FDA-AACR Public Workshop on

OPTIMIZING DOSAGES FOR ONCOLOGY DRUG PRODUCTS: QUANTITATIVE APPROACHES TO SELECT DOSAGES FOR CLINICAL TRIALS

February 15, 2024, 8 a.m. – 5 p.m.
February 16, 2024, 8 a.m. – 1 p.m.
Grand Hyatt Washington | Washington, D.C.

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DAY 1 WELCOME

Patricia M. LoRusso, DO, PhD (hc), FAACR
Yale Cancer Center

OPENING REMARKS

Marc Theoret, MD
U.S. Food and Drug Administration

WORKSHOP OVERVIEW

Stacy S. Shord, PharmD
U.S. Food and Drug Administration

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OPTIMIZING DOSAGES FOR ONCOLOGY DRUG PRODUCTS: QUANTITATIVE APPROACHES TO SELECT DOSAGES FOR CLINICAL TRIALS

February 15 and 16, 2024 I Washington, DC

Workshop Co-Chairs

Jiang Liu, PhD
FDA

Pat LoRusso, DO, PhD (hc), FAACR
Yale Cancer Center

Stacy Shord, PharmD
FDA

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Quantitative Approaches to Select Dosages for Clinical Trials

Dosage Optimization for Oncology Products and Project Optimus

Stacy S. Shord, PharmD, BCOP, FCCP
Deputy Division Director
Division of Cancer Pharmacology II
Office of Clinical Pharmacology
OTS/CDER/FDA

February 15, 2024

Disclaimer

Opinions presented are those of the speaker and should not be construed to represent FDA's views or policies.

Outline

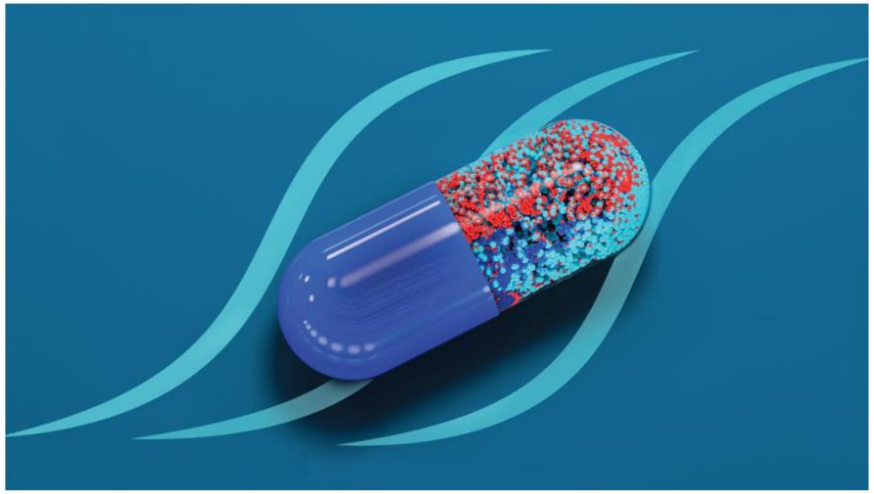
- Project Optimus
- Guidances and Tools
- Workshop

Project Optimus

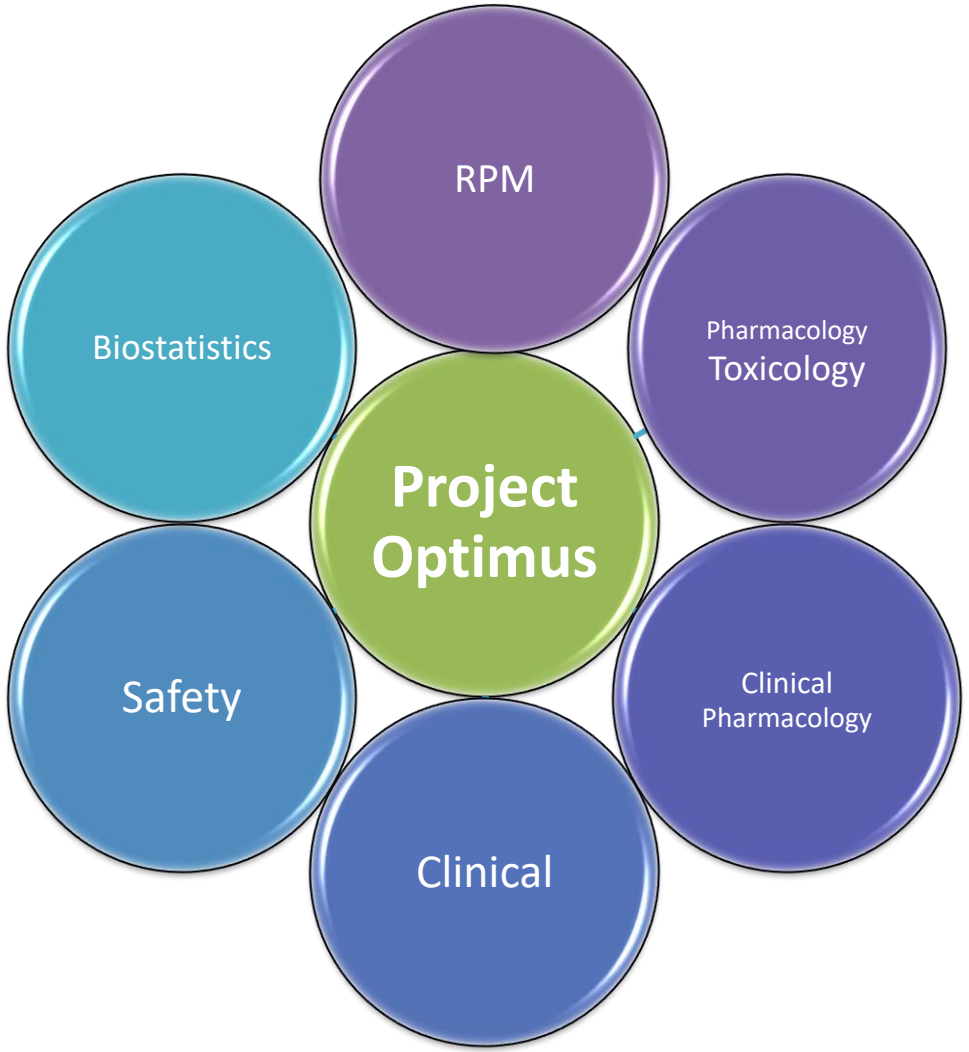
What? Initiative to reform the dosage optimization and dose selection paradigm in oncology drug development

Who? A multidisciplinary team of medical oncologists, clinical pharmacologists, biostatisticians, toxicologists, and other scientists with expertise in key facets of dosage optimization

More Information: Project Optimus



Multidisciplinary Team



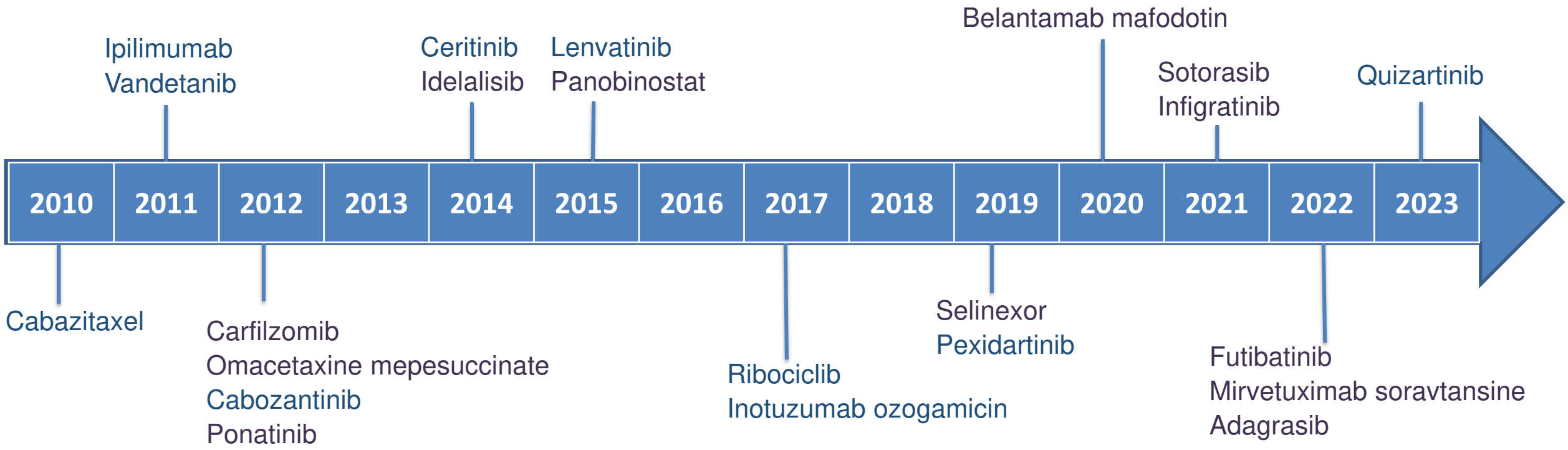
- **OCE:** Rick Pazdur, Marc Theoret
- **Leads:** Atik Rahman, Mirat Shah
- **RPM:** Pam Balcazar
- **Pharmacology/Toxicology:** Haleh Saber, Matthew Thompson
- **Clinical Pharmacology:** Brian Booth, Lanre Okusanya, Stacy Shord
- **Pharmacometrics:** Jiang Liu, Hao Zhu
- **OCP Policy:** Raj Madabushi
- **Clinical:** Brian Heiss, Jennifer Gao, Gwynn Ison, Elizabeth Duke, Shruti Gandhy, Cara Rabik, Pam Seam
- **Safety:** Abhi Nair
- **Biostatistics:** Joyce Cheng, Jonathon Vallejo, Gary Rosner
- **CBER:** Lianne Wu, Xiaofei Wang
- **Analysts:** Alex Akalu, Susan Jenney

Consequences of Not Optimizing Dosage Before Approval

- Drug is poorly-tolerated at the approved recommended dosage
  - Patients may stop taking a potentially effective drug
  - Patients choose to try a different drug
- Drug does not make it to market or must be withdrawn from the market
- Takes long time to evaluate alternative dosages following approval
  - Patients may not want to participate in trial if commercially available
  - Disease area moves on to other treatments

Dosage Optimization PMRs

- 24 PMRs issued for 21 new drugs (15% of 138 total approved new drugs)
- Took a median of 6.5 years to fulfill or release



J Clin Oncology Volume 41, Number 16_suppl https://doi.org/10.1200/JCO.2023.41.16_suppl.159

Project Optimus Supports Evaluating All Data to Inform Dosage Selection for Clinical Trials

- Consider all data: pharmacokinetic (PK), pharmacodynamic (PD), activity/efficacy, safety, and tolerability data at each step
- Evaluate safety information beyond DLTs, e.g., low-grade symptomatic toxicities, dosage modification frequencies, patient-generated data for treatment-related symptoms
- Identify a target dosage range early and then further evaluate several dosages (ideally in a randomized trial)
- Characterize dosage- and exposure-response relationships for efficacy and toxicity

Focusing on Dosage Before Approval

- Administering ‘optimized’ dosages in registration trial
  - Improves tolerability and adherence
  - Reduces dosage modifications (i.e., discontinuations)
  - Potentially increases likelihood of treatment response
- Earlier understanding of dose- and exposure-response relationships may allow for more rapid development of new therapies, such as
  - combination regimens, new dosing regimens & new formulations
- More efficient to evaluate multiple dosages early in development
- Challenging to conduct dosage optimization trials post-approval

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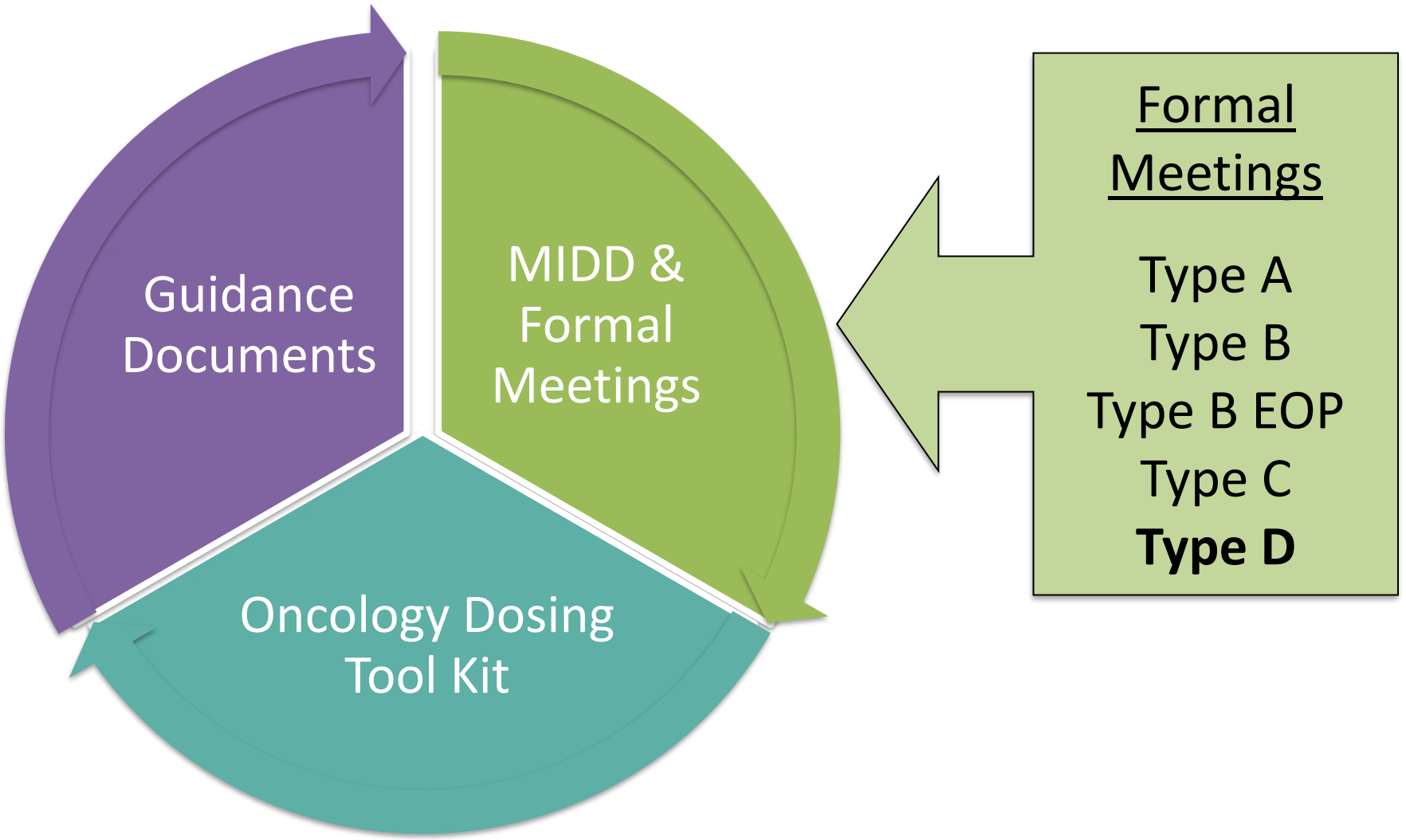
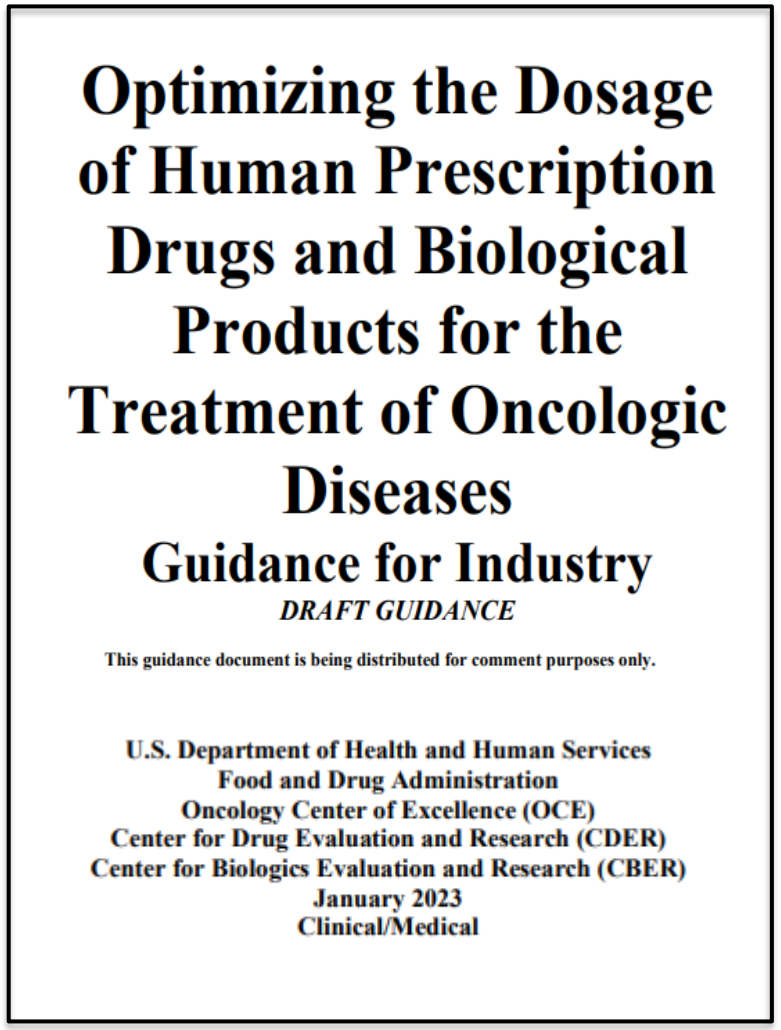
Guidances and Tools

Tools Available to Support Dosage Selection and Optimization



https://www.fda.gov/media/172311/download

Oncology Dosage Optimization Draft Guidance



Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

Guidance for Industry

DRAFT GUIDANCE

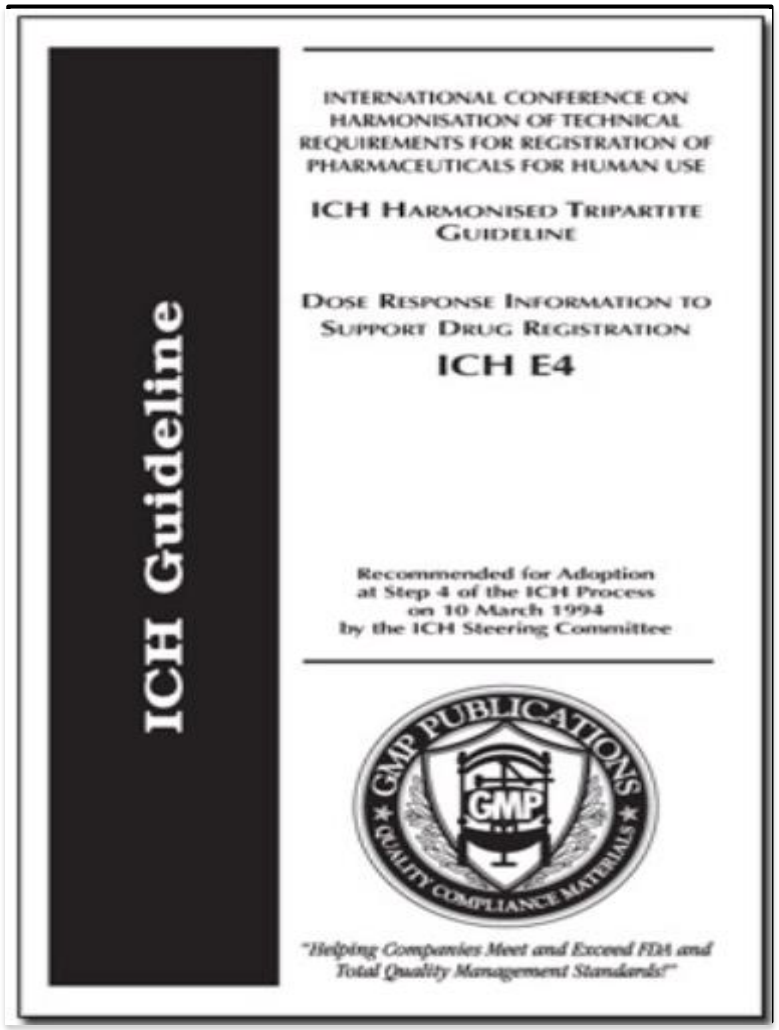
This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
January 2023
Clinical/Medical

2023

- Dosages must have justification appropriate to development stage
- Evaluate all data to select and support dosages
- Randomized comparisons support identification of optimized dosage(s)
- Safety assessments should include low-grade symptomatic toxicities
- Important for all products, including those with anticipated rapid development timelines

Guidance Documents



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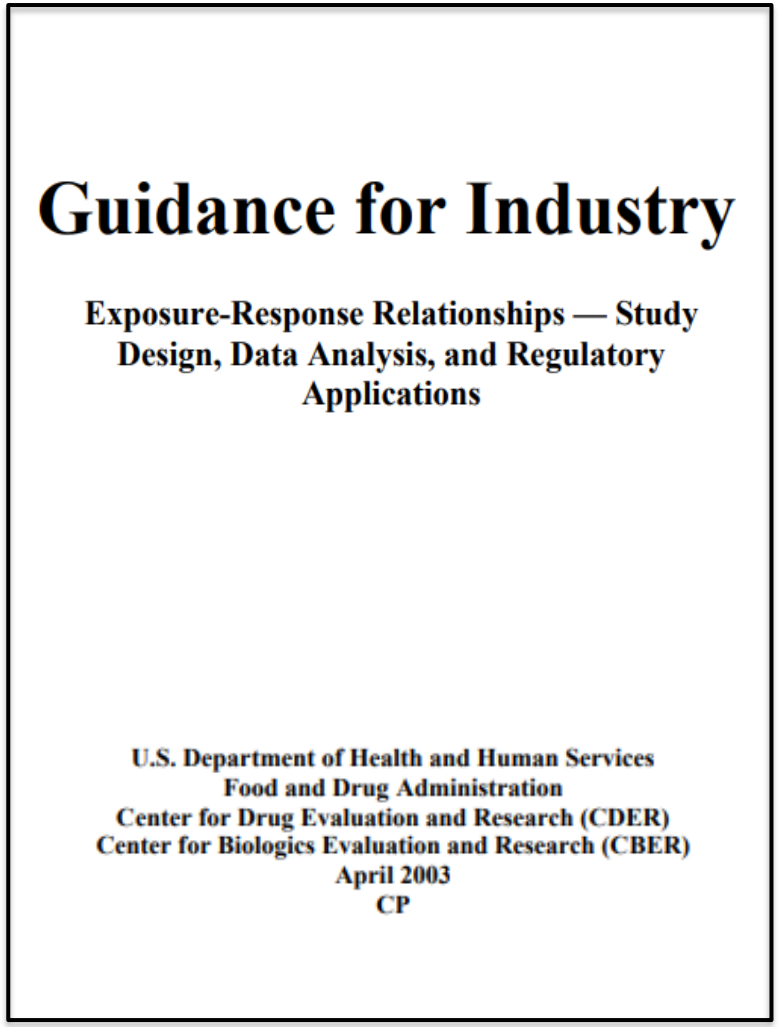
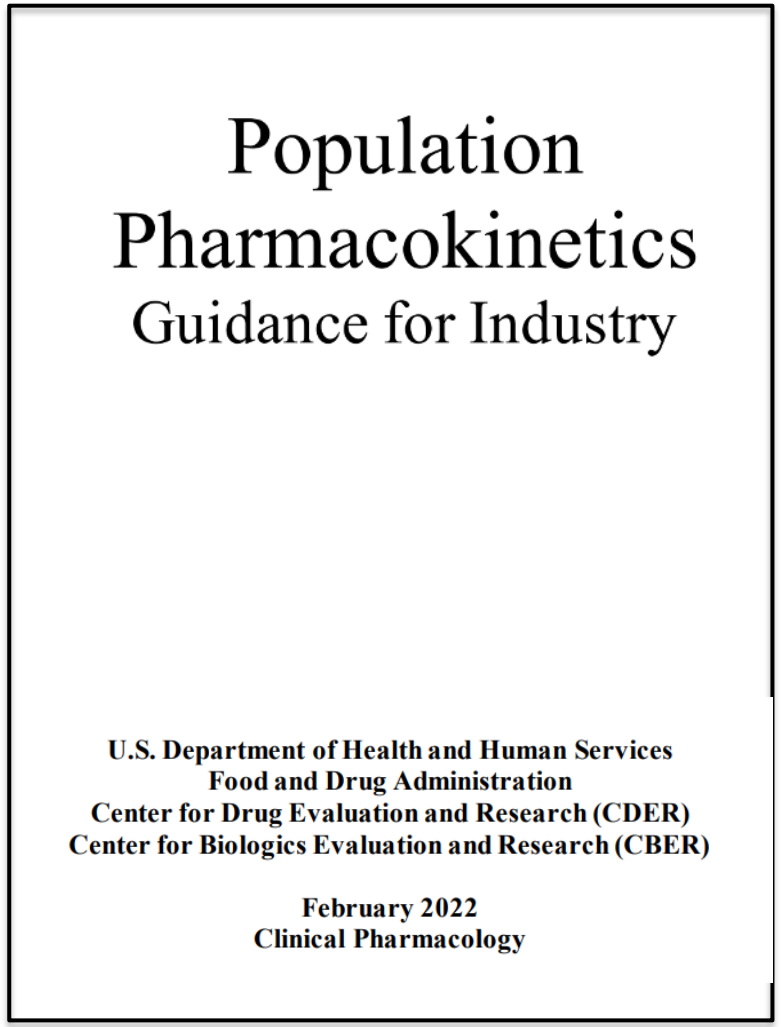
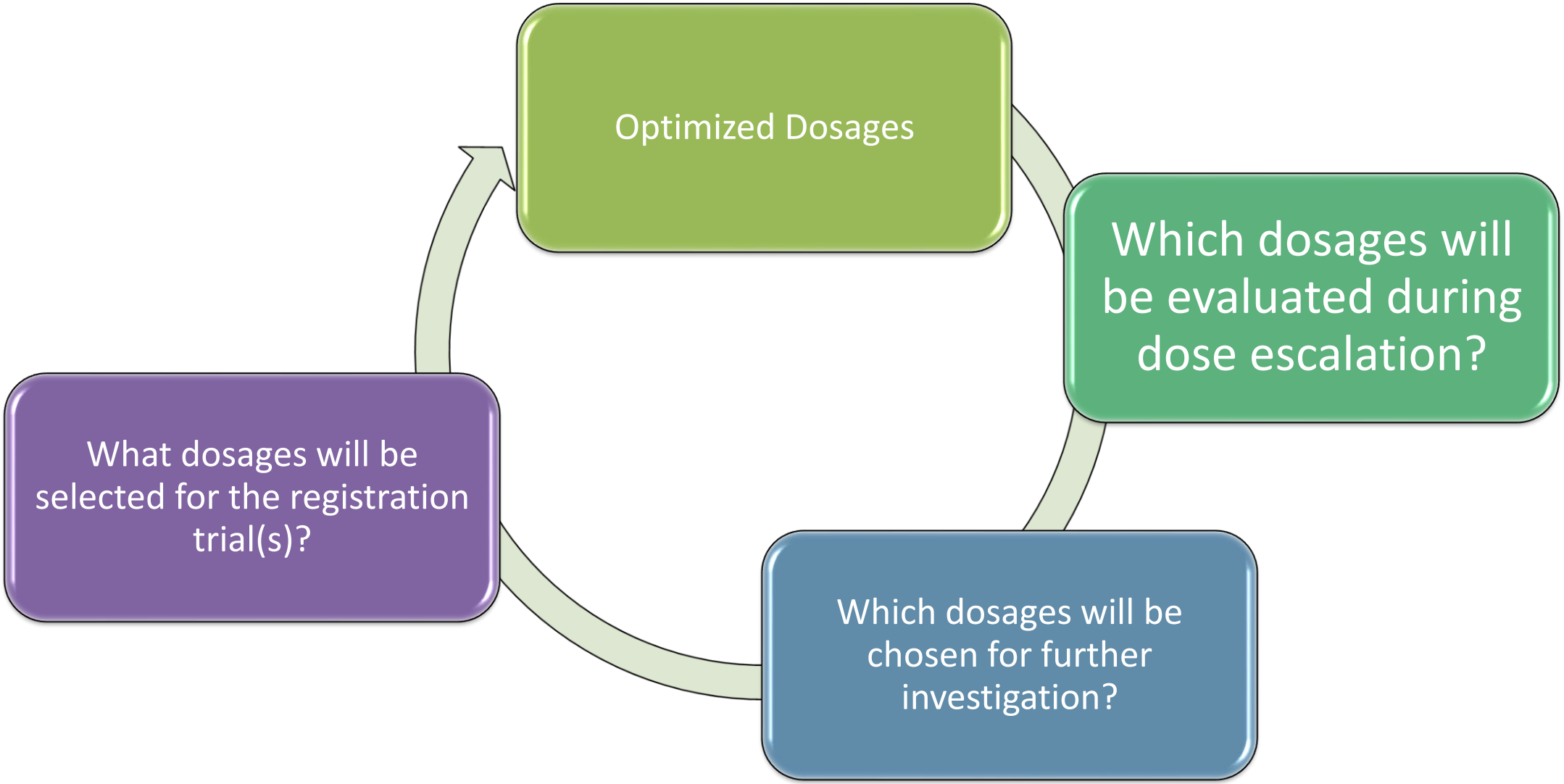


2003



2022

Oncology Dosing Tool Kit



https://www.fda.gov/about-fda/oncology-center-excellence/oncology-dosing-tool-kit

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Workshop

Quantitative Approaches to Select Dosages for Clinical Trials

Selecting Dosages for Dose-Escalation Portion of First-In-Human Trials

- Selecting Dosages for Dose-Escalation Portion of First-In-Human Trials
- Alternative Designs for Dose-Finding Trials: Ending Reliance on Short-Term Safety

Selecting Dosages for Additional Exploration Based on Nonclinical and Early Clinical Data

- Evaluating and Modeling All Early Data to Select Recommended Phase II Dose
- Novel Trial Designs to Enhance Dose-Selection Decision Making

Selecting Dosages for Registrational Trials

- Considering the Totality of Efficacy and Safety Data to Aide Registrational Trial Designs
- Implementing Seamless and Adaptive Registrational

Acknowledgements

Jiang Liu

Atiqur Rahman

Mirat Shah

Marc Theoret

Project Optimus


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SESSION 1: SELECTING DOSAGES FOR DOSE-ESCALATION PORTION OF FIRST-IN-HUMAN TRIALS

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Session 1A: Utilizing Nonclinical Data and Modeling to Support Dosage Selection for First in Human Trials

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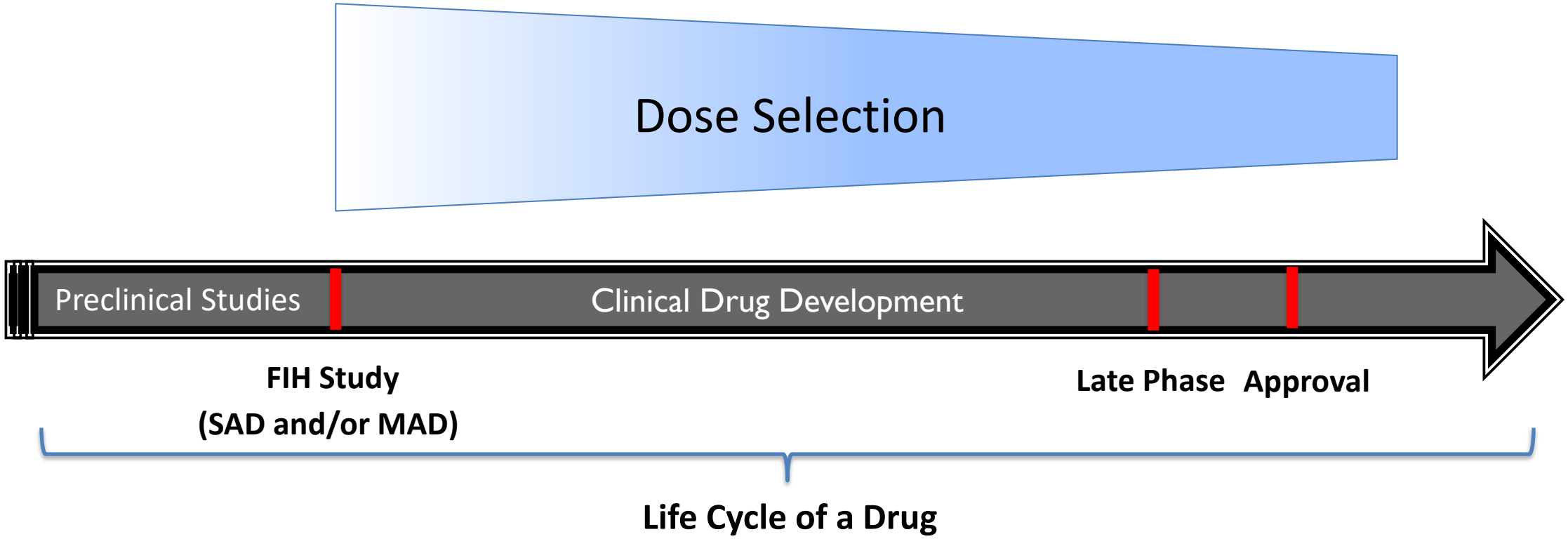
Dose Selection in Oncology First in Human Trials: Challenges and Opportunities

Hao Zhu, Ph.D., Mstat
Division Director
Division of Pharmacometrics,
FDA/CDER/OTS/OCP

FDA-AACR Public Workshop
(February 2024)

Dose Selection in Clinical Development



FIH studies

	Non - Oncology	Oncology
Subjects	Healthy volunteers	Cancer Patients
Objectives	Explore dose range based on short-term safety and tolerability findings.	• Explore dose range based on short-term safety and tolerability findings. • Identify maximum tolerated dose (MTD) • Proof of concept (POC) • Identify potentially efficacious dose.
Focus	Safety and tolerability	Safety and tolerability, efficacy-related findings
Dose range	Explore a wide dose range that is reasonably safe and well-tolerated	
Dose titration	Start low & titrate gradually	

Dose Selection in FIH Oncology Studies

Expectation on safety

Should not push the dose too high

Patients

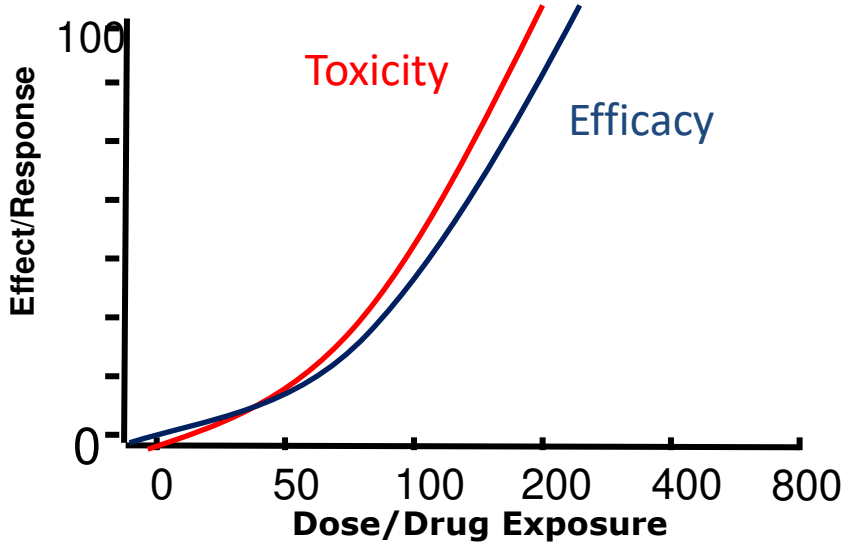
- Limited treatment options
- Unmet medical needs

Expectation on efficacy

Should not start the dose too low

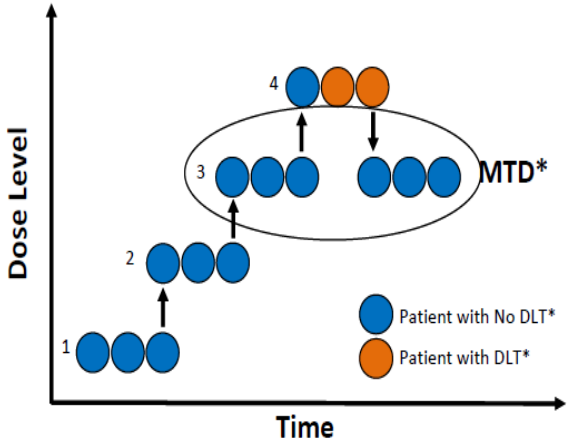
Oncology Dose Selection in the Past

Cytotoxic Chemotherapy



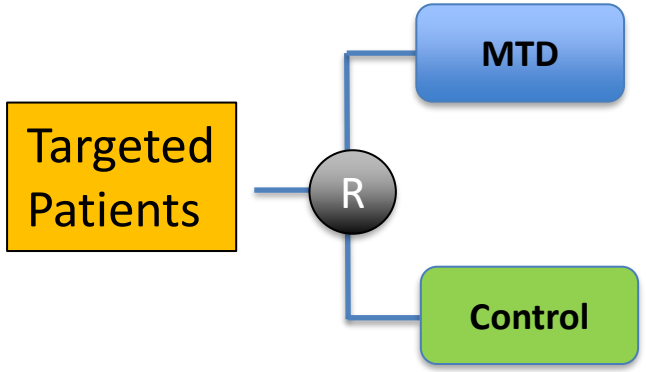
FIH Studies

Dose Escalation



Expansion / Efficacy Trials

Confirmation



Empirical Ways to Select Starting Dose

FIH Trial

*

NOAEL/NOEL

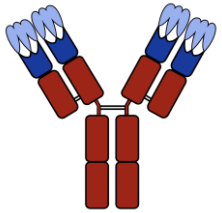
STD10 (rodent)

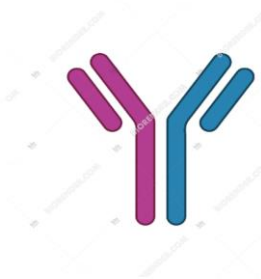
HNSTD (non-rodent)

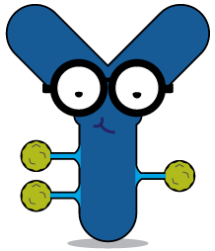
*: ICH S9 Guidance

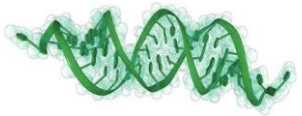
Novel Modalities in Oncology Development


Target Therapy

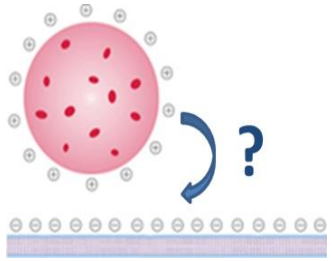

Monoclonal Antibodies


Bispecific Antibodies


Antibody Drug Conjugates


RNA Compounds

.....

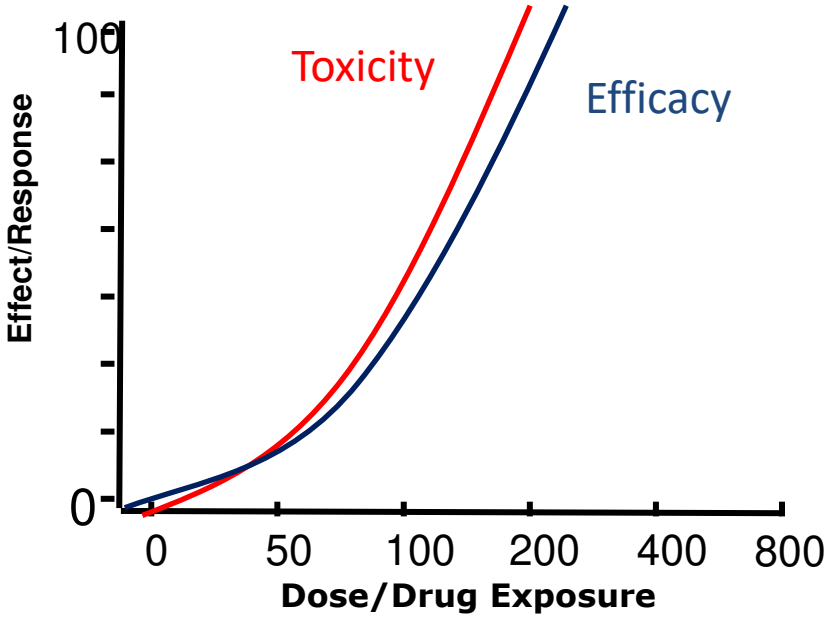


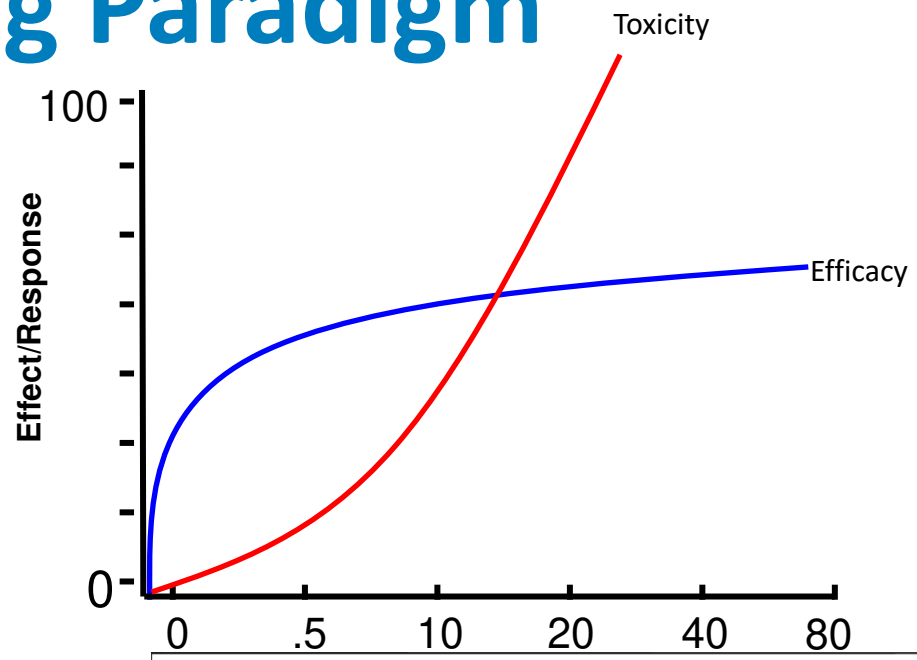
Novel Delivery System

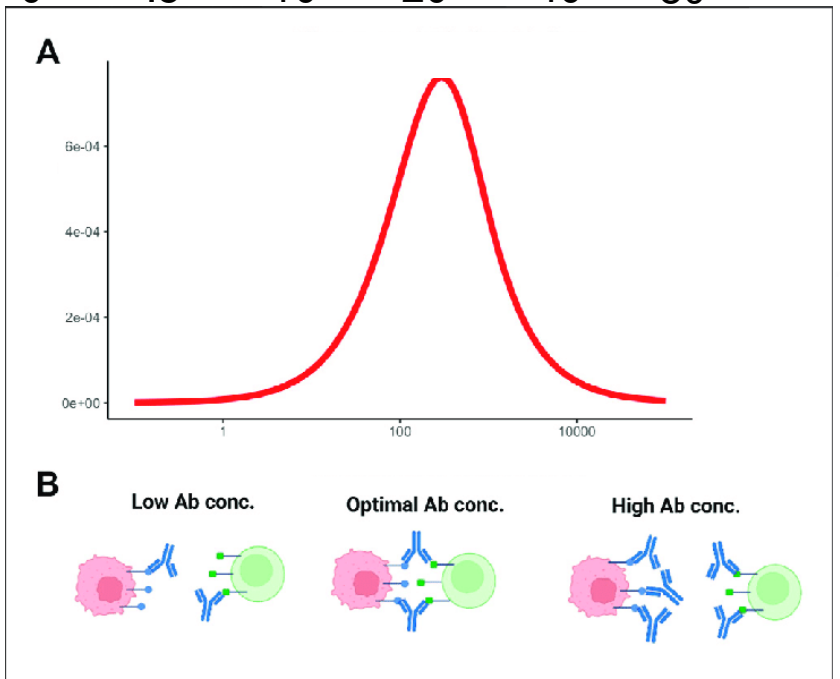
Novel Mechanism of Actions

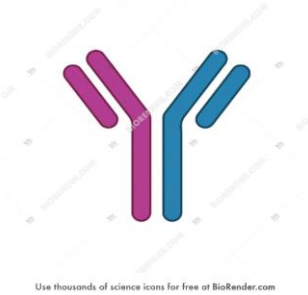
FIH Dose Selection

Changing Paradigm









Model-Based Dose Selection

Patients

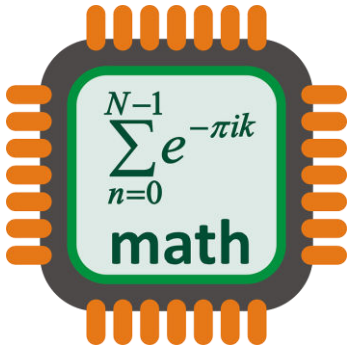
Novel Modalities

Clinical Experience

Preclinical Data

Disease Progression

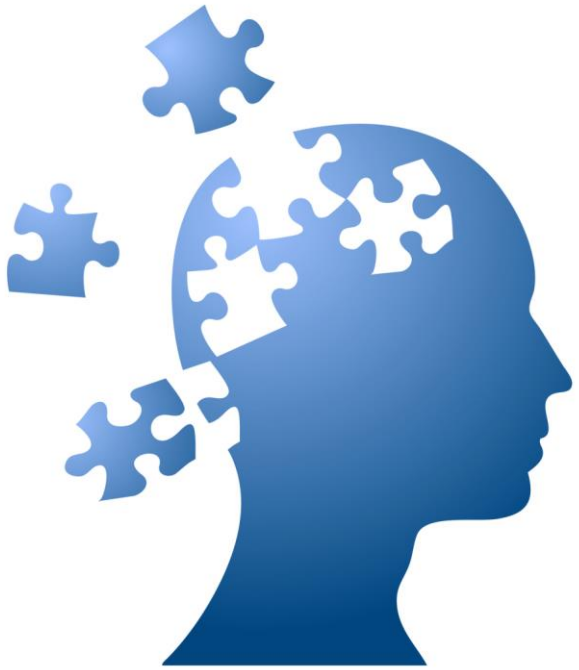
Mechanism Of Action



FIH Dose

Model as a holistic translational platform

Good Start is Half the Job Done



SESSION 1A: UTILIZING NONCLINICAL DATA AND MODELING TO SUPPORT DOSAGE SELECTION FOR FIRST IN HUMAN TRIALS

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AACR American Association for Cancer Research

MODERATOR

Hao Zhu, PhD
U.S. Food and Drug Administration

INTRODUCTORY SPEAKER

Alex Phipps, PhD
AstraZeneca

ADDITIONAL PANELISTS

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Ralph Parchment, PhD
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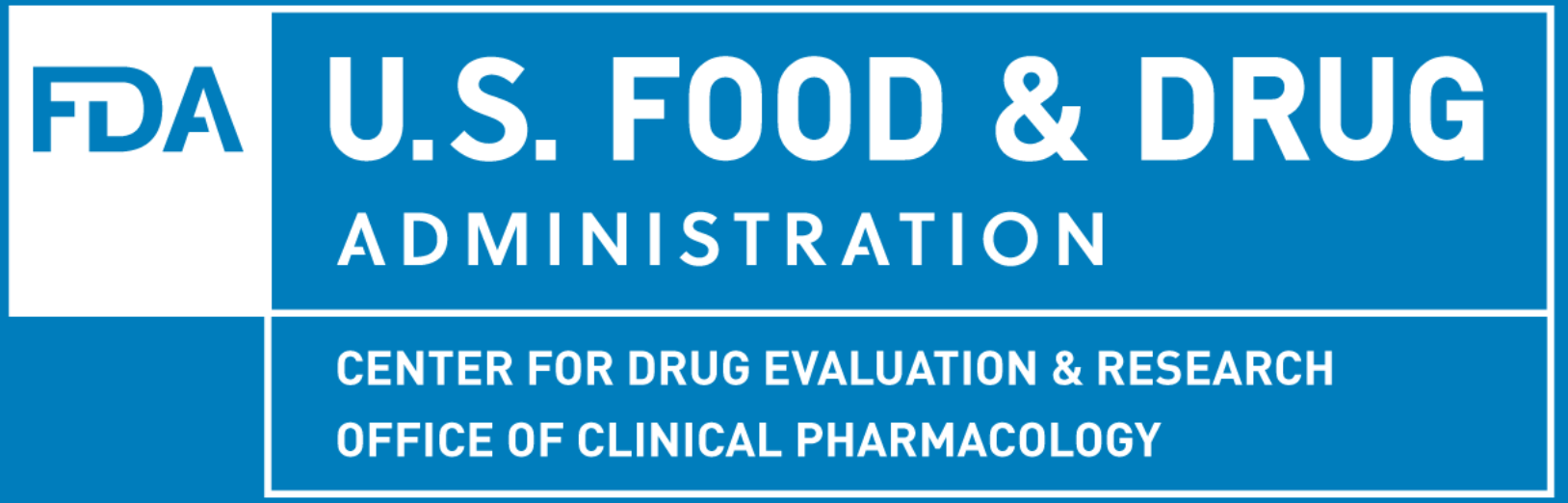
Manish Gupta, PhD
Genmab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OPTIMIZING DOSAGES FOR ONCOLOGY DRUG PRODUCTS: QUANTITATIVE APPROACHES TO SELECT DOSAGES FOR CLINICAL TRIALS
February 15 and 16, 2024 I Washington, DC

Applications of model-based approaches to select the starting dosages for first in human trials

Alex Phipps, PhD

on behalf of the AZ Project Optimus Advisory group

Alex Phipps, Ph.D.,
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Disclosure Information

Alex Phipps has the following relevant financial relationships to disclose:

Employee and Stockholder of: AstraZeneca

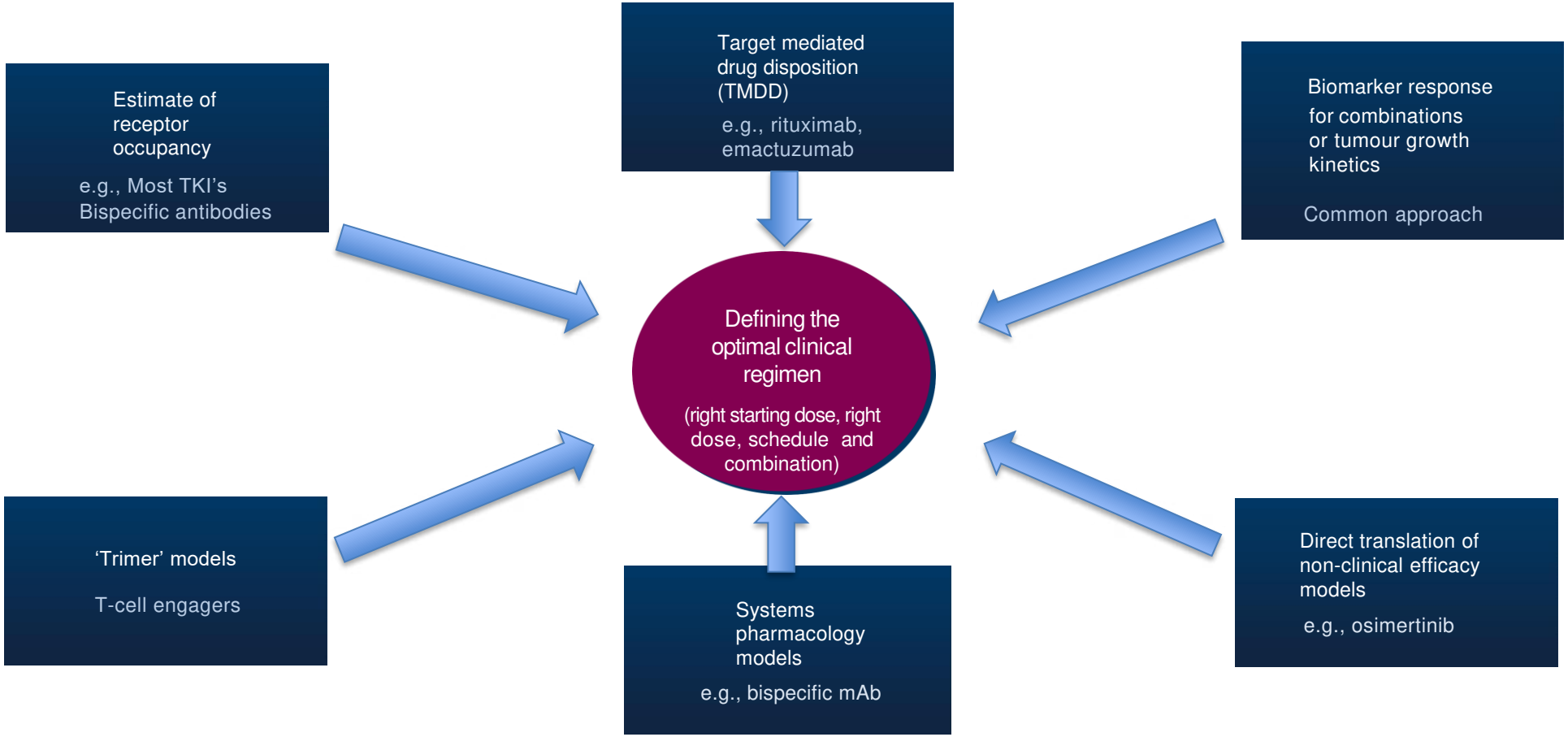
The views expressed in this presentation are my own and not necessarily reflective of AstraZeneca

Focus of the presentation

- Model-based approaches to impact starting doses in the following patient settings
  - Monotherapy
    - Case 1 T-cell engager
    - Case 2 – Small molecule
  - a New Indication
    - Case 3 – Bispecific mAb
  - a New Drug Combination
    - Case 4 – Modelling of advanced cellular in vitro systems

Whilst working with the urgency that patients require

Model-based approaches to starting dose and dose optimization based on efficacy



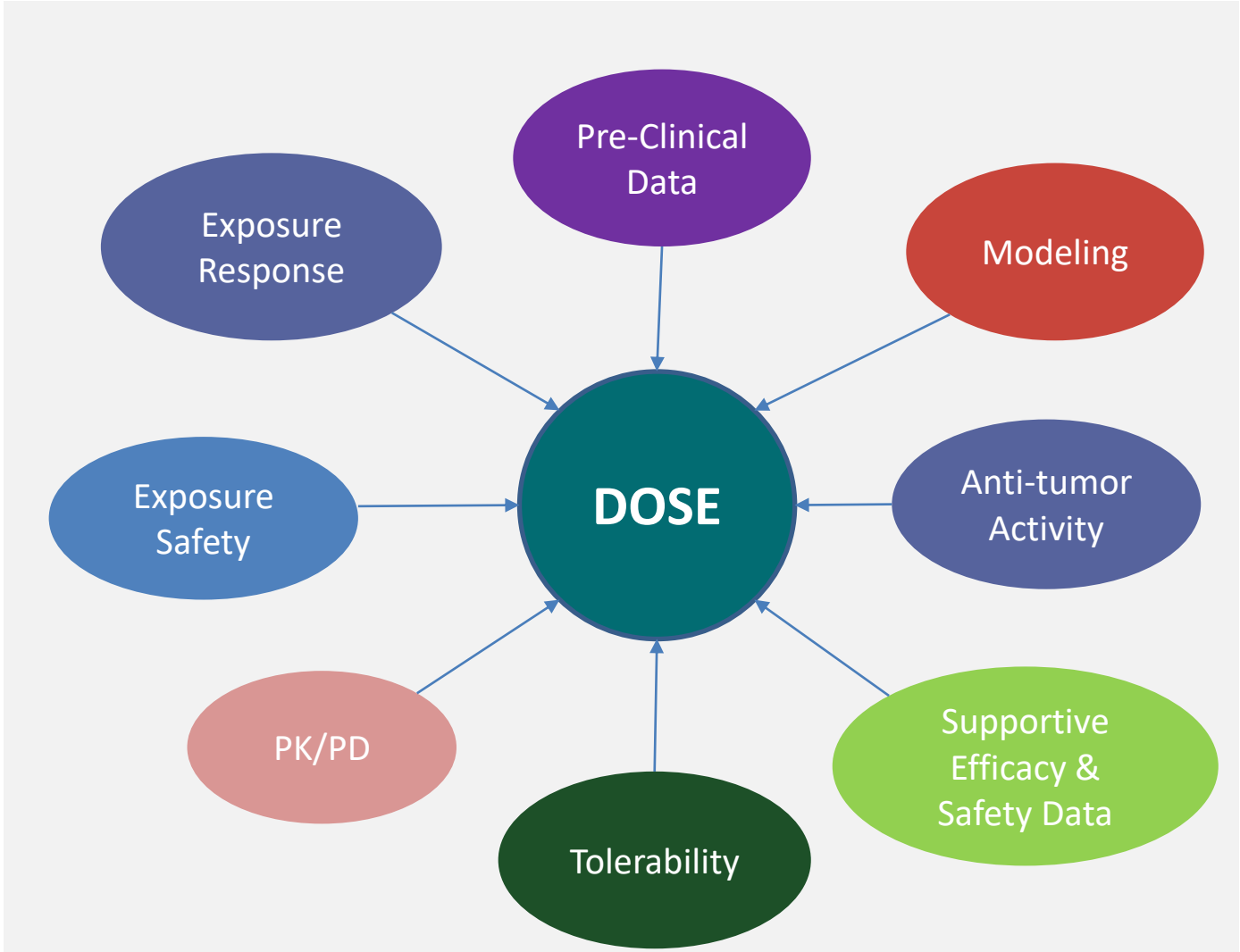
Always balanced against safety

Model-based approaches to dose optimization In monotherapy: Balancing efficacy against safety

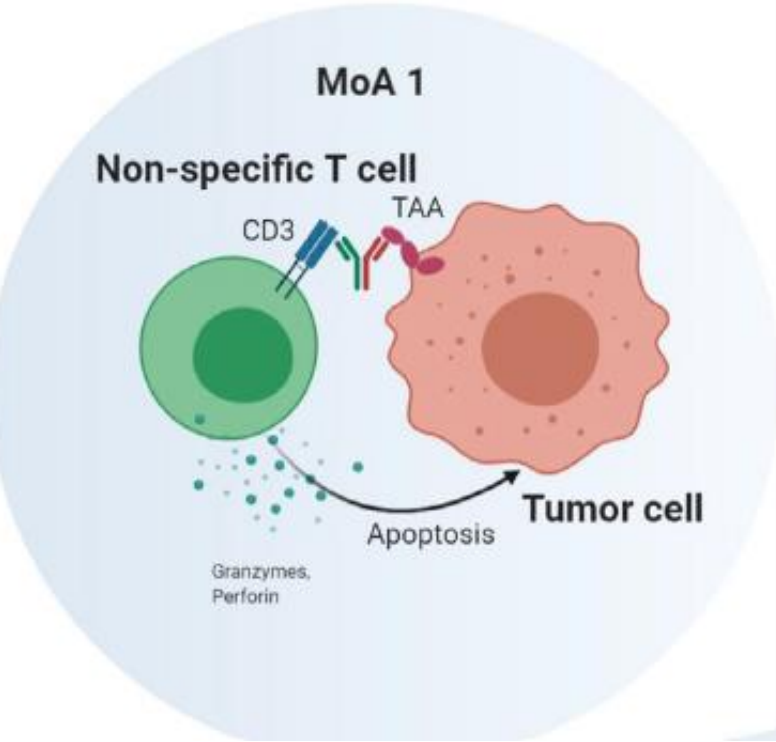
Identify a safe starting dose with some predicted efficacy

Identify an active dose range to explore

Make an informed decision on dose to take forward to a Phase 3 trial



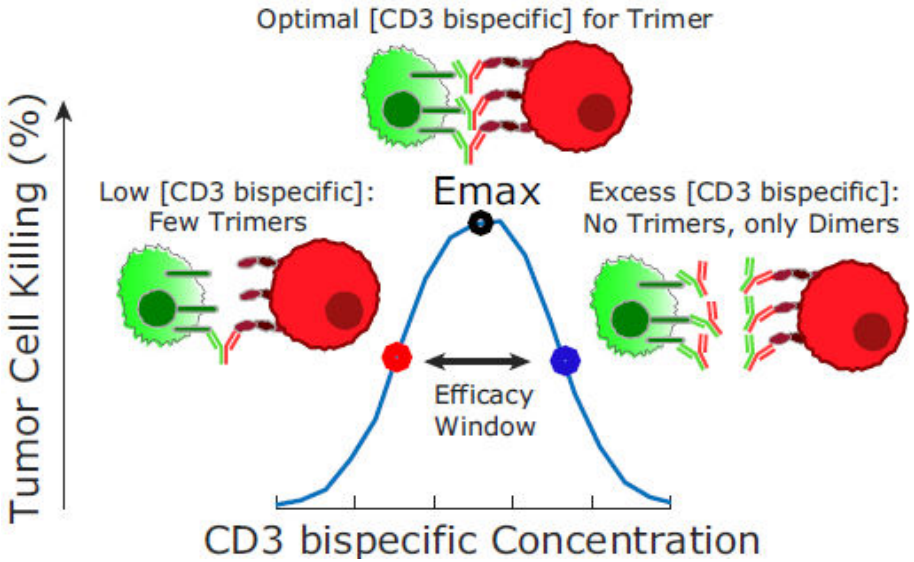
Case Study 1: Model based approach to optimizing Therapeutic Index – T-cell engagers



- Agonists of the immune system. *Blinatumomab approved in 2014*
- mAb binds T-cells and Tumour cells to form an active 'trimer' mimicking a synapse
- Challenges to starting dose prediction
- Nonclinical models can be limited by lack of antigen expression
- *In vitro* cytokine release experiments can overestimate clinical observation – resulting in starting doses up to 500x below activity

Betts and van de Graaf 2020

Selecting the starting dose for FIH – T-cell engagers



MABS
2023, VOL. 15, NO. 1, 2181016
https://doi.org/10.1080/19420862.2023.2181016

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

Strategies for clinical dose optimization of T cell-engaging therapies in oncology

Kathryn Ball[a], Simon J Dovedi[b], Pavan Vajjah[a], and Alex Phipps[a]

[a]Clinical Pharmacology and Quantitative Pharmacology, Biopharmaceuticals R&D, AstraZeneca, Cambridge, UK; [b]Early Oncology R&D, AstraZeneca, Cambridge, UK

- Betts et al 2019 devised a QSP model which predicted the concentrations of the active 'trimer'
- This trimer may be more reflective of the 'active' moiety
- The models also show that the trimer may saturate at higher concentrations. This may have implications on how high a dose is needed

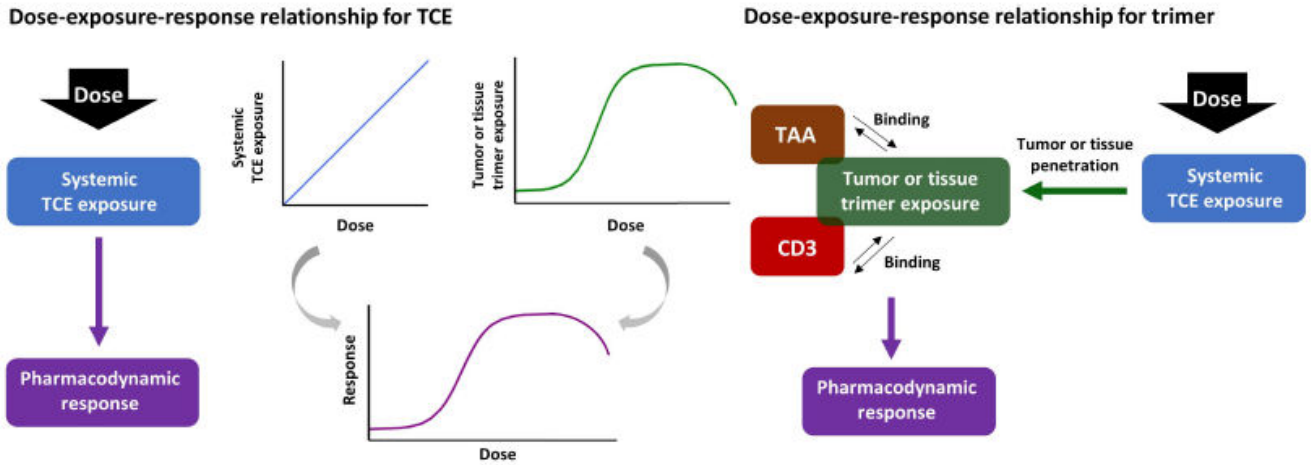
Betts, A et al 2019
Li et al 2022

Frances et al 2022
Hosseini et al 2020

T-cell engagers – Trimer model-based starting dose approach for solid tumour

1. PK/PD modelling to predict **in vitro** trimer concentration-response relationship for cytotoxicity and cytokine release

2. PBPK and PK/PD modelling to predict trimer concentration **in patients** across a range of potential dose levels



3. Rational choice of appropriate PD biomarkers and upper limit of pharmacological activity level for starting dose selection

Ball, K et al mAbs 2023

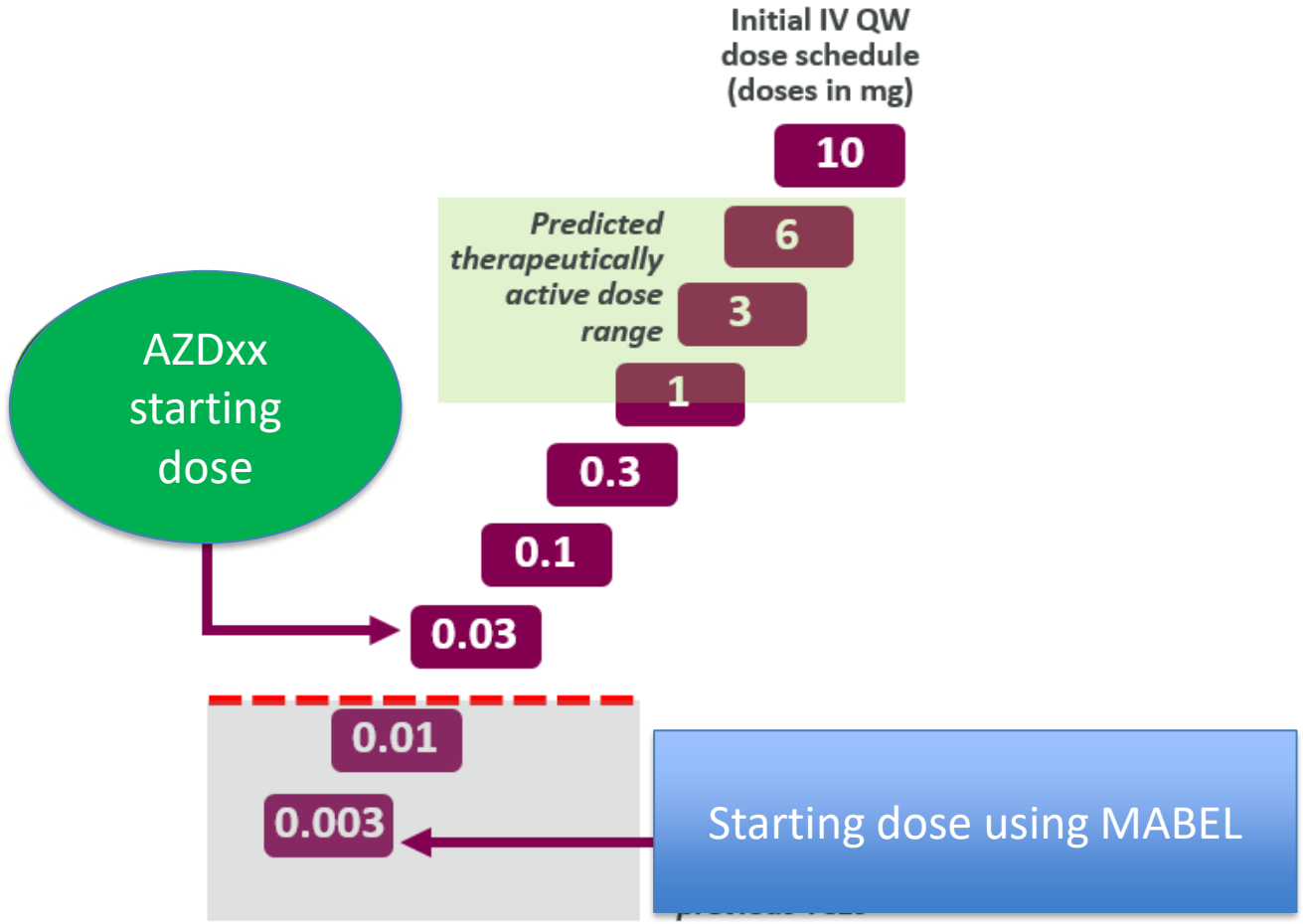
T-cell engagers – Trimer model may enable cycle time reduction

Starting dose was 10x higher using Trimer than MABEL. - Well tolerated clinically

Model informed on single patient cohorts to predicted dose range (0.003 – 0.3 mg/kg)

Reduces number of patients exposed to ineffective doses

Informs on doses for expansion
By incorporating what is known about target expression can inform on doses across indications



Case Study 2: Using non-clinical and clinical data for starting dose and informing on dose expansion cohorts

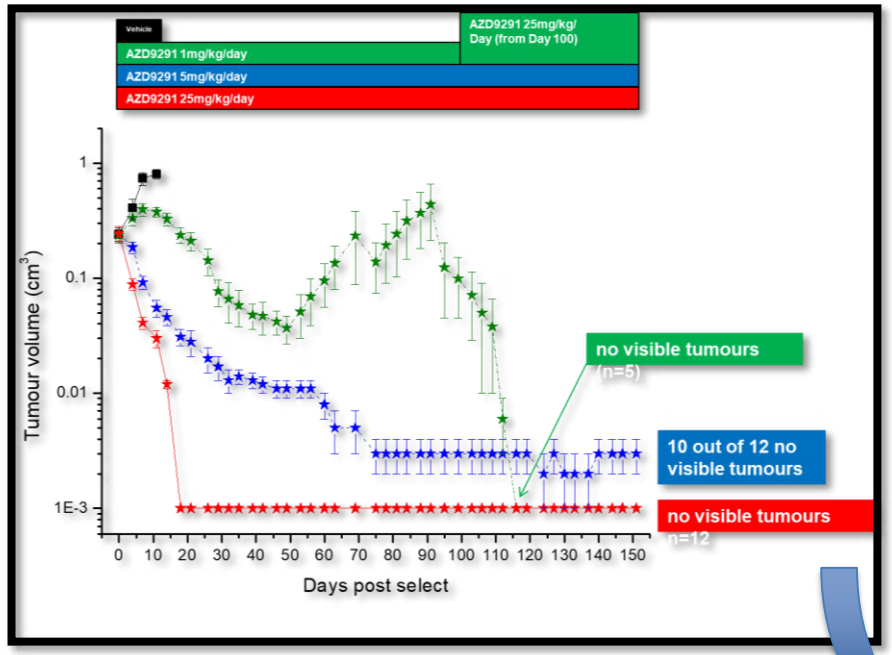
Osimertinib

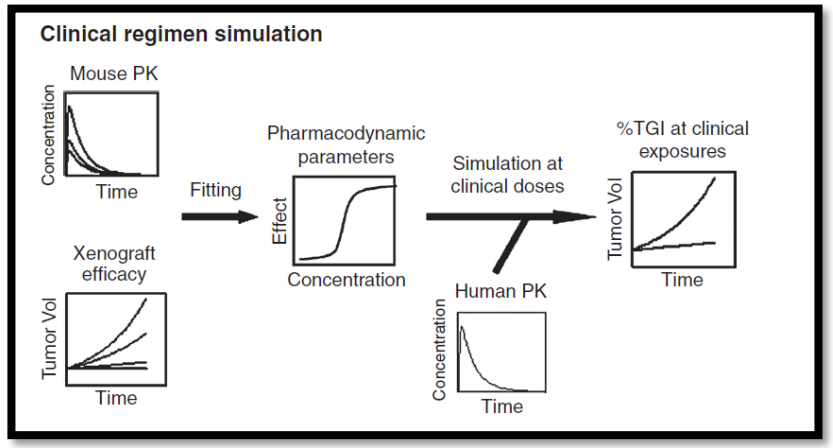
A brain penetrant mutant-selective EGFR inhibitor

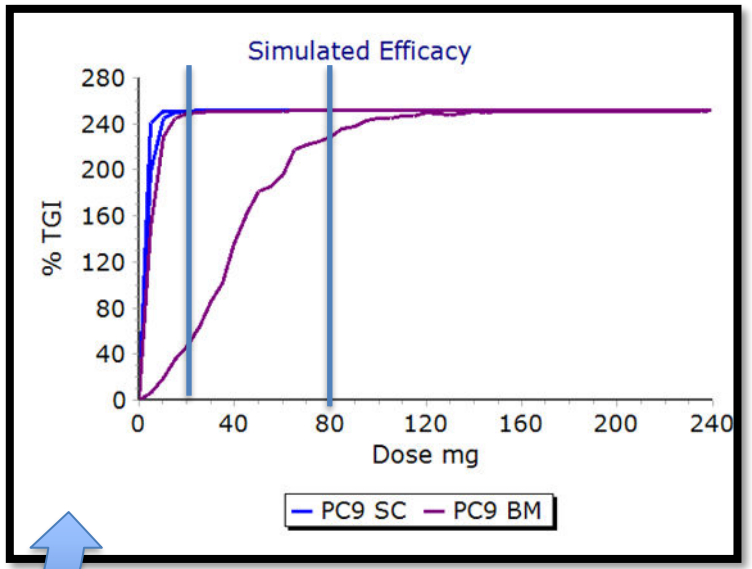
Approved for the treatment of EGFR-mutant NSCLC harboring sensitizing EGFR mutations, including T790M

A 'pre-Project Optimus', Optimus like design

Translational modeling enabled a starting dose predicted to have efficacy







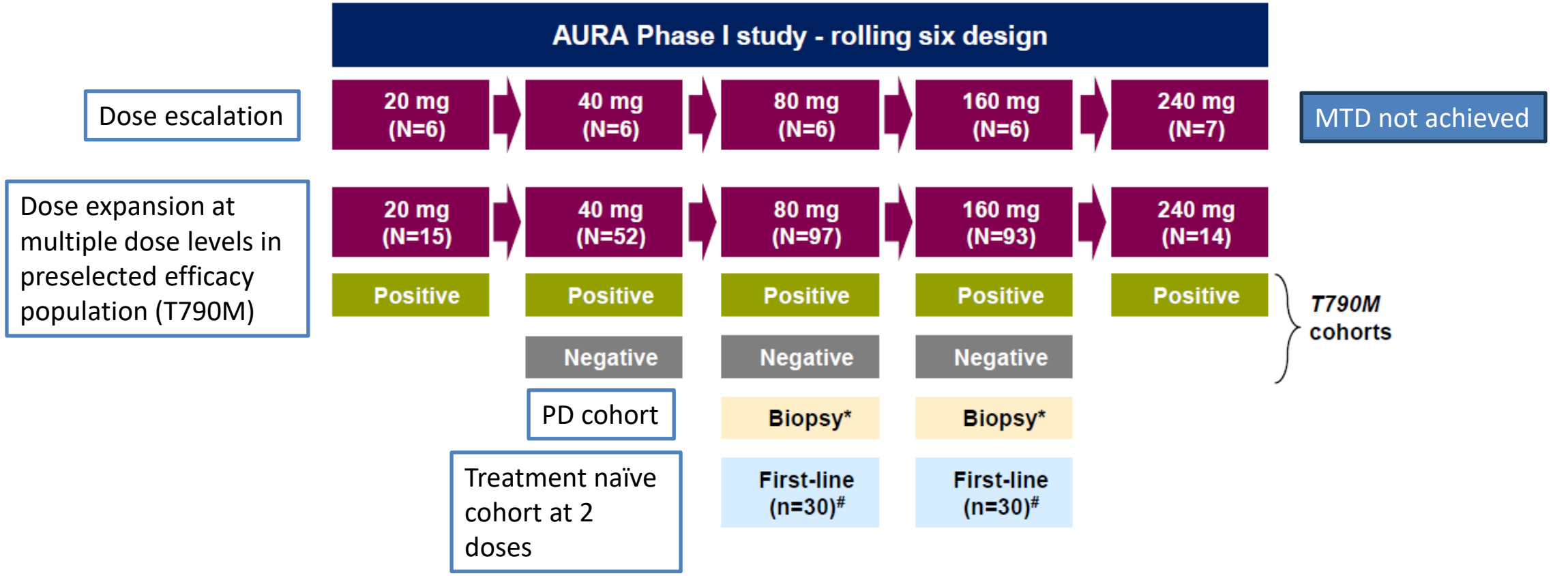
Preclinical studies shows 5 mg/kg is an efficacious dose in mouse

Translational PK-PD modeling to predict human efficacious exposure/dose

Starting dose of 20 mg is predicted to be efficacious; 80 mg for max efficacy.

BM = Brain metastases

Osimertinib dose selection followed an 'Optimus like' approach



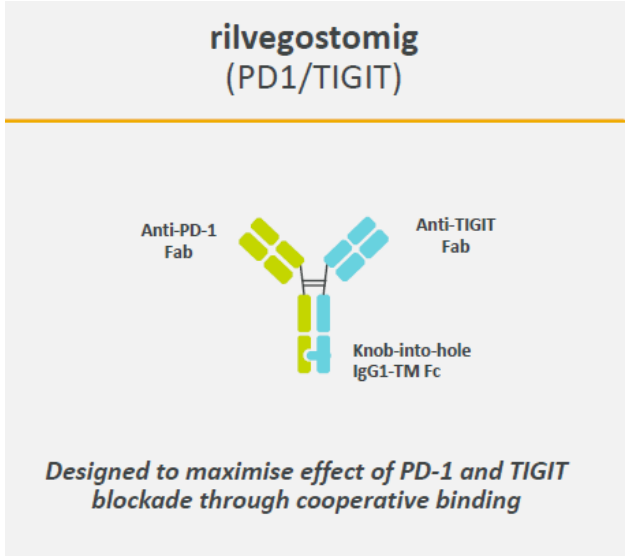
Considerations for selecting starting dose across new indications

	Considerations for starting dose
Dose	Established or expected in 1st indication
Mechanism of Action	Supporting non-clinical E-R similarity. But be aware of modality specific concerns – **e.g.,** . Bystander effect with ADC may vary . Tumour penetration and blood flow per indication . Receptor Expression (TMDD). Relevance to CAR-T? . Immune cell expression across tumours – also, 'cold' and 'hot' tumours
Clinical safety profile	Is the AE profile to date likely to be tolerated in the second?
DDI	Understand differences in con-meds between indications

Models may help with some of these questions

TMDD = target-mediated drug disposition

Case Study 3 - Rilvegostomig – PD1-TIGIT Optimizing for two targets

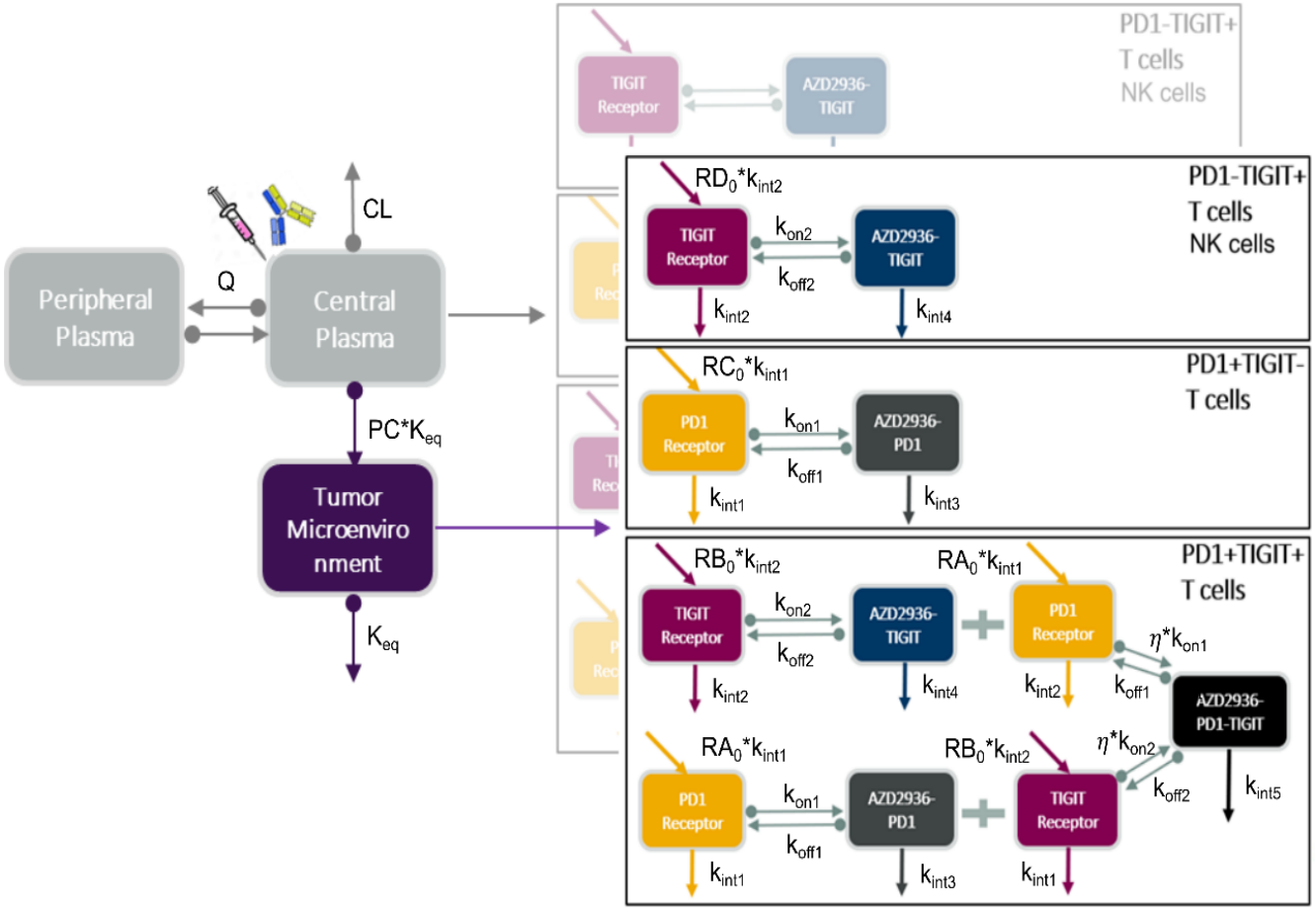


The anti-TIGIT component of rilvegostomig is derived from COM902 developed by Compugen Ltd

ACoP 2023 (Gong et al)

- Bispecific antibody - binds two checkpoint targets
- PD-1 well established through Keytruda, Opdivo, etc
- Motivation was to build a model that would inform on
-
  - starting dose and optimal dose range
  - dose across indications and combinations

Rilvegostomig – PD1-TIGIT Systems' approach



Two TMDD modules -

capture concentration and receptor binding dynamics

Couples PK and tumour dynamics -

to simulate receptor occupancy (RO) across dose levels.

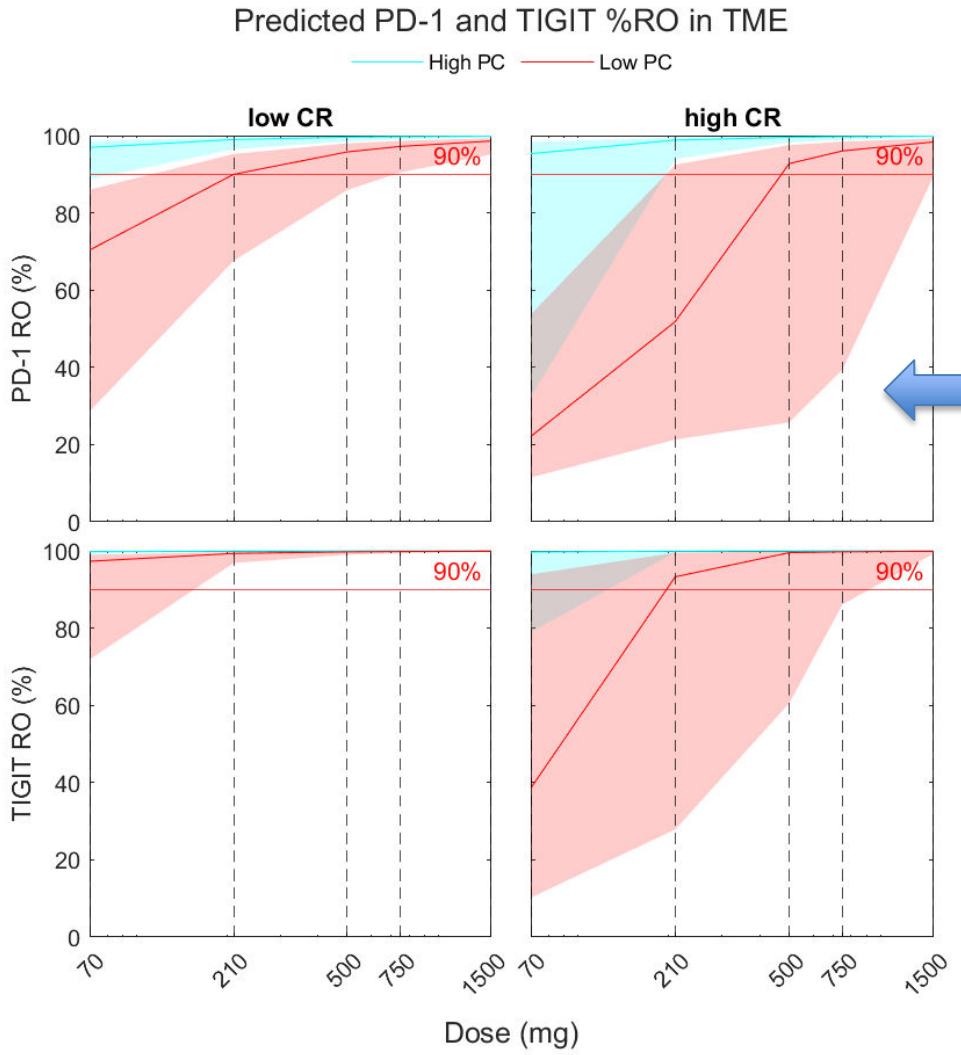
Compare RO for PD-1 and TIGIT drugs

Sensitivity analysis –

effect of variable tumour uptake (PC) and concentration of receptor (CR)

RO = receptor occupancy

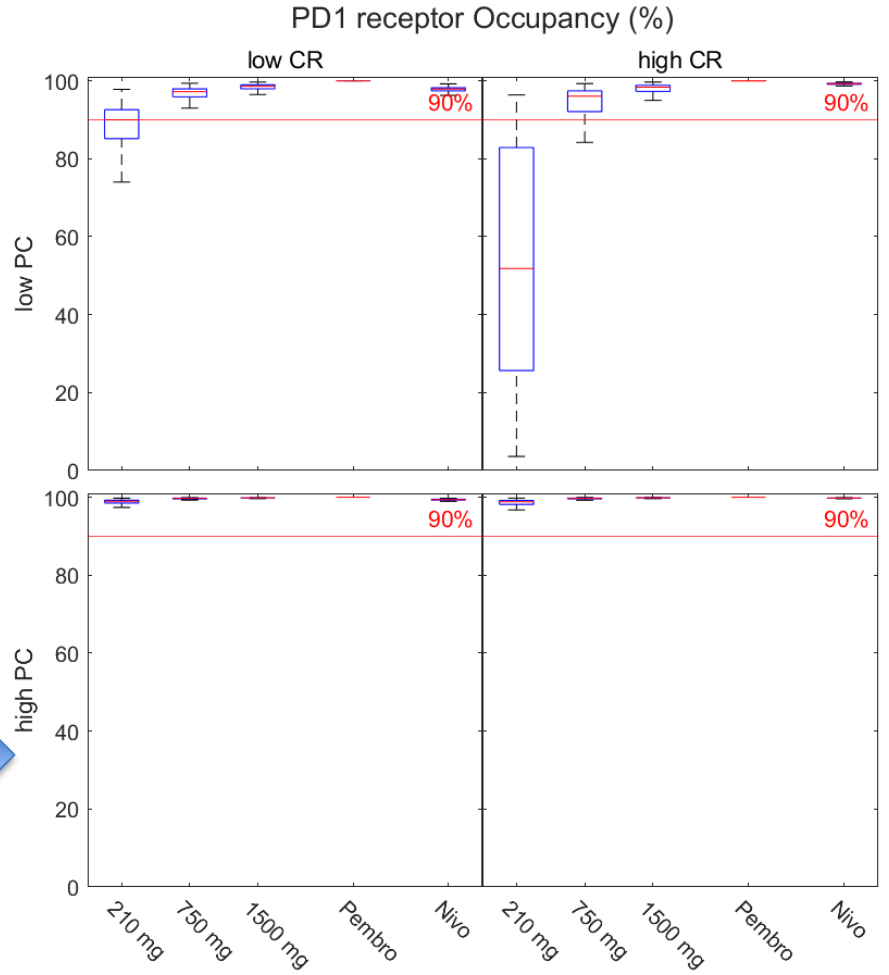
Rilvegostomig – Simulation results



Predicted PD-1 and TIGIT %RO in TME across dose range.

Compared to literature data for PD-1 drug

Predicted RO for rilvegostomig and other PD-1 mAbs



TME – tumour microenvironment

Rilvegostomig – Conclusions

Comparison to external meta-data informed on the dose range for expansion *a priori* ✓

Starting dose of 70 mg (~ 70% RO of PD1 and TIGIT) informed by the model ✓

Model was used to narrow the dose range for expansion (750 and 1500 mg) ✓

Other PD-1 and TIGIT have same dose across indications - *gives confidence to use the same dose to start indication expansions* ✓

Doses in combinations

To date we've considered first dose and dose optimization in monotherapy.

What about combinations?

I think the same approaches can apply. ✓

An example - combining novel experimental systems with modeling to optimize combination doses *a priori*

BENEFIT – Guides starting doses and can significantly reduce clinical combination dose ranging

Case Study 4
Modelling of advanced *in vitro* cellular systems is necessary for clinical translation

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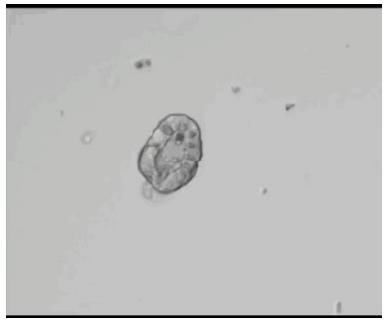
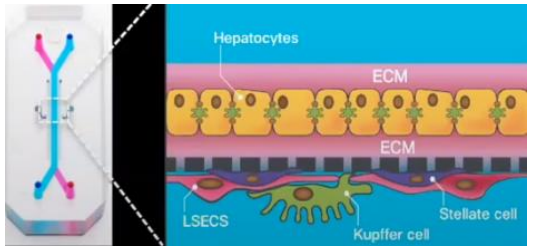
Exposure-Response Relationships

Organoids





Systems Model

In vivo

Patients

Quantitative systems models allow the prediction of time-series clinical responses with various what-if scenarios

Clinical Translation from MPS Data: Hematotoxicity

Human hematopoietic model

$$\frac{dHSC}{dt} = PHSC + \lambda_{SC} HSC\left(1 + fb(MLP)) + fb(CMP)\right) - (\sigma_{CMP} + \sigma_{MLP}) HSC \frac{HSC}{HSC_0} - E_{drug}\lambda_{SC} HSC$$

$$\frac{dMLP}{dt} = \sigma_{MLP} SC + \lambda_{MLP} MLP\left(1 + fb(CLP)) + fb(GMP)\right) - \sigma_{CLP} MLP - \sigma_{GMP1} MLP - E_{drug}\lambda_{MLP} MLP$$

$$\frac{dCMP}{dt} = \sigma_{CMP} SC + \lambda_{CMP} CMP\left(1 + fb(MEP)) + fb(GMP)\right) - \sigma_{MEP} CMP - \sigma_{GMP2} CMP - E_{drug}\lambda_{CMP} CMP$$

$$\frac{dCLP}{dt} = \sigma_{CLP} MLP + \lambda_{CLP} CLP\left(1 + fb(lym)\right) - \sigma_{proLym} CLP - E_{drug}\lambda_{CLP} CLP$$

$$\frac{dMEP}{dt} = \sigma_{MEP} CMP + \lambda_{MEP} MEP\left(1 + fb(ery) + fb(ret)\right) - \sigma_{CD71} MEP - \sigma_{MK} MEP - E_{drug}\lambda_{MEP} MEP$$

$$\frac{dGMP}{dt} = \sigma_{GMP1} MLP + \sigma_{GMP2} CMP + \lambda_{GMP} GMP\left(1 + fb(neut) + fb(mocy)\right) - \sigma_{myblast} GMP - \sigma_{moblast} GMP - E_{drug}\lambda_{GMP} GMP$$

$$\frac{dMK}{dt} = \sigma_{MK} MEP + \lambda_{MK} MK\left(1 + fb(plat)\right) - \sigma_{MKT} MK - E_{drug}\lambda_{MK} MK$$

$$\frac{dMKT}{dt} = \sigma_{MKT} MK - \tau_{MKT} MKT$$

$$\frac{dCD71}{dt} = \sigma_{CD71} MEP + \lambda_{CD71} CD71\left(1 + fb(ery) + fb(ret)\right) - \sigma_{CD71T} CD71 - E_{drugEry}\lambda_{CD71} CD71$$

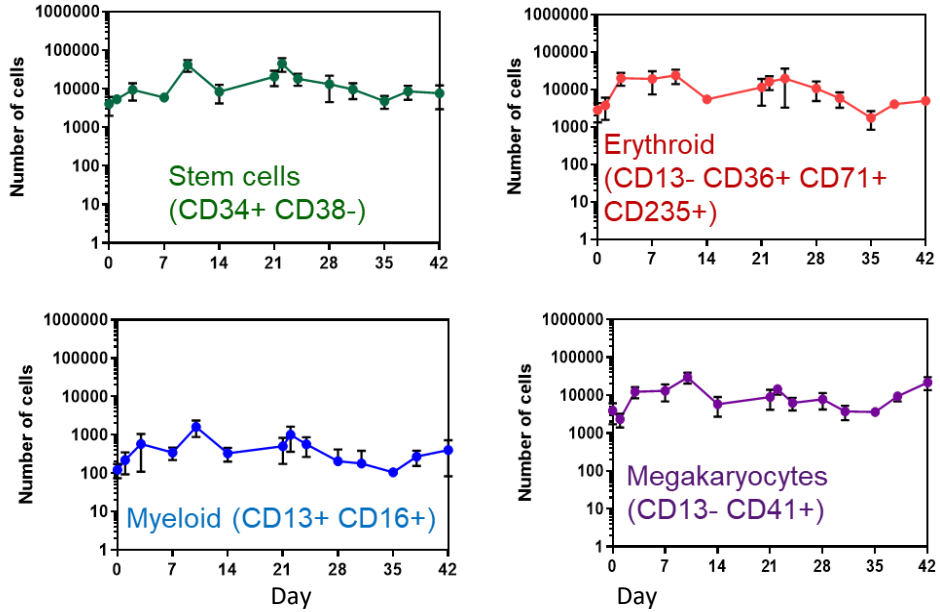
$$\frac{dCD71T}{dt} = \sigma_{CD71T} CD71 - \sigma_{ret} CD71T$$

$$\frac{dmyblast}{dt} = \sigma_{myblast} GMP + \lambda_{myblast} myblast - \sigma_{myblast} myblast - E_{drug}\lambda_{myblast} myblast$$

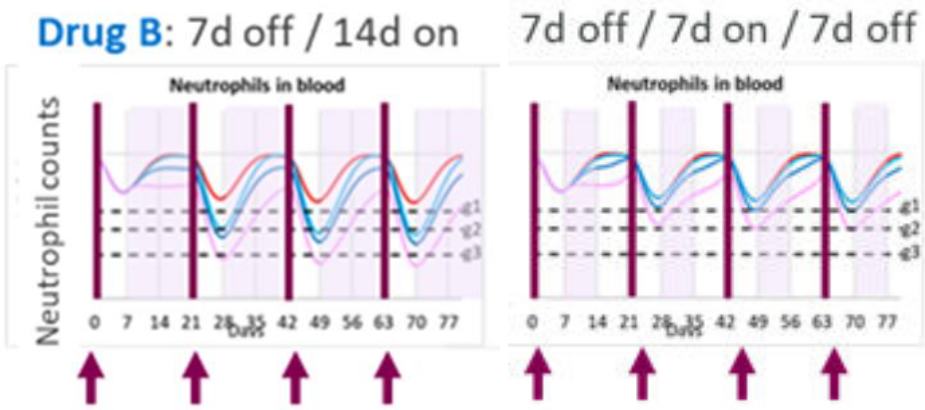
$$\frac{dmyblastT}{dt} = \sigma_{myblast} myblast - \sigma_{neut} myblastT$$

$$\frac{dmoblast}{dt} = \sigma_{moblast} GMP + \lambda_{moblast} moblast - \sigma_{moblastT} moblast - E_{drug}\lambda_{moblast} moblast$$

$$\frac{dmoblastT}{dt} = \sigma_{moblastT} moblast - \sigma_{mocy} moblastT$$



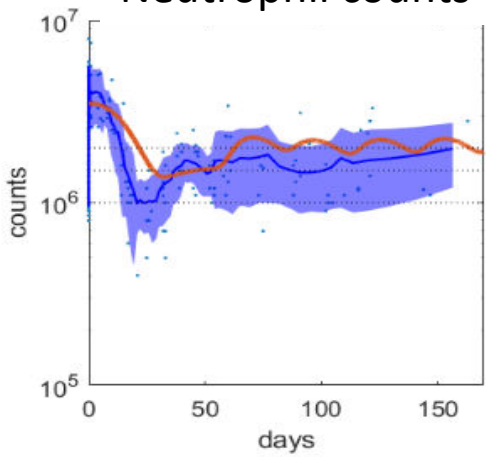
Identification of Drug A + Drug B dosing schedule to avoid clinical hematotoxicity



Clinical Translation Was Excellent!

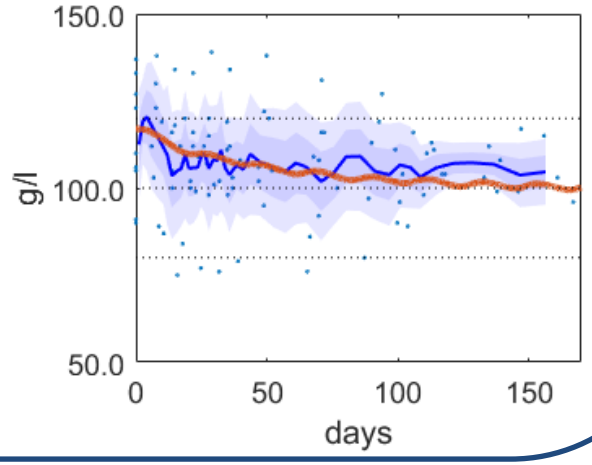
Prediction versus observation

Neutrophil counts



Red Lines: QST model predictions
Blue: Clinical observations

Haemoglobin



- The approach is currently being used to predict starting doses and schedule in combination.
- May result in significant reduction in clinical dose ranging

Summary

Advantages of and considerations for model-based approaches

Advantages

- Can inform on rational dosing strategies
- Bolsters rationale for HA submissions
- Facilitates a more accurate starting dose
- Amenable to most modalities
- Aids decision making on when to expand cohorts/switch indication/ combinations

Considerations

- Start early – data availability is key
- Discuss with teams the aims of and assumptions in the model
- Clear communication
- Capture learnings from one model to another – portfolio

- Keep models as simple as possible

Final thoughts

- Project Optimus has really helped focus the Industry on the question of the right dose/exposure, particularly in avoiding too high doses
- Model-based analysis, incorporating novel experimental systems, has the potential to decrease dose ranging across various indications and in combinations to speed drug development and reach patients sooner

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SESSION 1A: UTILIZING NONCLINICAL DATA AND MODELING TO SUPPORT DOSAGE SELECTION FOR FIRST IN HUMAN TRIALS

U.S. FOOD & DRUG ADMINISTRATION

AACR American Association for Cancer Research

MODERATOR

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U.S. Food and Drug Administration

INTRODUCTORY SPEAKER

Alex Phipps, PhD
AstraZeneca

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