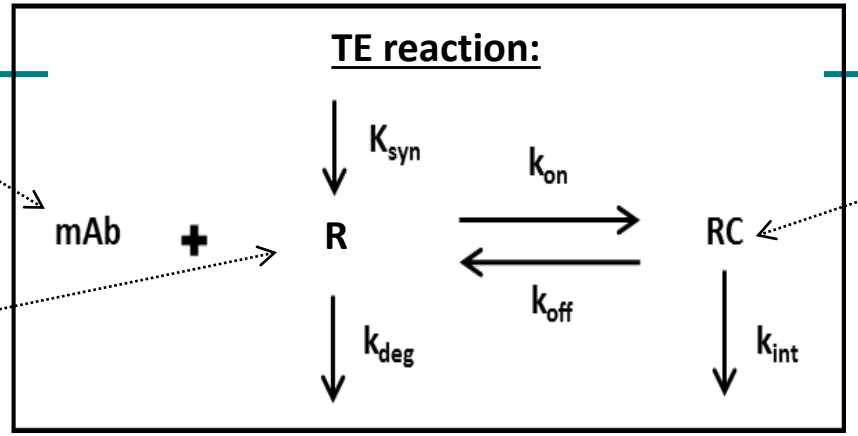
➢ Complexity vs. "fit for purpose"

- Systems biology/pharmacology models that inform regarding the target (and use in combination treatments)

# Characterization of target engagement (TE)

**How much mAb/drug?**

**How much receptor/ target?**




**Predict TE in blood & tumor**

## How much drug?

- Blood: Dose ranging PK data
- Tumor: Predict concentration using a published tumor model (*Baxter et al)*
  - Heterogeneity/spatial gradients in tumor characterized using sensitivity analysis
    - e.g., some parts of tumor are poorly vascularized → low mAb concentration

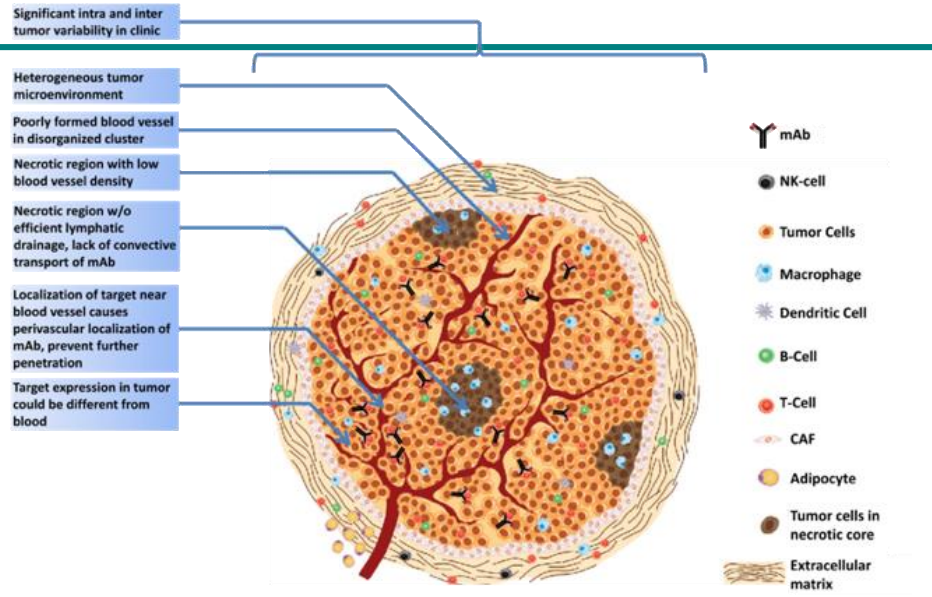
## How much target?

- Blood: Estimated target expression & turnover
  - High clearance at low doses of mAb depends on target expression/turnover
    - Data on change in CL with escalating dose can be used to estimate target properties
- Tumor: Assumed similar to blood
  - Possibility of different target expression assessed using sensitivity analysis

# Tumor Characterization

Structure and mAb penetration in the tumor is based on Baxter et al, Cancer Research 1995
**Rakesh Jain's lab, Harvard University** (developed using concentration of a mAb in human colorectal cancer)

Tumors are complex.
**Fit-for-purpose modeling approach**:
- Assess the effect of this complexity using sensitivity analysis (i.e., what-if scenarios by changing model parameters)




**Tumor-microenvironment heterogeneity (i.e. drug properties)**

e.g., lower mAb concentration → higher dose for target saturation

**Represented using simulations**
Deeper parts of the tumor represented by changing tumor penetration: as low as 10%

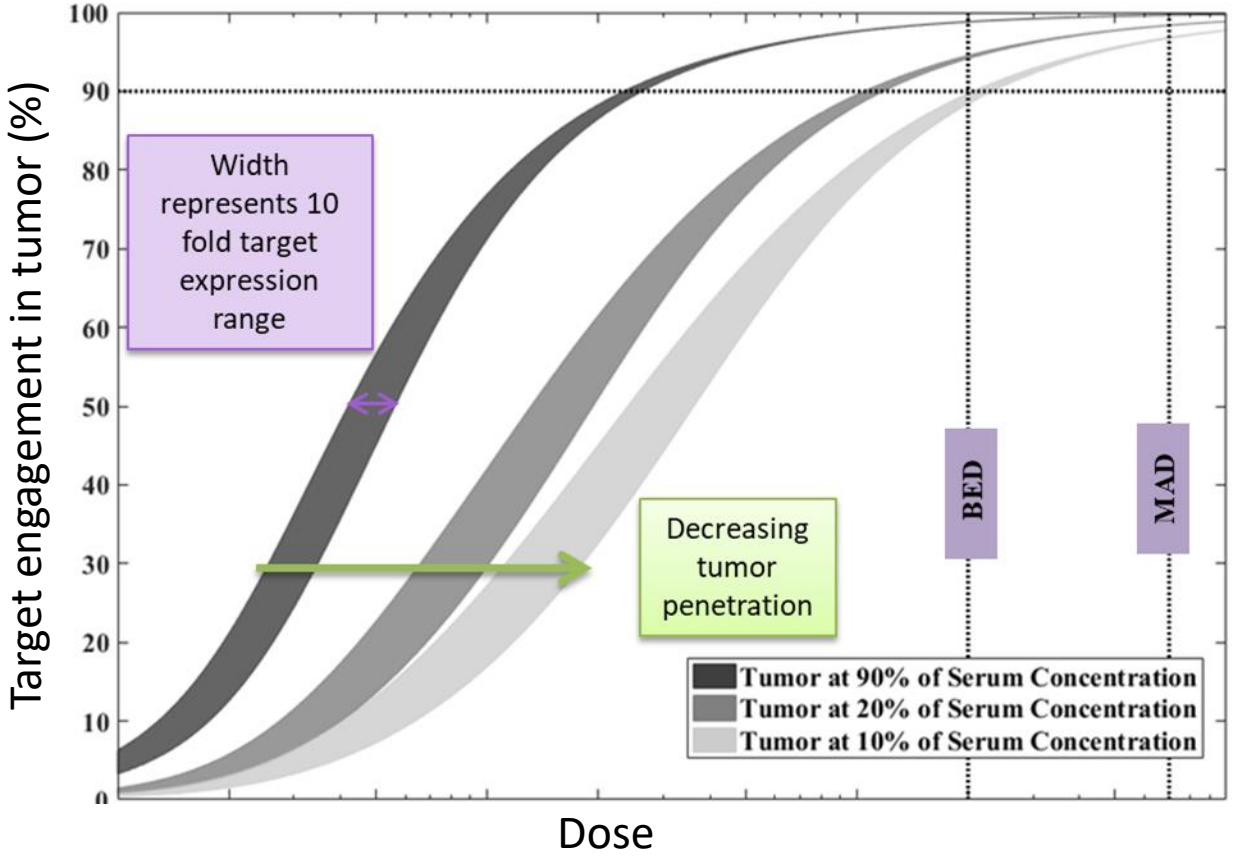
**Target expression in tumor can be different compared to blood (i.e. target properties)**

e.g., higher target expression → higher dose for TIGIT saturation

**Represented using simulations**
High intra-tumoral target expression:
up to 10-fold (a conservative scenario)

Baxter LT, Zhu H, Mackensen DG, Butler WF, Jain RK. Cancer Res. 1995 Oct 15;55(20):4611-22

# Biologically Effective Dose
# Target saturation in tumor




**Heterogeneity/unknowns in tumor microenvironment considered using sensitivity analysis**

- **mAb penetration in tumor: As low as 10% (representing deep parts of the tumor)**
- **Target expression in tumor: As high as 10-fold higher**

# A Recent Experience

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion for a new extended dosing schedule ...[1]

"In the study, efficacy of the every-6-weeks dosing schedule was bridged via examining projections of both pharmacokinetic drivers of efficacy, such as the average concentration over the dosing interval ($C_{avg}$ or AUC) and trough concentration (Cmin). Additionally, an exposure-response analysis was conducted to predict overall survival at the longer dosing interval .. Moreover, safety was bridged based on an established exposure-safety analysis ……Additionally, a PBPK model-based prediction of pembrolizumab tumor target engagement showed that, … All doses maintained target engagement above 90% throughout the dosing interval suggesting physicians could have the flexibility to dose at a frequency that is tailored toward patients' needs and/or personal preferences."

[1]European Medicines Agency Adopts Positive Opinion .. Published March 4, 2019. https://bit.ly/2UkbGP5.

# Industrialization of QSP

1. Various consortiums, white papers, working groups, conferences or webinars focusing on quantitative and systems modeling

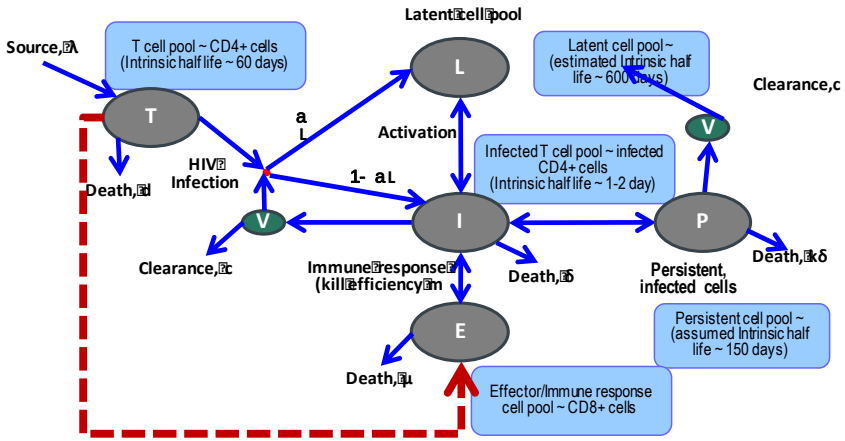
2. Systems and mathematical-based training programs

3. Industry examples of QSP based modeling

4. “Acceptance” of quantitative systems pharmacology (QSP) models by regulators

# Integrating experimental and Models: Treatment of Hepatitis

**Latent Viral Dynamics Modeling**




## Data

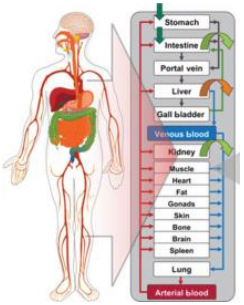
Discovery:

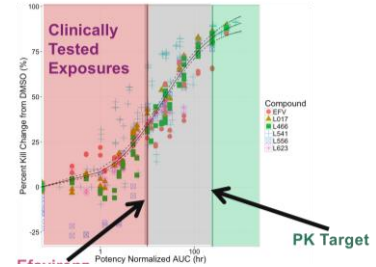
- In-vitro potency and washout experiments
- Preclinical animal experiments
- PET tracers
- Preclinical Safety Data

Clinical:

- Key PoC
- Published clinical efficacy and safety

**PBPK Modeling**




- What is the clinical target concentration to achieve efficacy?
- What concentration of drug is necessary at the site of action to stop or eradicate?

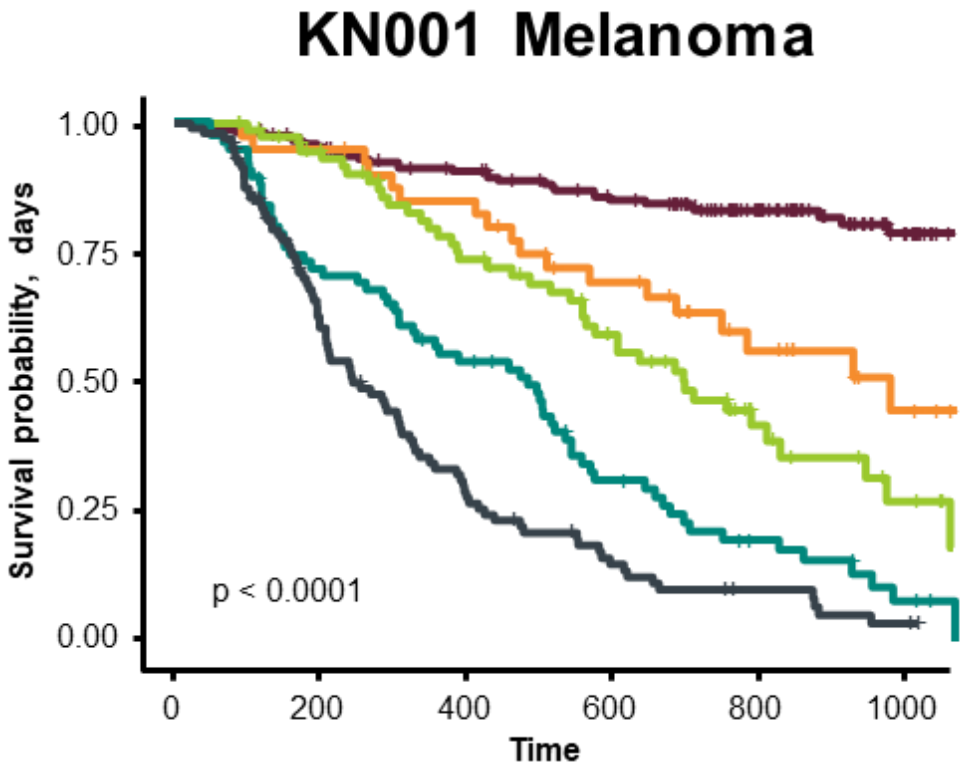
**How should a trial be designed?**

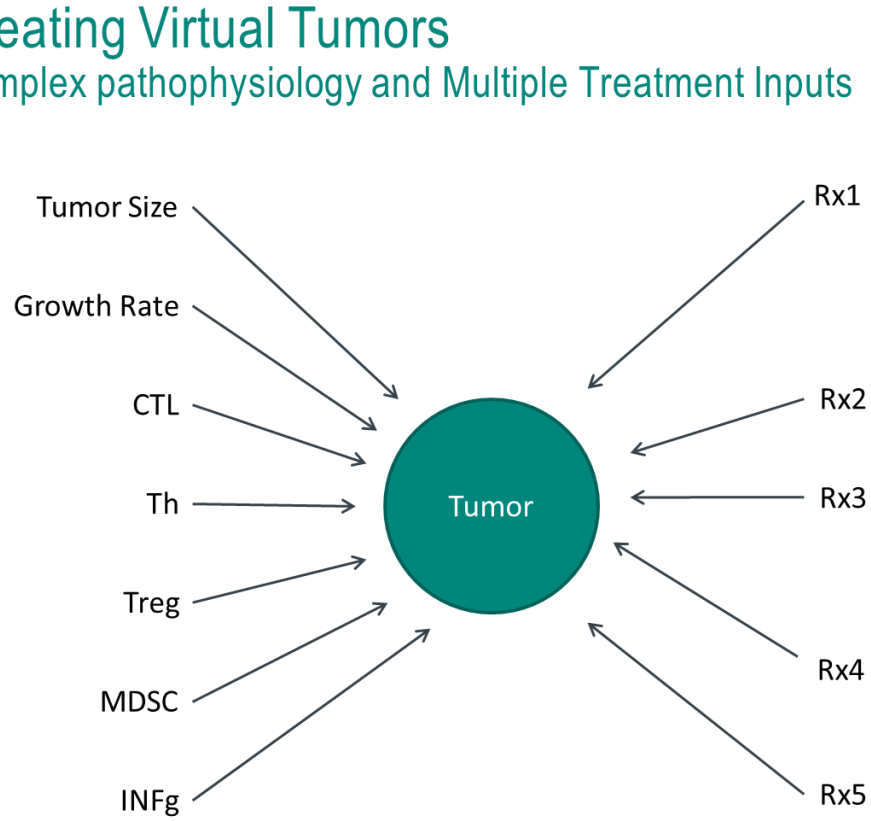
# Predicting response and identifying responders to combination Cancer Immunotherapy in using Quantitative Systems Pharmacology (QSP) models – Melanoma as an Example

**Contributors:** Vantage Research
Presented at PAGE 2018

Merck Research Laboratories

# Quantitative Systems Pharmacology (QSP) : Predicting response and identifying responders to combination Cancer Immunotherapy

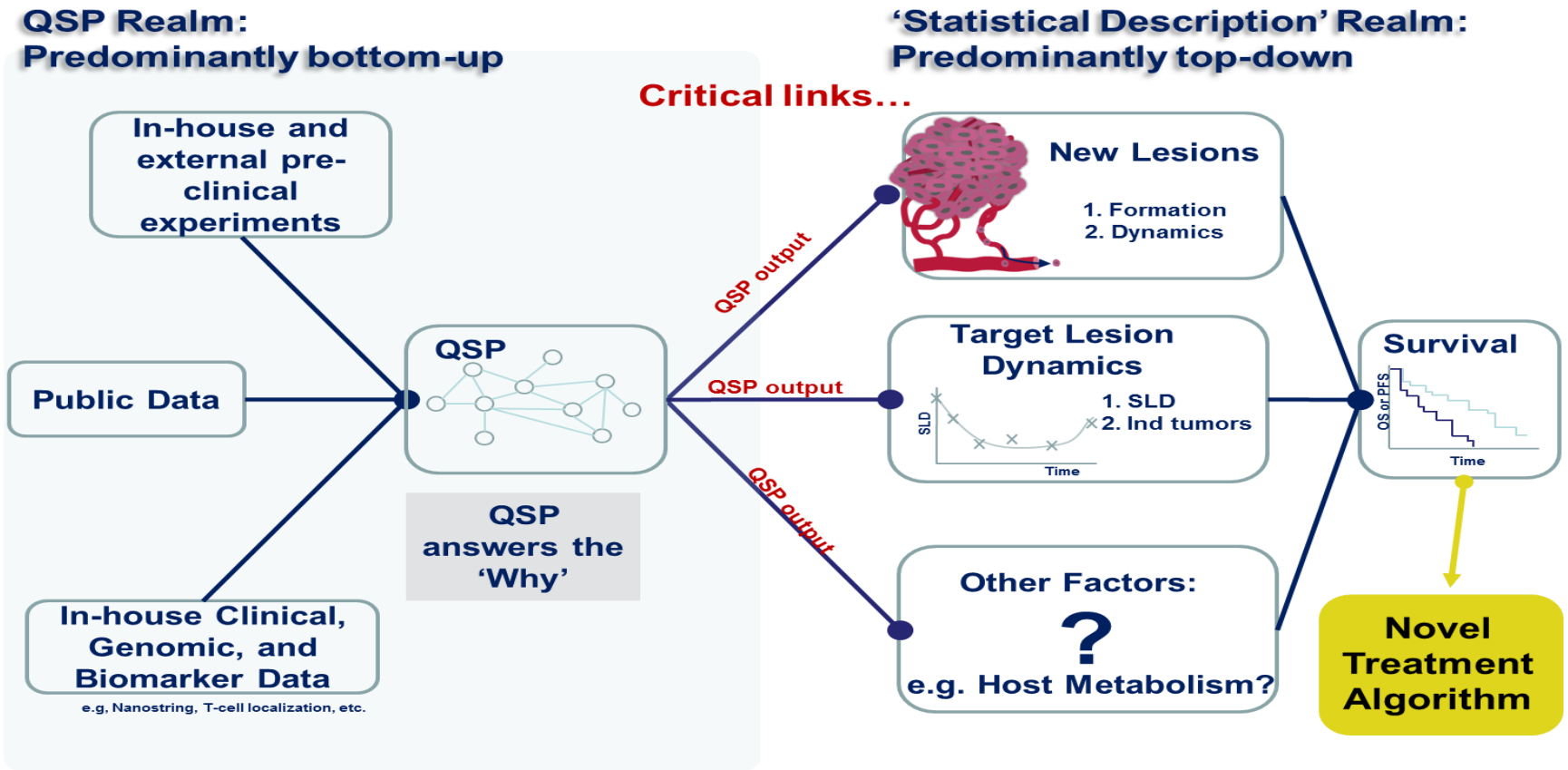



Median post-progression survival for NG-, NG+, MG, and AG subgroups were 16.0, 14.2, 9.1, and 7.5 months, respectively ($p<0.001$).

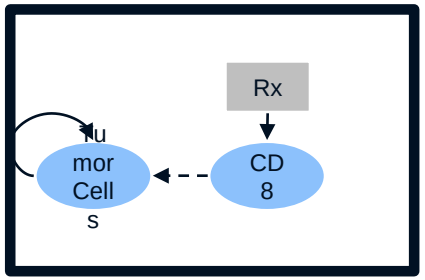
Topp, Robey et al., DOI: 10.1200/JCO.2018.36.15_suppl.3017 *Journal of Clinical Oncology* 36, no. 15_suppl (May 2018) 3017-3017)

# Integration of QSP and empirical modeling for simulation of novel treatment paradigms in oncology

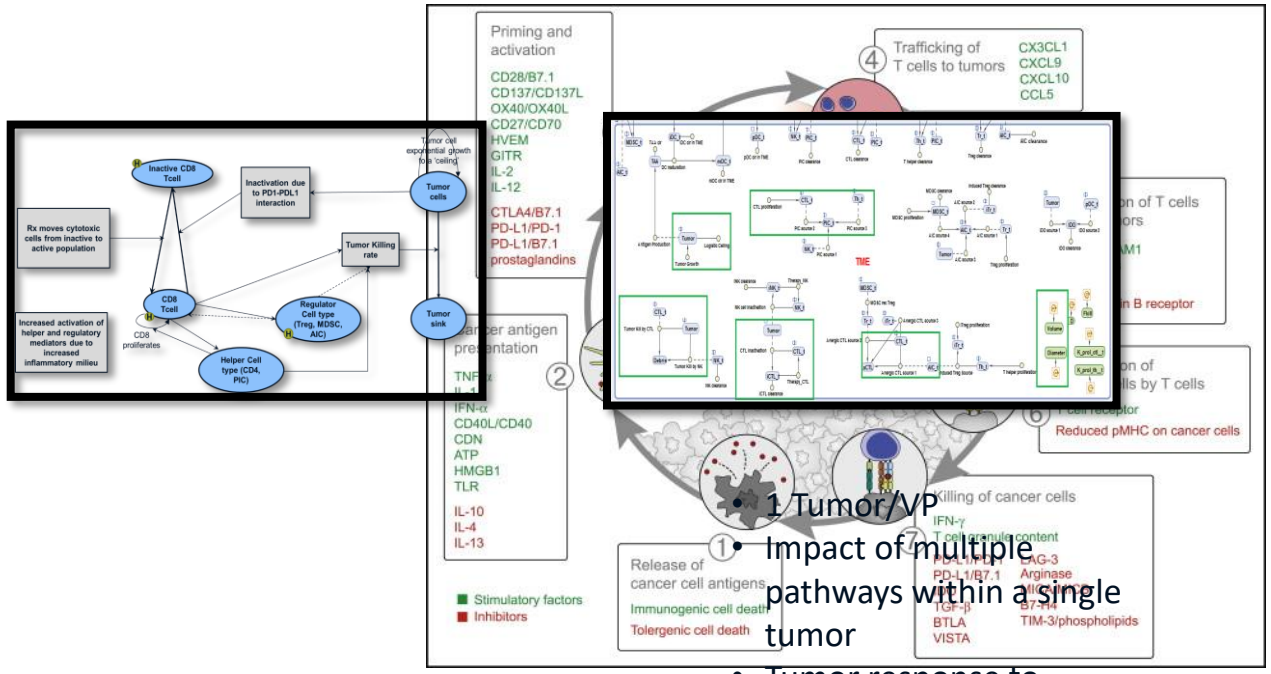



*Kumar et al, PAGE 2018*

# Approach to Model Design Varies With the Question




- 5 tumors/ VP
- Impact of within patient tumor heterogeneity, metastases
- Tumor ‘waterfall’ plots & RECIST scores
- **Ideal to simulate clinical trials**

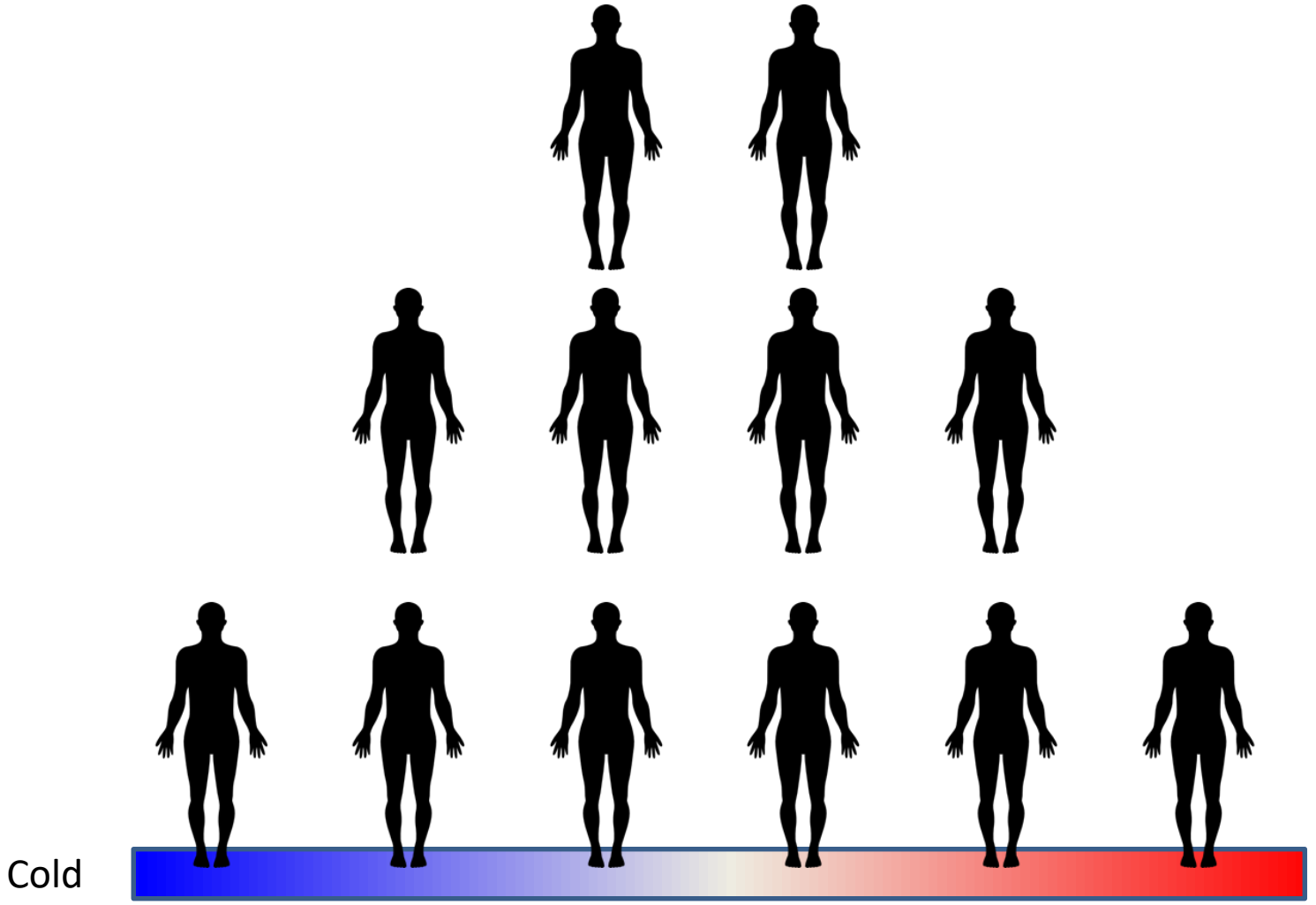



- 1 Tumor/VP
- Impact of multiple pathways within a single tumor
- Tumor response to treatment
- **Ideal to prioritize/ simulate targets in discovery**

Chen and Mellman, Immunity 2013

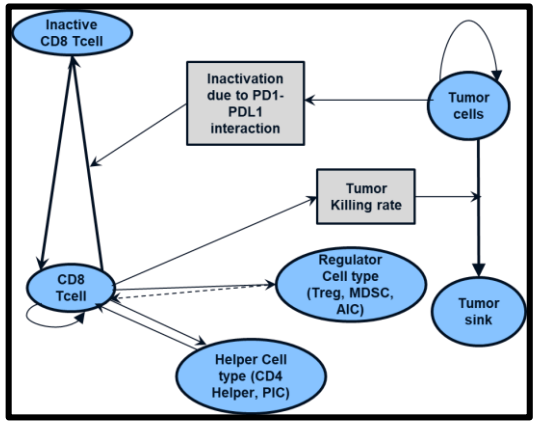
# Creating Virtual Populations

## e.g. Cancer Types, Stage of Disease, Biomarker Classes




**Kumar et al, PAGE 2018**

# Model quantification and assimilation of the public literature

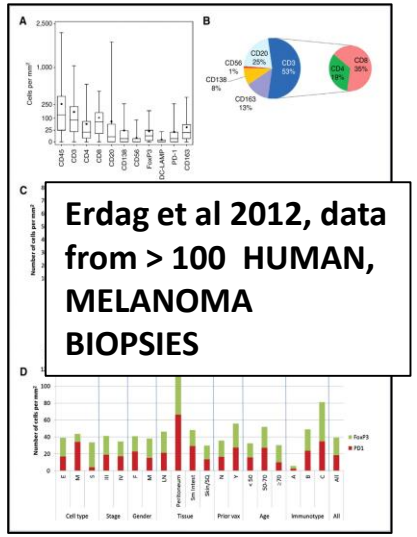



Tumor approximated to sphere
- Tumor density: ~2e8 cells/mL
- Tumor diameter: 16mm

Initial immune cell densities as % of tumor cells
- CD8: 1-12%
- Tregs: 0-3%
- Thelpers: 0-8%

Rates of Tcells lifecycle
- Clearance : ~1-4%/day
- Proliferation: ~1%/day

Rates of interaction
- CD8 killing of Tumor: 0.2-2 target/effector/day
- Thelper incr of CD8 prolif: 2-4 fold increase



**Erdag et al 2012, data from > 100 HUMAN, MELANOMA BIOPSIES**

**Breart et al,2008 data from MOUSE, IN VITRO**

# Model quantification and assimilation of the public literature

What are the kinds of data that are used to constrain the model ?

1. Overall tumor volume, estimated from cell densities and used to estimate cell numbers; directly from melanoma literature
2. Initial condition, clearance rates, proliferation rates for cell types from multiple papers
3. Best available information on interaction between these components that can usually only be obtained from experimental data[1]

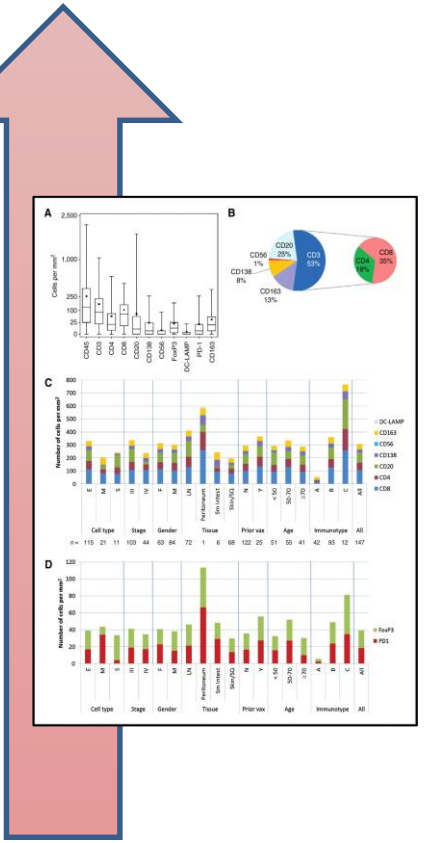
- **1000s of Papers**
- **100s of papers documented,**
- **10s of papers used for direct parametrization**

➢ **Recorded for future evaluation as needed**

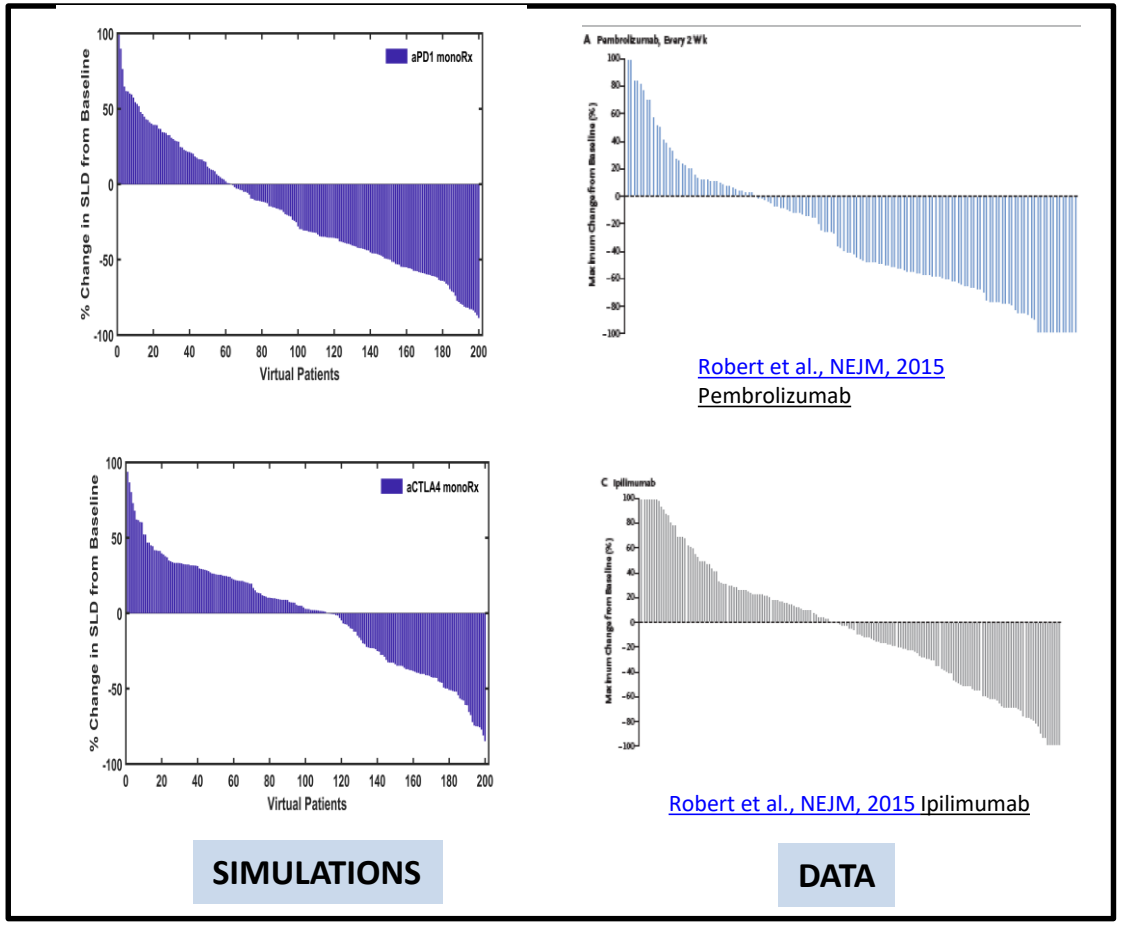
[1]**Erdag et al 2012, data from > 100 HUMAN, MELANOMA BIOPSIES**

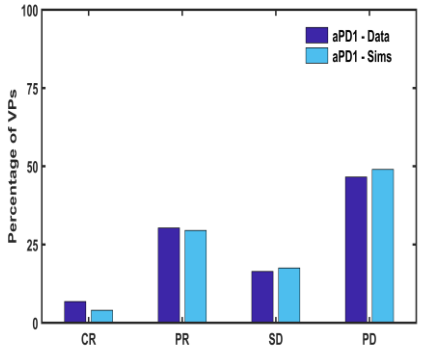
**Relevant, Reliable**
**Used as-is**

**Used for initial parameterization**
**Adjusted to fit clinical time-course data**

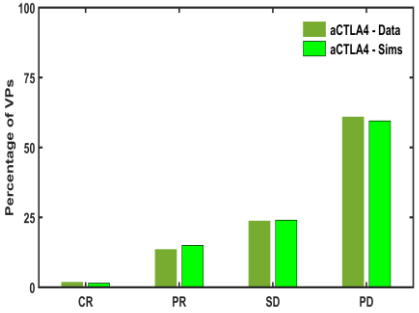


# Virtual Population calibrated to match aPD1 and aCTLA4 clinical data




**DATA vs. SIMULATIONS**



# The Changing Regulatory Perspective

## Regulatory agencies worldwide are investing in model-informed drug development

### *PDUFA6: Advancing Model-Informed Drug Development*

a. FDA will develop its regulatory science and review expertise and capacity in MIDD approaches. This staff will support the highly-specialized evaluation of model-based strategies and development efforts.

b. FDA will convene a series of workshops to identify best practices for MIDD. Topics will include: (1) physiologically-based pharmacokinetic modeling; (2) design analysis and inferences from dose-exposure-response studies; (3) disease progression model development, including natural history and trial simulation; and (4) immunogenicity and correlates of protection for evaluating

FDA

EDITORIAL

### Regulatory Modeling and Simulation Moves Into the Next Gear in Europe

*CPT: Pharmacometrics & Systems Pharmacology* (2013) **2**, e32; doi:10.1038/psp.2013.8; advance online publication 27 February 2013

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

### Quantitative Modeling and Simulation in PMDA: A Japanese Regulatory Perspective

Since quantitative M&S can be helpful for various types of decision-making during drug development and regulatory reviews (e.g., dosing regimens and sample size in clinical trials, appropriate language in product label, etc.), these analyses by PMDA reviewers themselves are expected to help improve both the quality of the PMDA's reviews and consultations and contribute to improve the efficiency of new drug development.

pmda

# Fit for Purpose Initiative and Model Qualification

| Disease Area | Submitter | Tool | Trial Component |
|---|---|---|---|
| Alzheimer's disease | The Coalition Against Major Diseases (CAMD) | Disease Model: Placebo/Disease Progression | Demographics, Drop-out |
| Multiple | Janssen Pharmaceuticals and Novartis Pharmaceuticals | Statistical Method: MCP-Mod | Dose-Finding |

**EMA Qualification opinion *2013*- A novel data-driven model of disease progression and trial evaluation in mild and moderate Alzheimer's disease**

[1]https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative

# *"System Therapeutics"*

Reviews • INFORMATICS

## The future of drug development: the paradigm shift towards systems therapeutics

Meindert Danhof[1,2], Kevin Klein[3,4], Pieter Stolk[3,4], Murray Aitken[5] and Hubert Leufkens[3]

Drug Discovery Today • Volume 23, Number 12 • December 2018

**TABLE 1**

**Features of the pharmacology-based fixed formulations versus pathology-targeted precision treatments with regard to their scientific concepts, R&D, clinical use, and therapeutic evaluations**

| Pharmacology-based 'fixed formulations' | Pathology-targeted 'precision treatments' |
|---|---|
| Scientific concepts | |
| Single drugs targeting single targets<br>'One-size-fits-many' fixed formulations aimed at symptomatic relief<br>Industrial manufacturing of fixed formulations | Multitarget drugs (combinations) targeting complex biological networks<br>Personalized precision treatments aimed at disease modification and/or cure<br>Bedside assembly of personalized treatments |
| R&D | |
| Monodisciplinary expert teams<br>Stand-alone research hubs<br>Closed innovation | Interdisciplinary research teams<br>Shared knowledge infrastructure<br>Open innovation |
| Clinical use | |
| Treatments applied in an intuitive manner<br>Monitoring of product quality<br>Monitoring of treatment response on basis of limited number of clinical measures | Treatments applied in a pre-emptive and preventive manner<br>Monitoring of process quality<br>Monitoring of treatment response on basis of complex array of biomarkers |
| Therapeutic evaluations | |
| Data collection focus in preclinical usage space<br>'Big data' to identify patterns that could indicate new pathways, mechanisms of disease, and mechanisms of drug action<br>'Learn & confirm' based on randomized clinical trial data | Data collection focus in real-world clinical usage space<br>'Smart data' to assess individualized drug treatments by accounting for interindividual variation<br>Iterative learning cycles for continuous evaluations based on RWD |

Interdisciplinary research teams
Shared knowledge infrastructure
Open innovation

Treatments applied in a pre-emptive and preventive manner
Monitoring of process quality
Monitoring of treatment response on basis of complex array of biomarkers

Data collection focus in real-world clinical usage space
'Smart data' to assess individualized drug treatments by accounting for interindividual variation
Iterative learning cycles for continuous evaluations based on RWD

# Closing Thoughts

- ❑ Most (if not all) R&D establishments invest/apply Modeling & Simulation
- ❑ Established approaches – Population analysis, Exposure-response, PBPK
- ❑ Systems Pharmacology is varied; Use Of PBPK is high (DDIs)

- ➢ Established approaches have reached peak “applications”. Fundamental challenge with drug discovery are not being solved with established approaches.
- ❑ Newer science - will require a fundamentally new “organizations” and “scientists” with the broadest understanding of disease, quantitative sciences and drug development.

# Thank You!

ご清聴ありがとうございました

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