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 2 WELCOME

Qi Liu, PhD
U.S. Food and Drug Administration

SECTION 3: SELECTING DOSAGES FOR REGISTRATIONAL TRIALS

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Quantitative Approaches to Select Dosages for Clinical Trials

Considering the Totality of Efficacy and Safety Data to Aide Registrational Trial Designs

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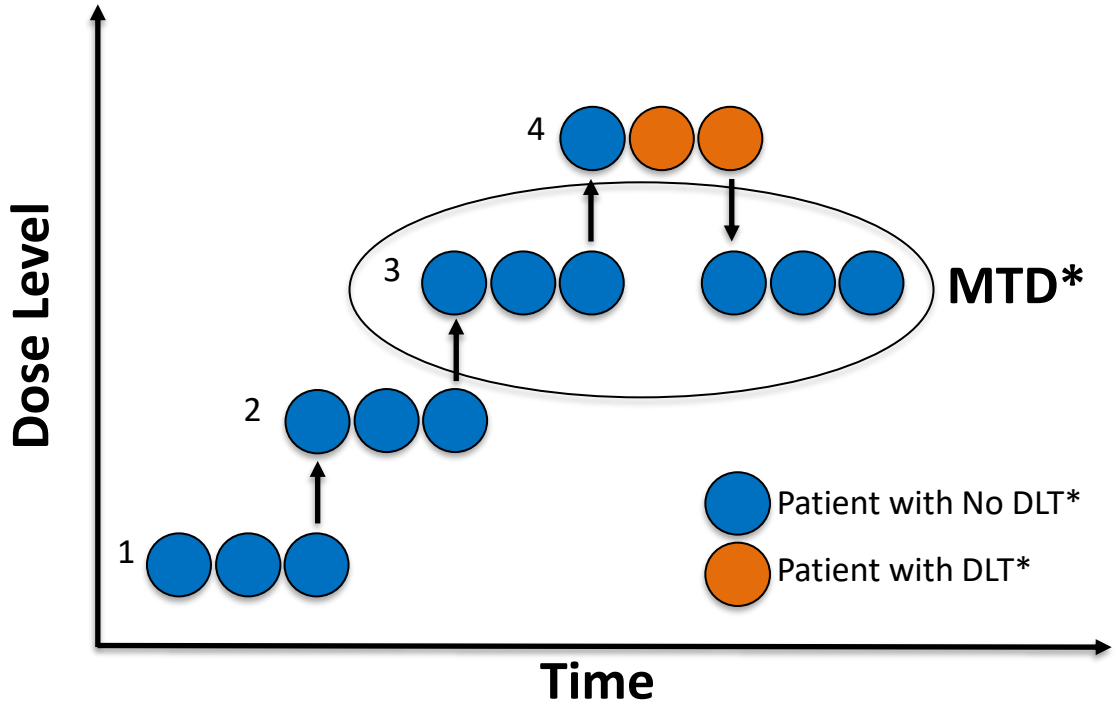
February 16, 2024

Disclaimer

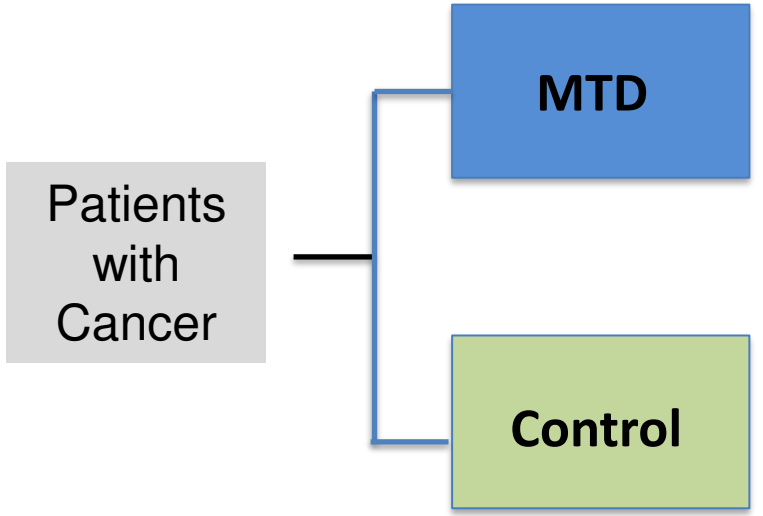
Opinions presented are those of the speaker and should not be construed to represent FDA's views or policies.

Classic Dose-Finding for Oncologic Products

Dose Escalation



Registration



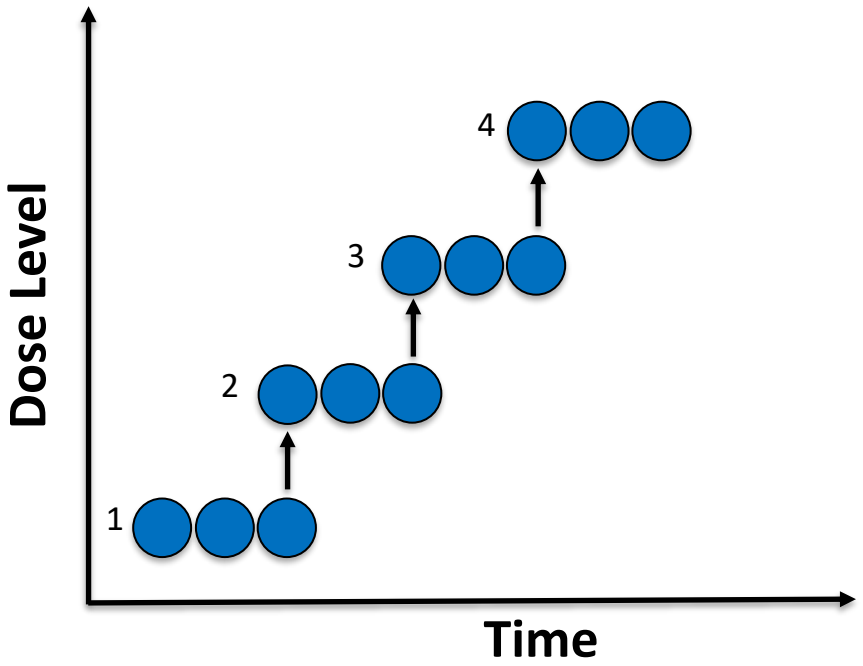
Hallmarks:

- Few patients at each dosage
- Short observation period for DLTs
- Emphasis on DLTs, but not other safety or data

*DLT = Dose-limiting toxicity
*MTD = Maximum tolerated dose

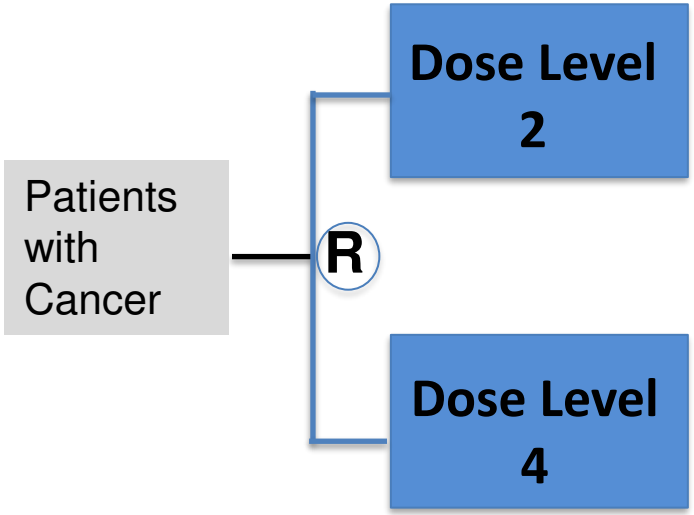
Possible Dosage Selection Strategy

Dose Escalation



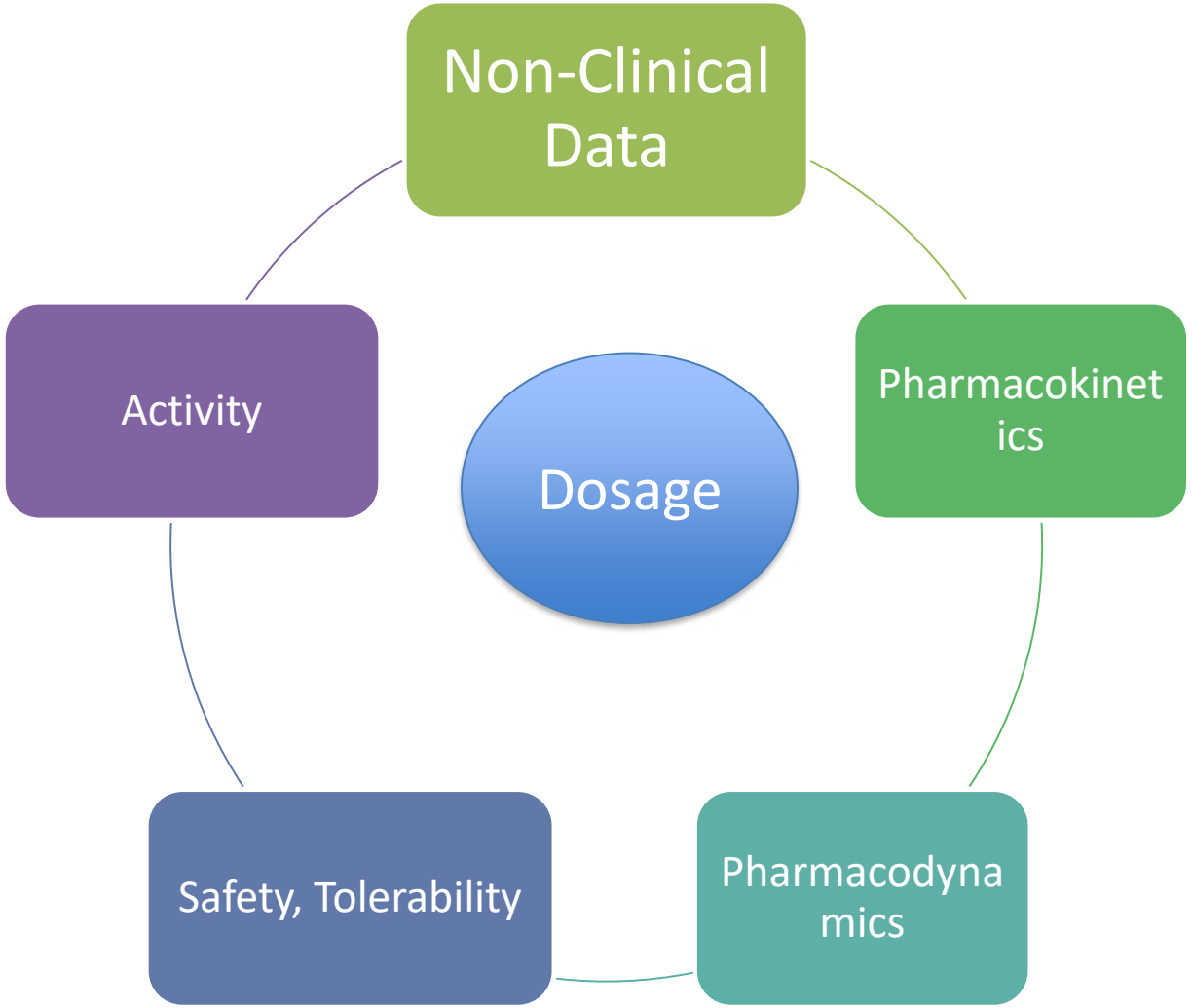
Select Dosage for Further Exploration

Dosage Optimization

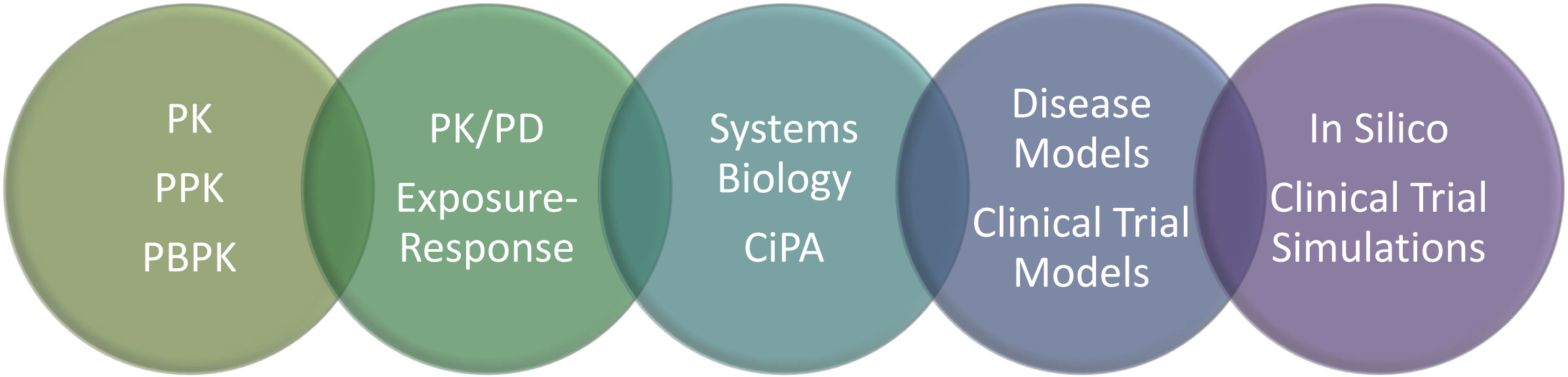


Evaluate Several Dosages

Holistic Approach



How do we systematically evaluate all available nonclinical and clinical data?



Adapted from Dr. Youwei Bi update on MIDD program
PK = pharmacokinetics, PD = pharmacodynamics, PBPK = physiologically based pharmacokinetics, CiPA = comprehensive in vitro proarrhythmia assay

Model-Informed Drug Development

- Leverage a thorough understanding of the drug, a disease, and how a drug affects the human body, as well as how the body responds to the drug.
- Quantify information by developing mathematical models based on full use of all available data, from sources such as in vitro, nonclinical and clinical studies
- Apply this knowledge to address issues pertaining to drug development or clinical use.

Adapted from CDER Conversation with Dr. Madabushi

MIDD Can Facilitate Drug Development

- Predict concentrations at different moments in time, including doses and times not yet studies
- Test effects of covariates to identify differences in exposure in specific subpopulations
- Characterize dose- and exposure-response relationships at any stage of development
- Facilitate a thorough understanding of the therapeutic index
- Leverage published data to help understand drug class effects and inform trial design

Considering the Totality of Efficacy and Safety Data to Aide Registrational Trial Designs

1. Using Modeling-Based Approaches to Understand Dose- and Exposure-Response Relationships for Activity
   Dr. Jin Y. Jin

2. Using Pharmacokinetic-Pharmacodynamic Modeling and Simulation to Understand Dose and Exposure-Response Relationships for Adverse Reactions
   Dr. Scott Van Wart

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February 15 and 16, 2024 I Washington, DC

Using Modeling-Based Approaches to Understand Dose- and Exposure-Response Relationships for Activity

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Disclosure Information

Jin Y. Jin

I have the following relevant financial relationships to disclose:

Employee of: Genentech, A Member of the Roche Group

Stockholder in: F. Hoffmann-La Roche

The views expressed in this presentation are my own and not reflective of Roche/Genentech

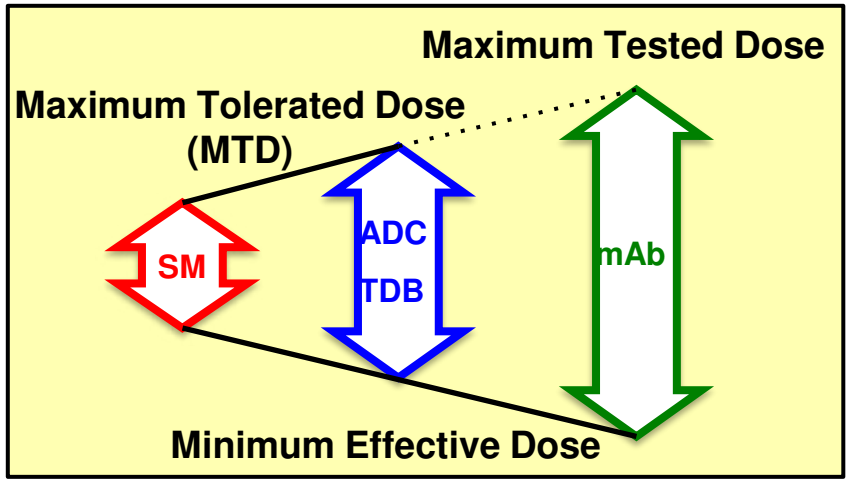
Outline

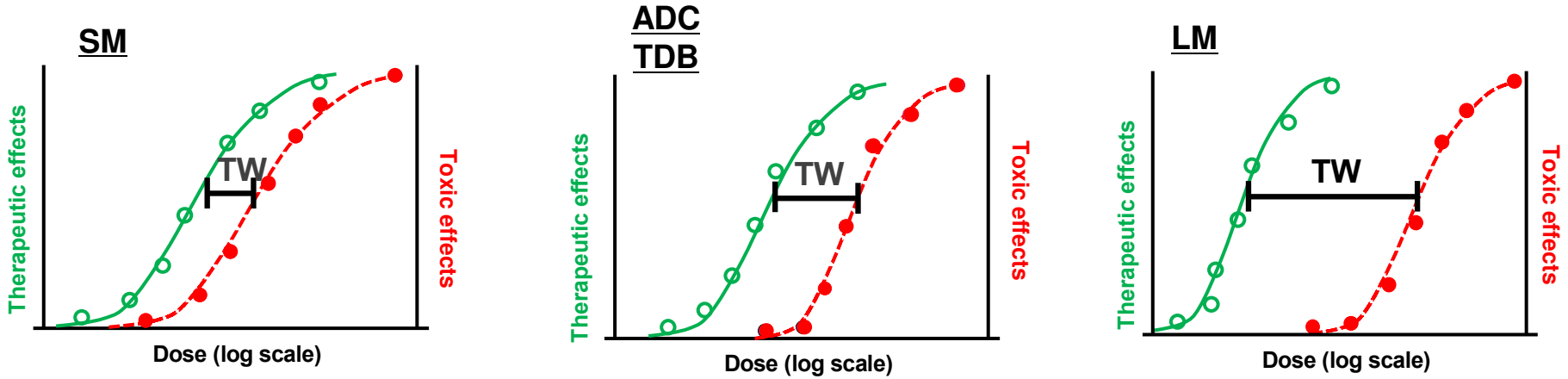
- Challenges and Opportunities for Dose Optimization in Oncology
- Modeling-Based Approaches for Dose Selection (Registrational Trial)
  - PERJETA® pertuzumab for injection mAb, solid tumor *(population PK & exposure target)*
  - Lunsumio™ TDB, heme *(QSP, RO-based exposure-response)*
  - Ipatasertib SM, solid tumor *(biomarker PK/PD, exposure-response, clinical utility index)*
- Summary

PD – pharmacodynamics, PK – pharmacokinetics, QSP – quantitative system pharmacology, RO – receptor occupancy, SM – small molecule, TDB – T-cell dependent bispecifics, TI – therapeutic window

Challenges and Opportunities for Dose Optimization in Oncology

- Therapeutic window
- Translation from preclinical-to-clinical and early-to-late clinical
- Phase 1 in patients – both challenge and opportunity
- Biomarkers (target, pathway, disease; circulating/biopsy; imaging/digital)
- PK confounding
- Immunogenicity (ADA)
- Confounding factors in patients
- Confounding of dose reduction, hold, missing
- Dose by body weight or flat dosing, administration route
- Combinations (PK DDI, efficacy, safety)
- Special population (pediatric, geriatric, renal/liver dysfunction, race/ethnicity)

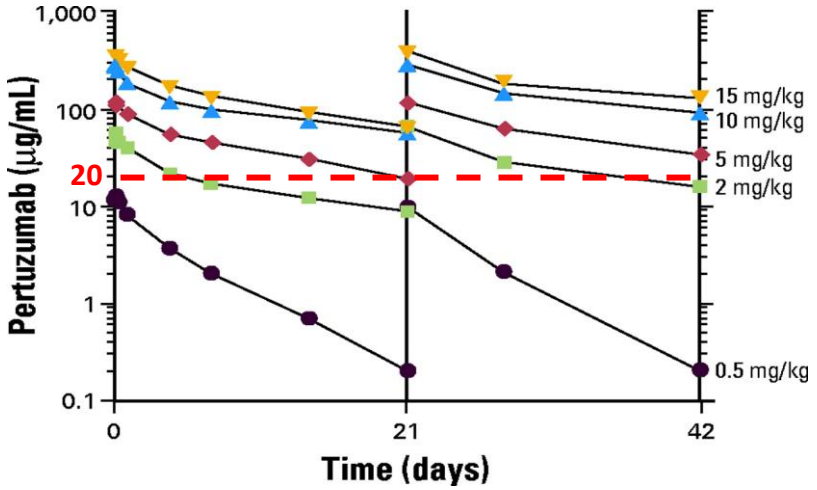


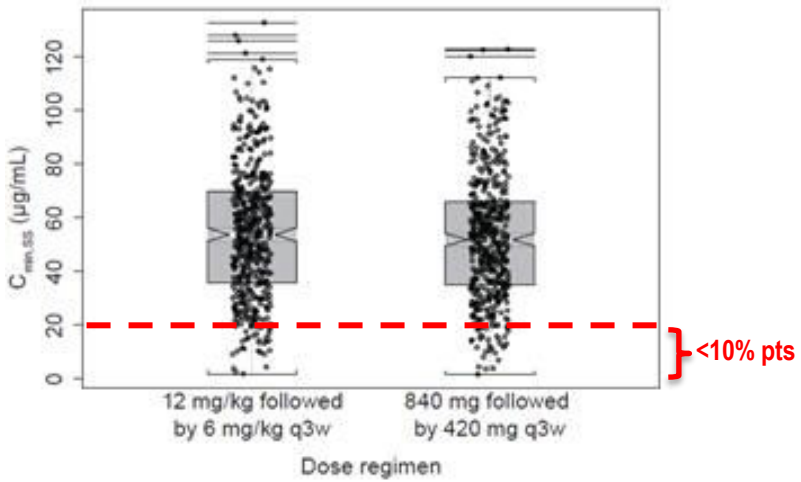


ADA – anti-drug antibody, ADC – antibody-drug conjugate, DDI – drug-drug interaction, LM – large molecule, PK – pharmacokinetics, SM – small molecule, TDB – T-cell dependent bispecifics, TW – therapeutic window

Case Example #1

Pertuzumab Dose Selection Based on Clinical PK and M&S





Trial simulation based on population PK model

- Trough concentration >20 µg/mL target
  - Loading dose for Cycle 1 C_{trough} >20 µg/mL
- Dose to be in linear range of PK: 2~15 mg/kg
  - Saturate receptor-mediated clearance
  - Reduce clearance variability
- Low incidence of immunogenicity
- No effect of body weight on PK
- **840 mg loading dose followed by 420 mg Q3W maintain trough concentrations above the 20 µg/mL target in >90% of patients in all cycles based on M&S**

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12.3 Pharmacokinetics

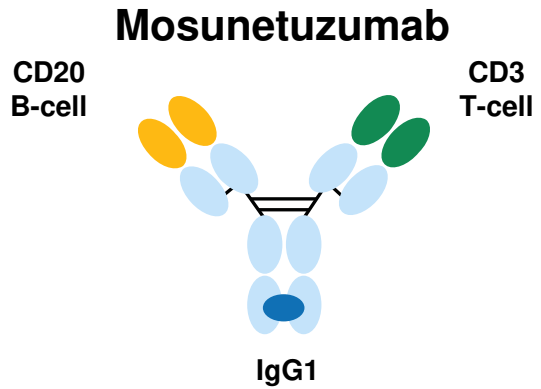
Pertuzumab demonstrated linear pharmacokinetics at a dose range of 2 – 25 mg/kg. Based on a population PK analysis that included 481 patients, the median clearance (CL) of pertuzumab was 0.24 L/day and the median half-life was 18 days. With an initial dose of 840 mg followed by a maintenance dose of 420 mg every three weeks thereafter, the steady-state concentration of pertuzumab was reached after the first maintenance dose.

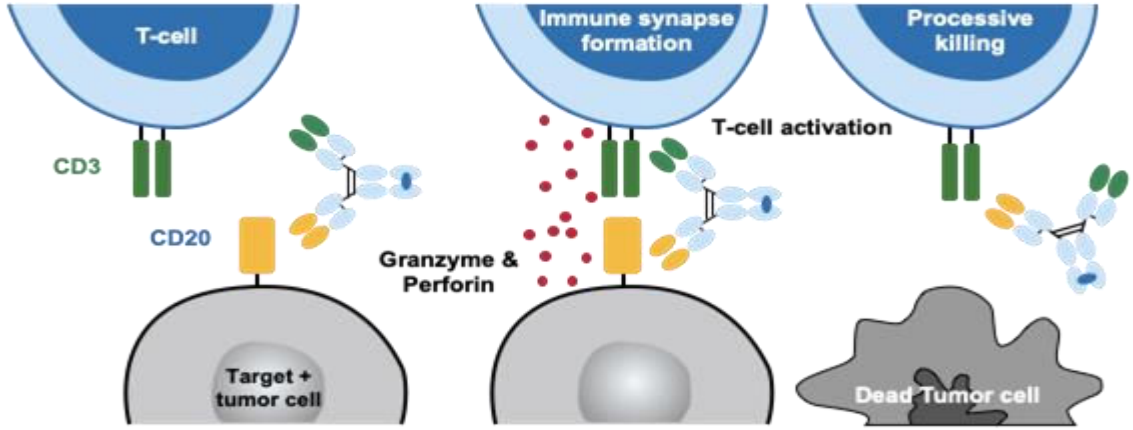
The population PK analysis suggested no PK differences based on age, gender, and ethnicity (Japanese vs. non-Japanese). Baseline serum albumin level and lean body weight as covariates only exerted a minor influence on PK parameters. Therefore, no dose adjustments based on body weight or baseline albumin level are needed.

Garg A et al. Cancer Chemother Pharmacol. 74(4):819-29 (2014)

Case Example #2

Mosunetuzumab Dose Selection Based on Mechanism-Based Model-Informed Strategy





Lunsumio

Mosunetuzumab is a CD20/CD3 Bispecific Antibody for B-cell Malignancies:

- PK properties enable q3w dosing
- Does not require *ex-vivo* T-cell manipulation
- Off the shelf, readily available treatment

Mechanism of Action:

- Redirects T cells to engage and eliminate malignant B cells
- Potent tumor killing as single agent

Development Challenges:

- On-target acute toxicity for T-cell directing therapies
  - Cytokine release syndrome (CRS) occurs acutely following first doses and dissipates with time
- Challenges in dose finding
  - Complex target engagement
  - No simple PK target based on preclinical data
  - Phase I dose-response relationship was confounded by patients' prior lines of therapies and on-board residual rituximab

Budde LE et al. J Clin Oncol. 40(5):481-491 (2022)
Budde LE et al. Lancet Oncol. 23(8):1055-1065 (2022)

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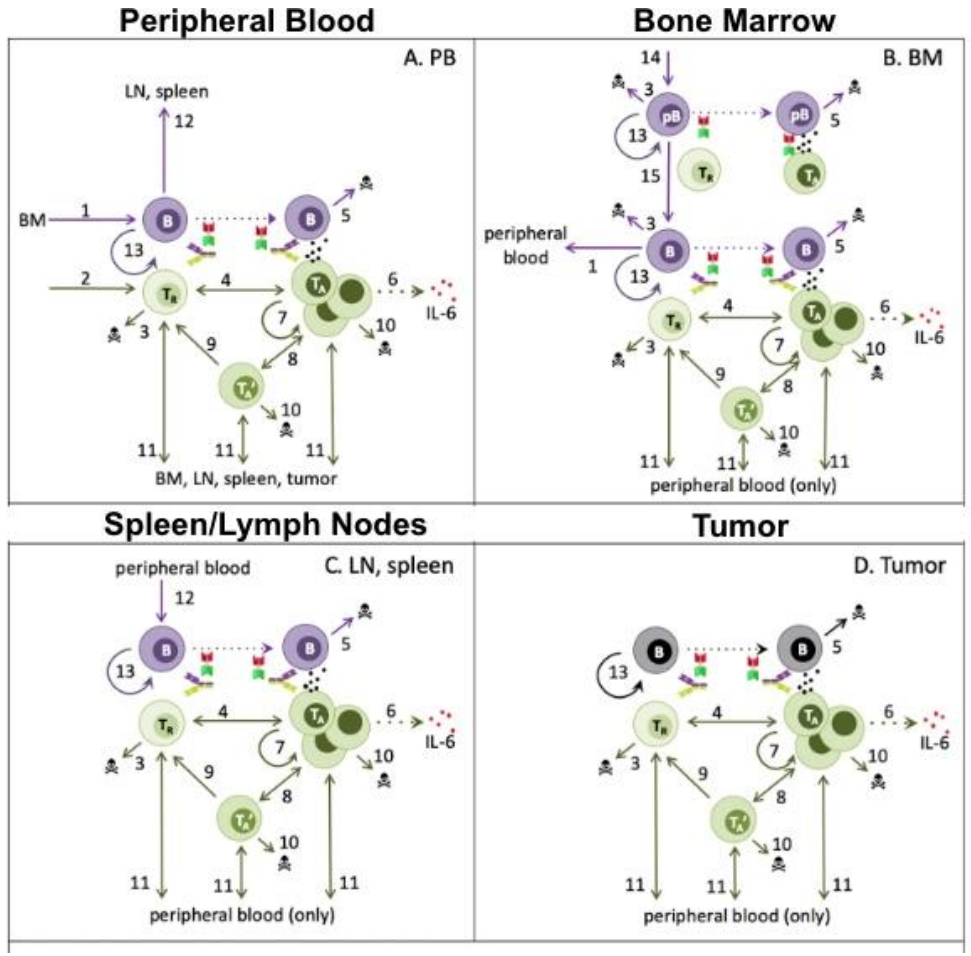
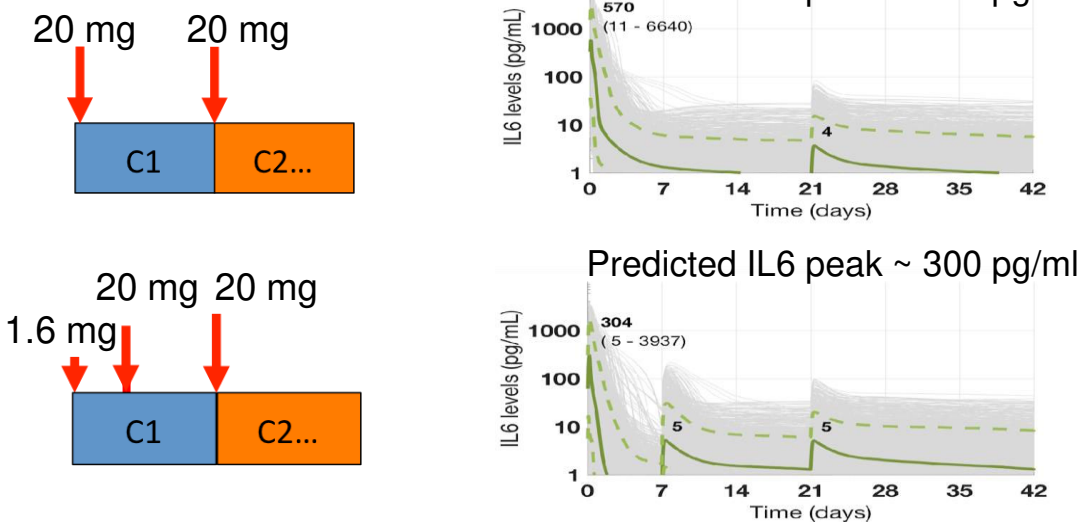
Case Example #2

Mosunetuzumab Step-Up Dosing Strategy Supported by QSP Modeling

QSP Modeling to Describe IL6

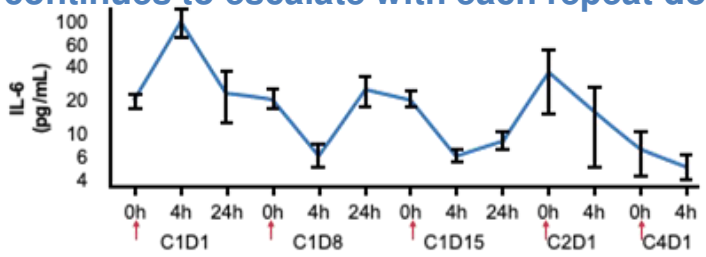


Model-Predicted IL6 Following Fixed Dosing vs. Step-up Dosing Regimens



Clinical PD Consistent with Pharmacological Expectations:

Maximal IL6 elevation occurs after C1D1 dose even though PK continues to escalate with each repeat dosing



Hosseini I, et al. NPJ Systems Biology and Applications. 6: 28 (2020); Susilo ME, et al. Clinical and Translational Science. 16: 1134-48 (2023)

Case Example #2

Characterizing the Driver (RO) for Mosunetuzumab Clinical Response

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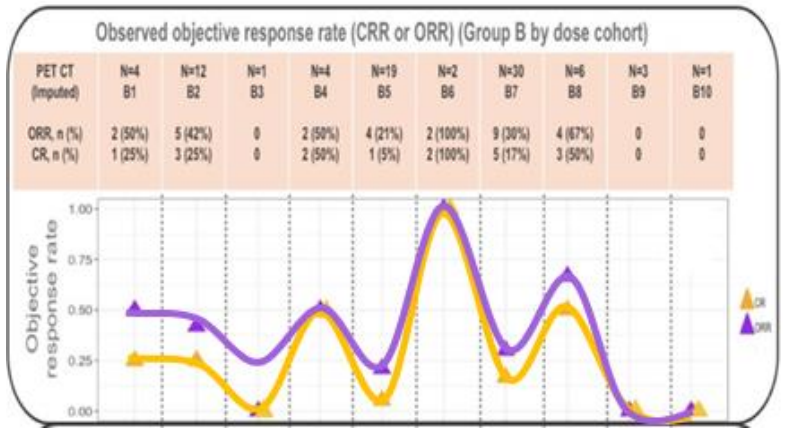
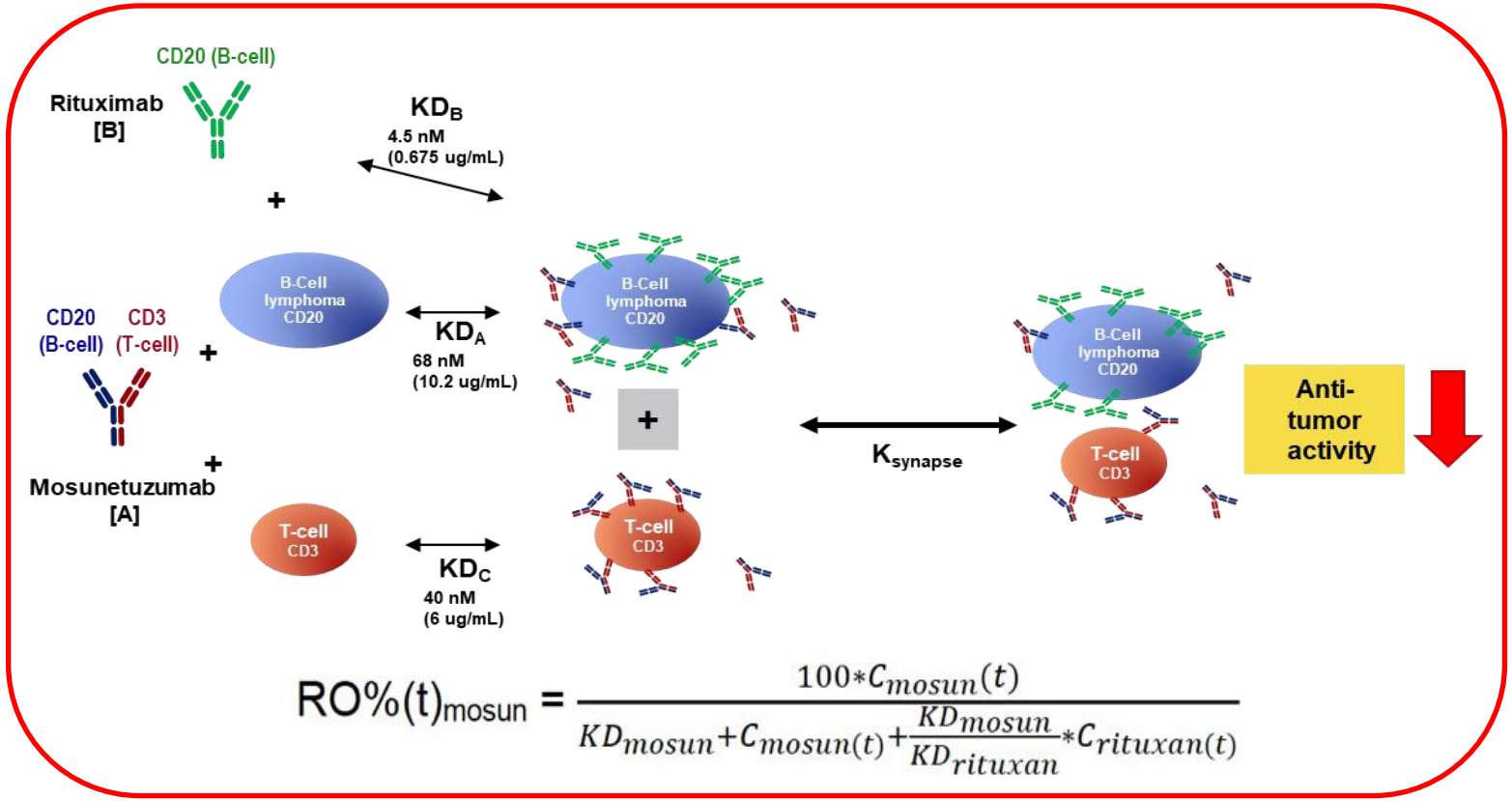
Dose → **PK** → **Receptor Occupancy** → **Clinical Response**



Clinical dose-response un-informative:
1) small sample size, 2) confounded



Li C-C, et al. Blood. 134 Suppl 1: 1285 (2019); Modified from: Chi-Chung Li, ACoP (2019), Brendan Bender, ACoP (2020), Chi-Chung Li, Certara Webinar (2021)

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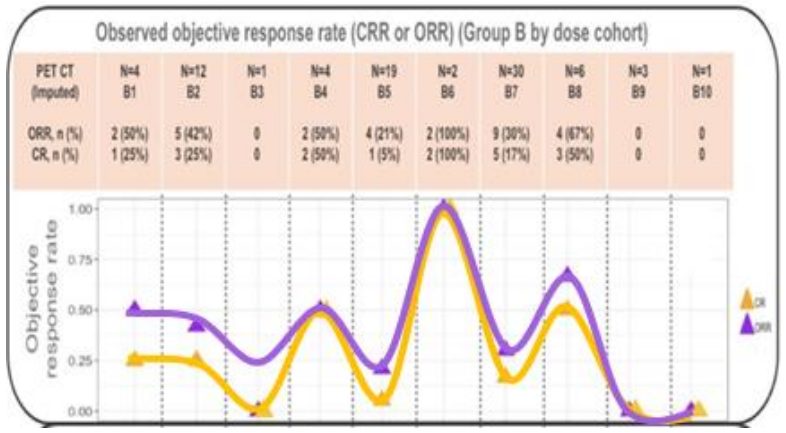
Case Example #2

Characterizing the Driver (RO) for Mosunetuzumab Clinical Response

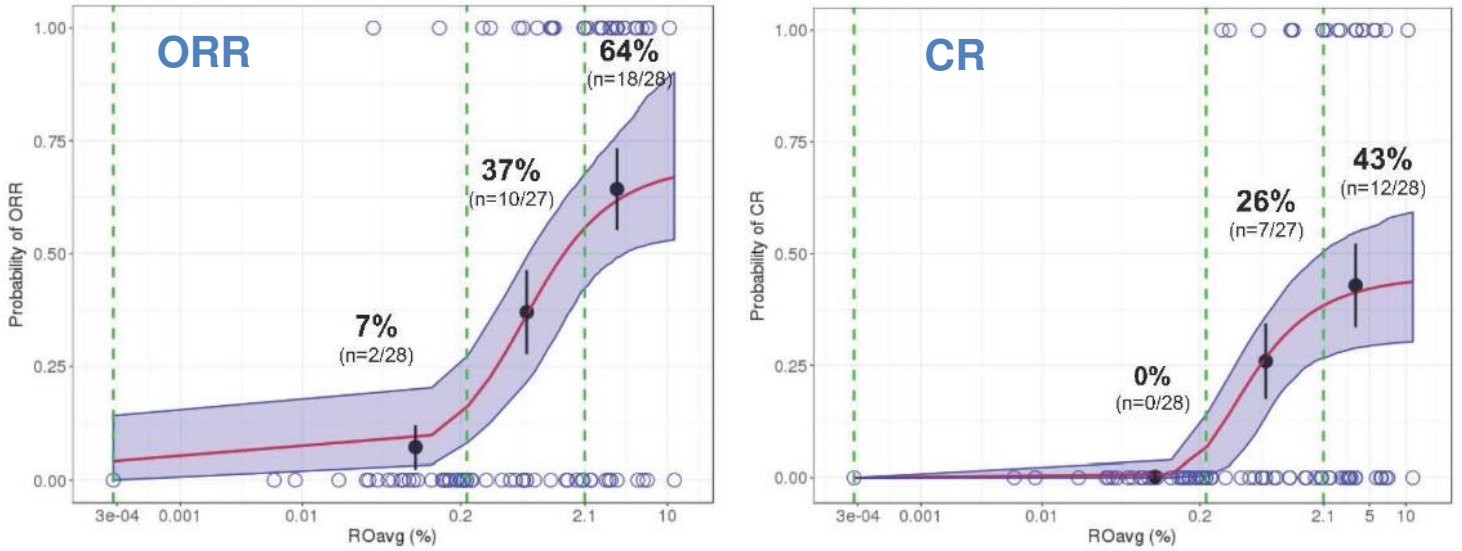
Dose → PK → **Receptor Occupancy** → Clinical Response

Lunsumio



Clinical dose-response un-informative:
1) small sample size, 2) confounded

RO-Based Exposure-Response in aNHL



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Case Example #2

Model-Based Dosing Strategy Expands the Therapeutic Window and Accelerates Mosunetuzumab Development

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Table 1. Recommended LUNSUMIO Dose and Schedule (21-Day Treatment Cycles)

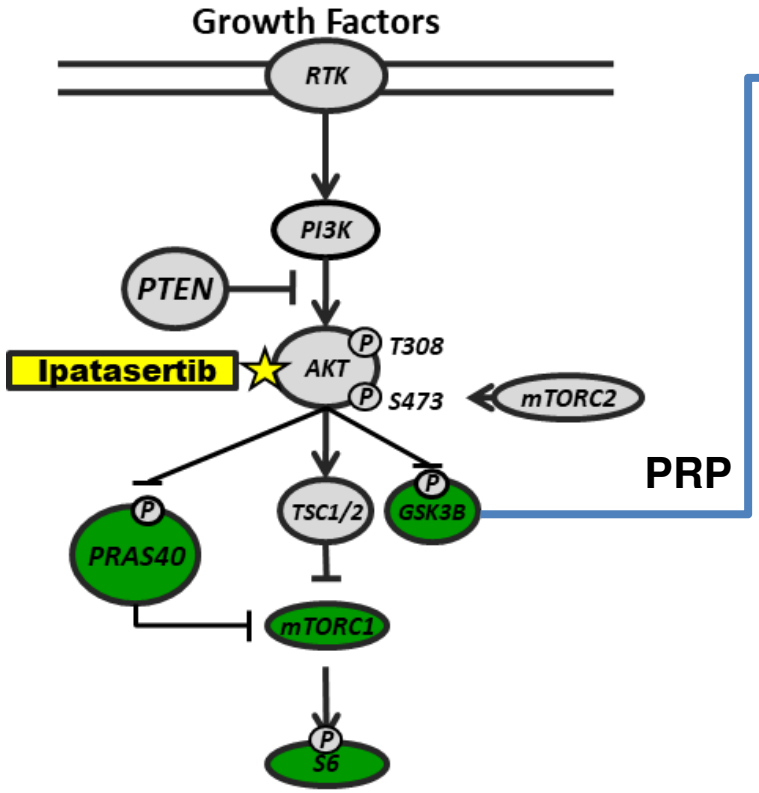
Day of Treatment		Dose of LUNSUMIO	Rate of Infusion
Cycle 1	Day 1	1 mg	Administer over a minimum of 4 hours.
	Day 8	2 mg	
	Day 15	60 mg	
Cycle 2	Day 1	60 mg	Administer over 2 hours if infusions from Cycle 1 were well-tolerated.
Cycles 3+	Day 1	30 mg	

Li C-C, et al. Blood. 134 Suppl 1: 1285 (2019); Modified from: Chi-Chung Li, ACoP (2019), Brendan Bender, ACoP (2020), Chi-Chung Li, Certara Webinar (2021)

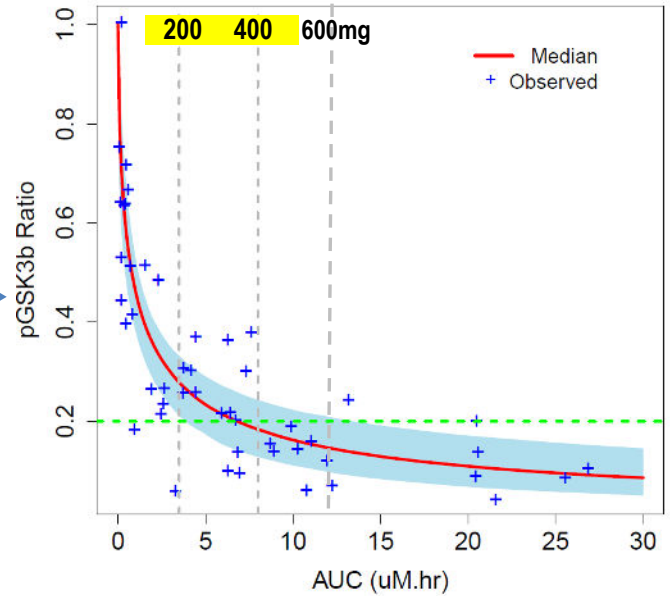
Case Example #3

Ipatasertib Phase 2 Dose Selection: Biomarker PK/PD

- The PI3K/AKT pathway is central for cancer cell growth and survival
- Ipatasertib (GDC-0068) is a potent, oral, ATP-competitive AKT inhibitor
- Optimal biological dose selected for Phase 2 based on target specific biomarker response and PK/PD



PRP



Ipatasertib 2L mCRPC Phase 2 (A.MARTIN) Study Design

n= 80/arm

Randomize 240 pts 1:1:1 stratify:
- Prior treatment with enzalutamide (Y/N)
- Progression Factor (PSA only vs other)
- # prior chemotherapies for metastatic disease (1 vs >1)

- Abiraterone* + GDC-0068 400 mg QD
- Abiraterone* + GDC-0068 200 mg QD
- Abiraterone* + Placebo (1:1 ratio to 400mg QD/placebo and 200mg QD/placebo groups)

Comparison 1

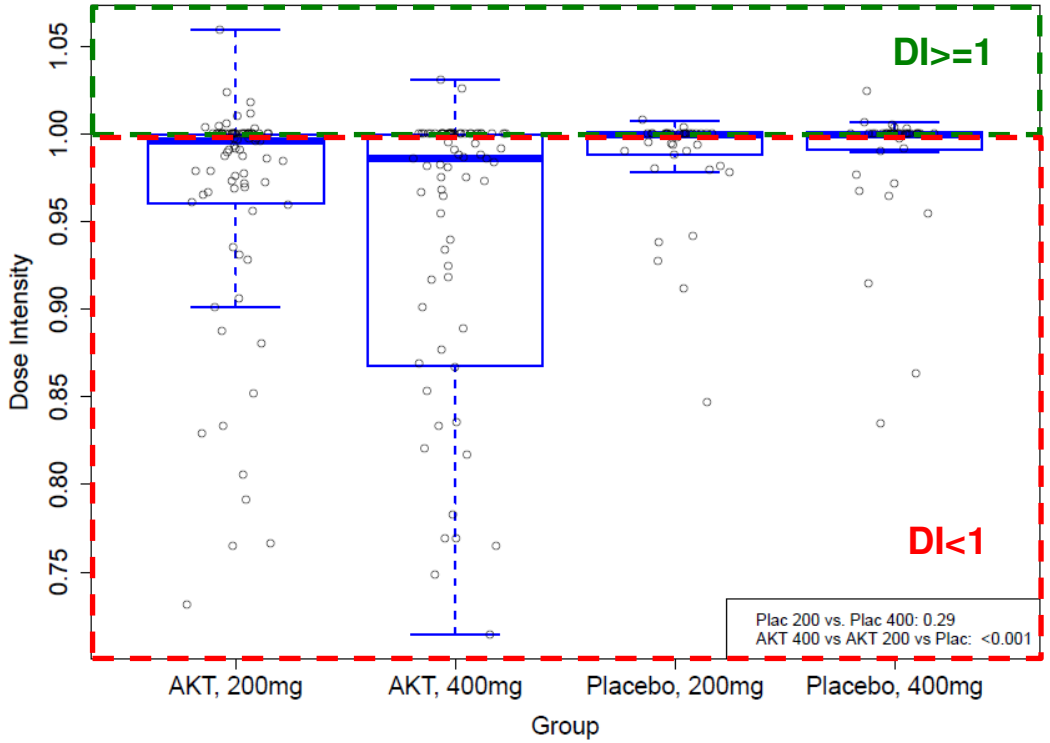
Comparison 2

*Abiraterone (1000mg) and prednisone/prednisolone (5mg BID). Assignment to the 200 mg/placebo or 400mg/placebo group is known, treatment is blinded

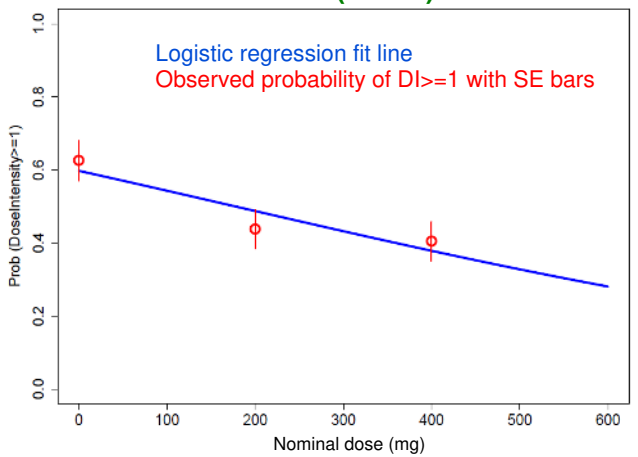
Yan Y et al. CCR (2013)

Case Example #3

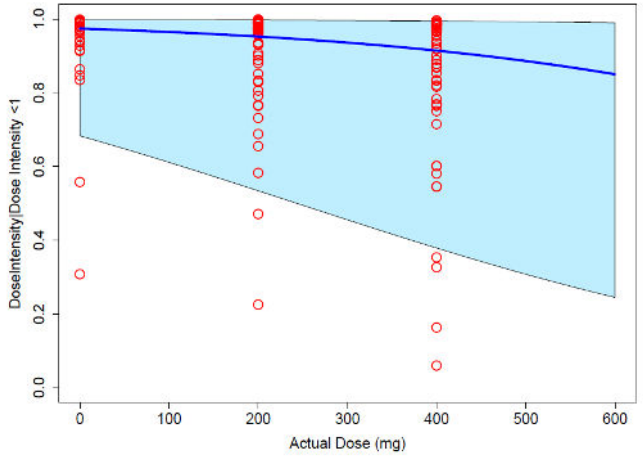
Ipatasertib Phase 3 Dose Selection: Account for Confounding of Dose Reduction



DI Model 1: Prob(DI>=1) vs. Dose



DI Model 2: DI distribution in DI<1 population

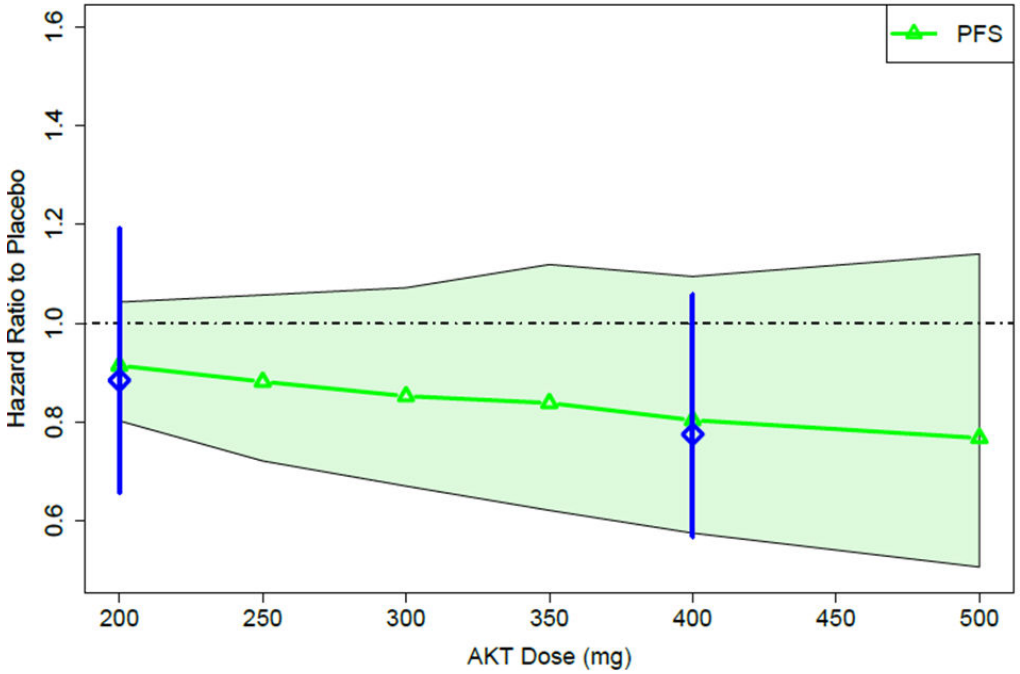


Zhu R et al, CPT Pharmacometrics Syst Pharmacol. 8:240–248 (2019)

Case Example #3

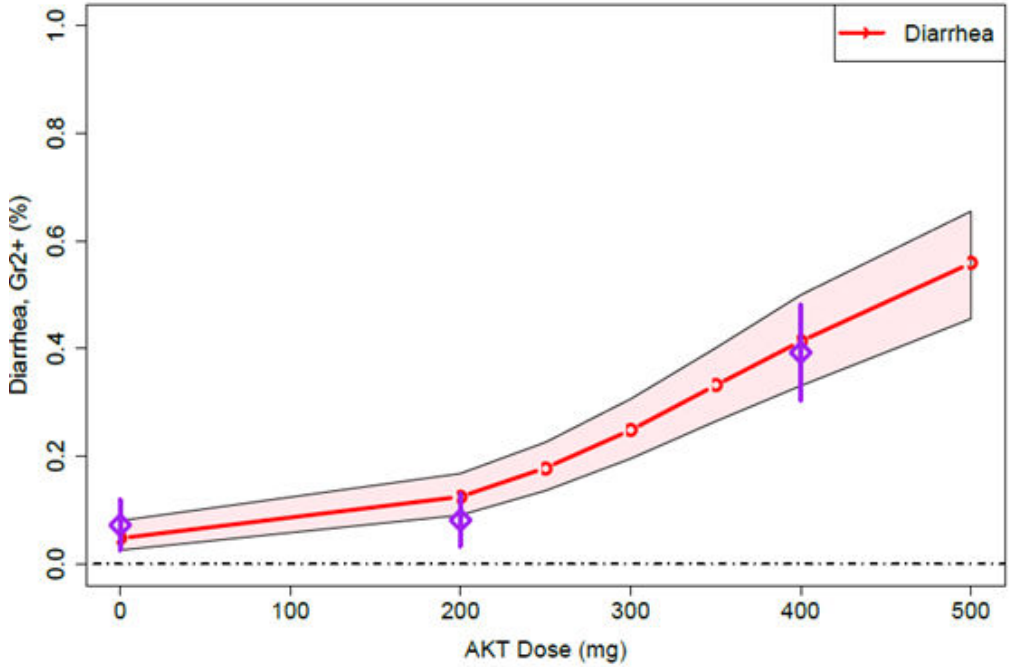
Ipatasertib Phase 3 Dose Selection: Exposure-Response Analyses

Exposure-Efficacy: radiographic PFS



Dose-rPFS projections from Cox regression model of exposure-rPFS coupled with dose intensity model

Exposure-Safety: Gr2+ Diarrhea



Dose-safety projections from logistic regression model of exposure-safety coupled with dose intensity model (Gr2+ diarrhea*)

**Similar analyses conducted for: Gr3+ diarrhea, Gr2+ rash, Gr3+ rash*

Zhu R et al, CPT Pharmacometrics Syst Pharmacol. 8:240–248 (2019)

Case Example #3

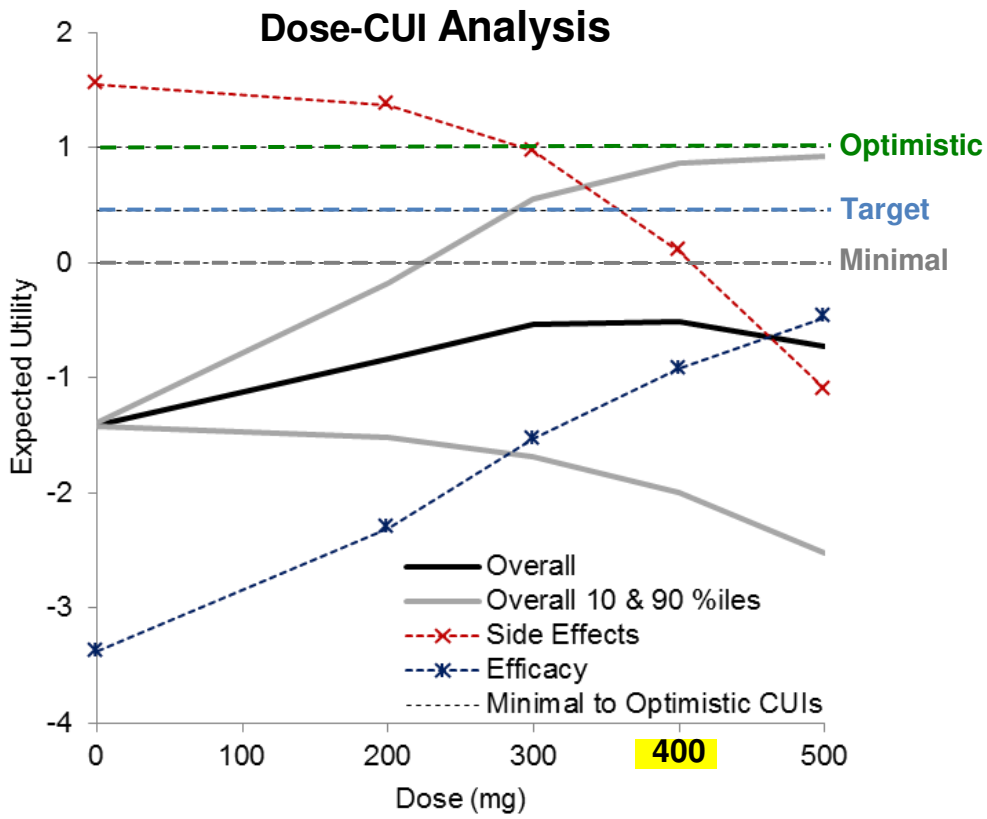
Ipatasertib Phase 3 Dose Selection: Clinical Utility Index

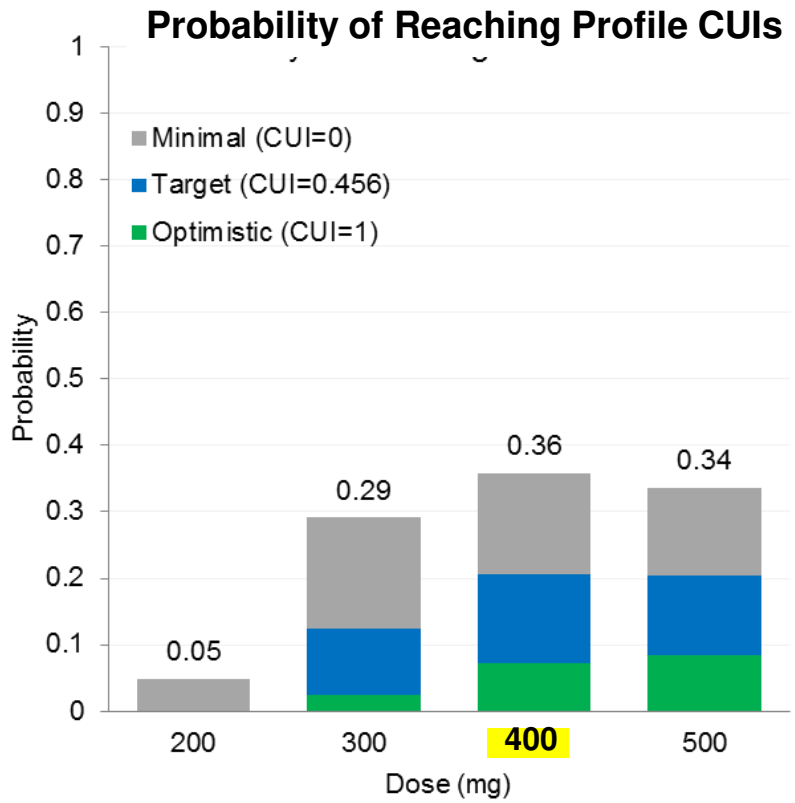
- **Benefit-risk analysis via exposure-response and clinical utility index (CUI) approaches indicated that Ipatasertib 400 mg QD has the highest probability of achieving the minimal Product Profile (PP) with best benefit/risk balance, which was thus selected for Phase 3**

Optimistic, Target, and Minimal Product Profile (PP)
(Scenario #4)

- rPFS HR (weight: 0.6)
  - 0.65 0.7 0.73
- G2+ Diarrhea (weight: 0.3)
  - 25% 35% 45%
- G2+ Rash (weight: 0.1)
  - 6% 12% 18%

4 scenario tested varying Efficacy & Safety criteria & weight





Zhu R et al, CPT Pharmacometrics Syst Pharmacol. 8:240–248 (2019)

Summary

- **Dose optimization strategy should be seamlessly integrated into clinical development plan across life-cycle (Dosing CDP)**
  - **Multiplicative considerations: molecule mode of action, indication specific efficacy need, patient tolerance/quality-of-life, CMC feasibility, cost and speed**
  - **Cohesive cross-functional partnership is essential**
- **Modeling-based approaches play an integral role in drug development and dose selection**
  - **Effectively integrate totality of evidence (PK, biomarker, efficacy, safety)**
  - **Leverage knowledge/data across molecules**
  - **Provide mechanistic insight and dosing projections**
  - **Guide study design and early go/no-go decision making potential**
  - **Wide range of modeling approaches are available (empirical, mechanistic, artificial intelligence). Selection of approach should be science/data driven and fit-for-purpose.**

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Lunsumio

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Amit Garg
Bert Lum
Angelica Quartino

Ipatasertib

Nageshwar Budha
Qi Liu
Luna Musib
Bill Poland
Russ Wada
Rui Zhu

2022 Offsite (Monterey Bay, CA)

Amita Joshi
Chunze Li
Samantha Roberts

Genentech Clin Pharm Team
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External Collaborators
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Patients

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Using Pharmacokinetic-Pharmacodynamic Modeling and Simulation to Understand Dose and Exposure-Response Relationships for Adverse Reactions

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Enhanced Pharmacodynamics, LLC, Buffalo, NY

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Disclosure Information

Scott Van Wart

I have the following relevant financial relationships to disclose:

I am the founder and Chief Scientific Officer of Enhanced Pharmacodynamics, LLC (ePD)

ePD consults with or has received research funding from various companies including: Adagio, Arcturus, AstraZeneca, Biogen, Boston Biomedical, Daiichi Sankyo, EMD Serono, Elevar Therapeutics, Eli Lilly, Enlaza Therapeutics, Enliven Therapeutics, EUSA, Genentech, Genmab, Glenmark, GSK, Halozyme, ICPD, Ionis Pharmaceuticals, Ironwood Pharmaceuticals, Jazz Therapeutics, Leyden Labs, Merck, Nektar Therapeutics, Nurix Therapeutics, Nutcracker Therapeutics, Oncoceutics, Praxis Therapeutics, PharmaEssentia, Roche, Sarepta Therapeutics, Seagen, Servier, Takeda, Teva, Tubulis, UCB Pharma, Veradermics, Via Nova, Windtree Therapeutics, and Zogenix.

Introduction

- Exposure-response PK-PD analyses for safety are a critical component of model-based drug development
  - Used to provide decision-support criteria initially to guide dose escalation and later optimization during Phase 1 of development and to identify the RP2D
  - Safety AE and efficacy PK-PD models can be linked together to determine realistic patient dropout rates when performing simulations of ORR, OS and PFS
  - Can be used to understand potential impact of combination therapy or prophylactic use of other concomitant medications (e.g., GCSF) to counteract side effects
- This presentation will provide a few examples of how we have been asked to use PK-PD modeling and simulation for safety AE to help support dose regimen selection for clinical trials

Example 1:

Combining Logistic Regression Analysis of Safety AE Data with PK-PD Model for Tumor Growth to Optimize Dose

Review Totality of Safety AE Data

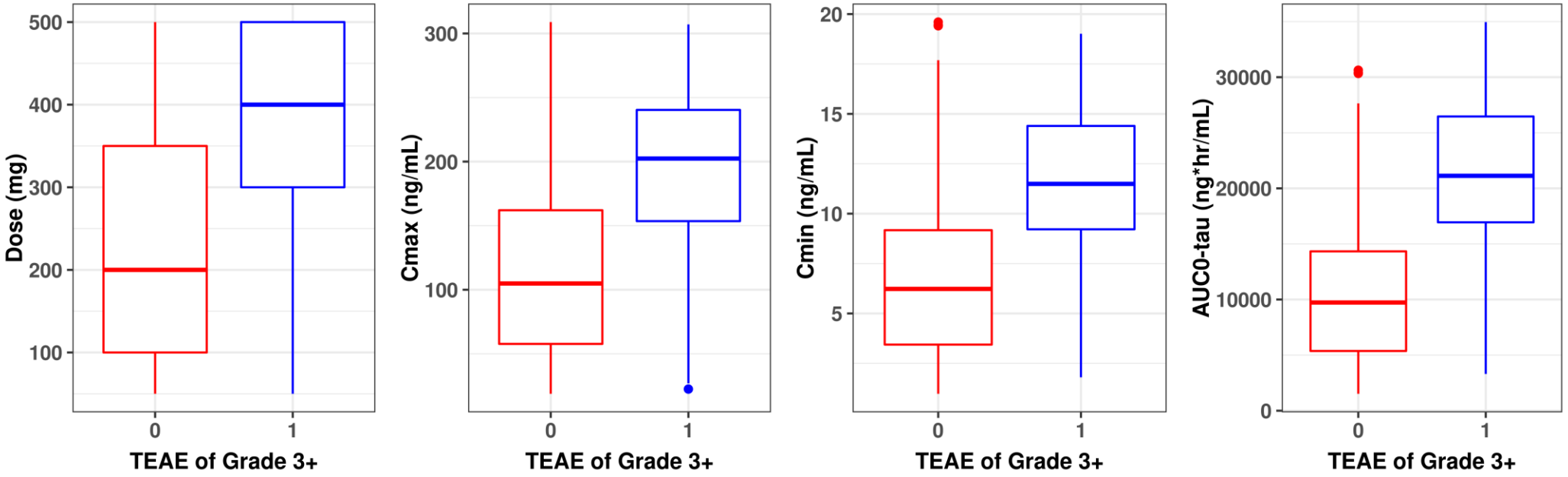
- Review totality of treatment-emergent AE (TEAE) classification data across clinical trials, and if possible by Body System / Organ Class or Preferred Term

AE Classification	All Clinical Studies Combined (N=1000)		
	No. Events	No. Patients	Rate
All TEAE (any grade)	1623	797	79.7%
All TEAE of Grade 3+	324	297	29.7%
TEAE of Blood and Lymphatic System Disorders (any grade)	412	375	37.5%
TEAE of Blood and Lymphatic System Disorders (Grade 3+)	212	115	11.5%
TEAE of Thrombocytopenia (any grade)	512	285	28.5%
TEAE of Grade 3+ Thrombocytopenia	112	61	6.1%
TEAE of Neutropenia (any grade)	217	179	17.9%
TEAE of Grade 3+ Neutropenia	84	54	5.4%

Note: Rate is the percentage of the population with at least one TEAE of the given category

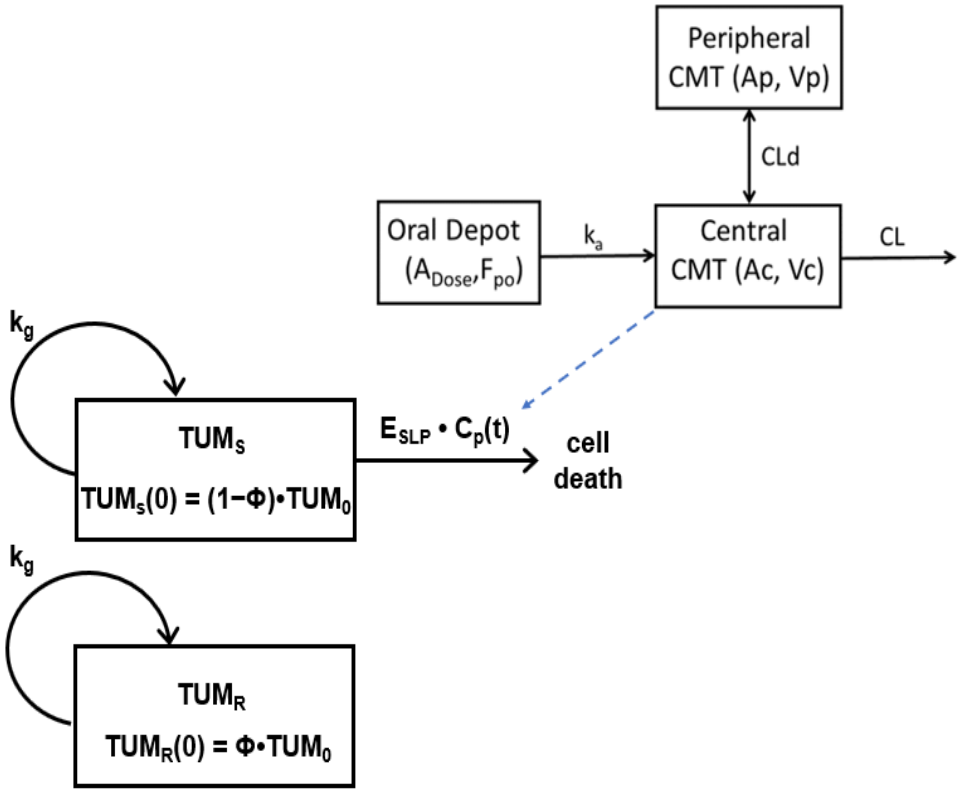
Exploratory PK-PD Analysis for Safety AE Data

- Boxplots can be used to show dose- and exposure-response relationships
- Examining different PK exposure metrics can help determine if there is signal and which metric might be most predictive prior to running the logistic regression

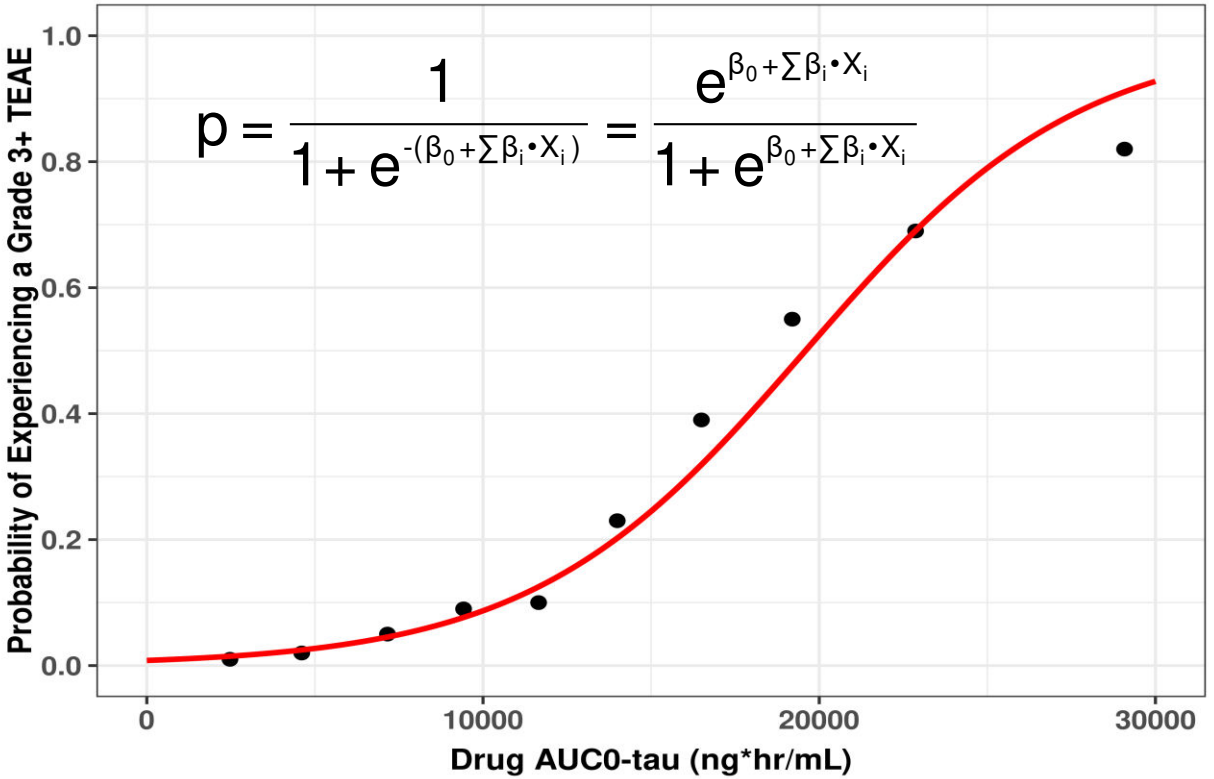


PK-PD Models for Efficacy and Safety AE

PK-PD Model for TGI

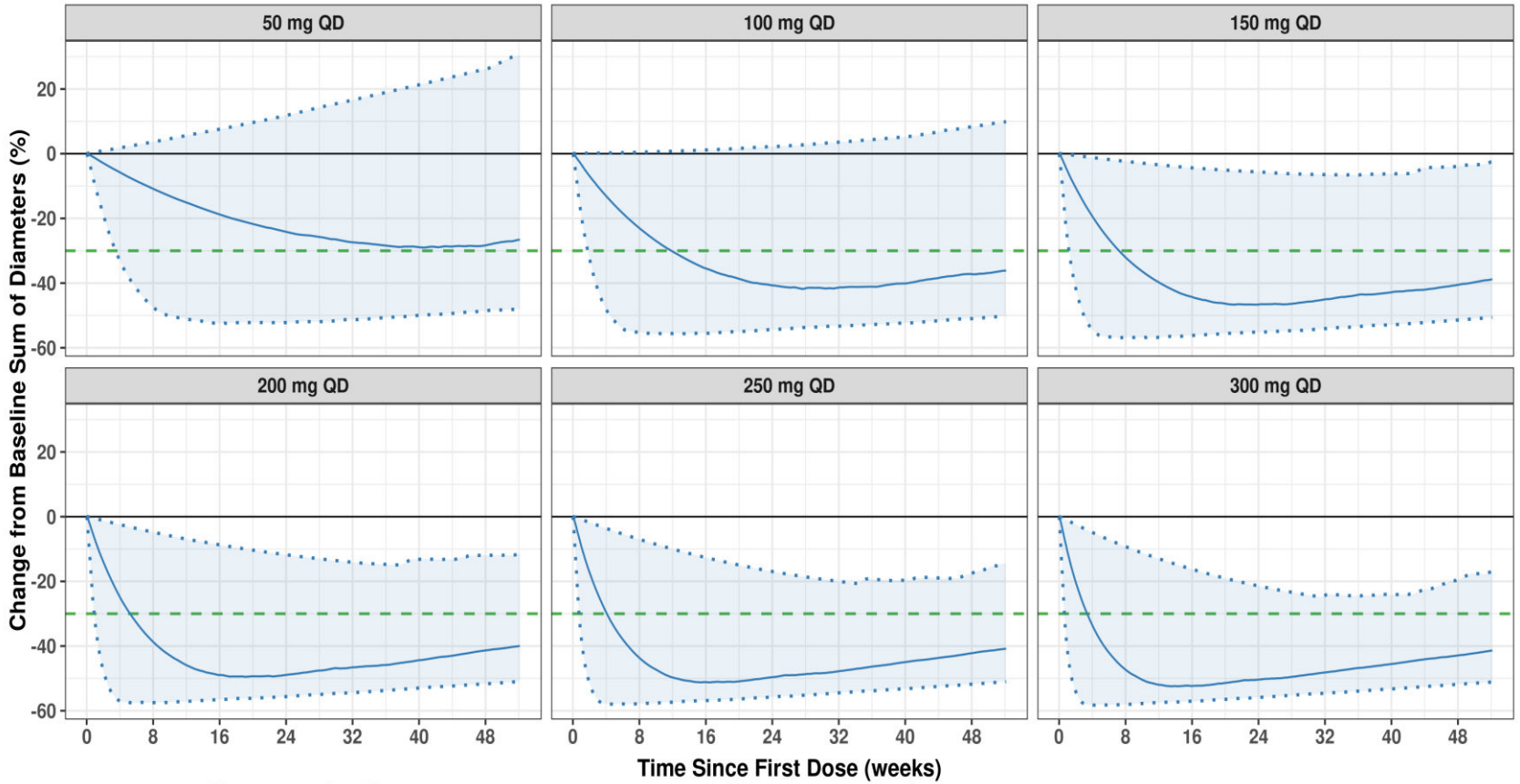


Logistic Regression PK-PD Model for Safety AE



Predicted probability of Grade 3+ TEAE plotted vs. observed incidence rate within each AUC quantile

PK-PD Simulations to Optimize Dose



Note: Median and 90% PI shown for 500 virtual subjects. Dashed green line denotes 30% decrease in sum of diameters relative to baseline (solid black line).

Dose (mg QD)	% of Simulated Subjects with Grade 3+ TEAE
50	5.2%
100	7.1%
150	12.4%
200	23.0%
250	36.5%
300	48.1%
350	62.9%
400	71.4%
450	75.5%
500	88.2%

Example 2:

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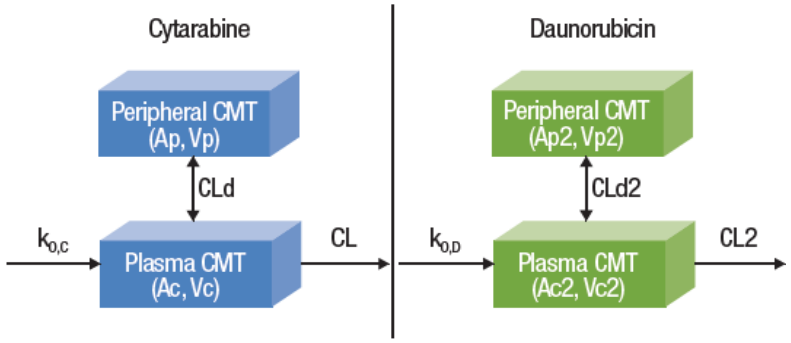
Longitudinal PK-PD Models for Myelosuppression to Inform Dose Regimen and Clinical Trial Design

Comparison of Myelosuppression for Vyxeos® vs. Standard 7+3 Therapy

- Vyxeos® (CPX-351) is a liposomal encapsulation of daunorubicin (44 mg/m^2) and cytarabine (100 mg/m^2) approved for newly diagnosed therapy-related AML or AML with myelodysplasia-related changes in adults and pediatric (aged ≥ 1 year) patients

- Population PK and PK-PD models were developed to characterize the impact of daunorubicin and cytarabine on ANC and platelets to compare liposomal Vyxeos® to standard 7+3 therapy

PK-PD Models for Myelosuppression for Vyxeos® vs. Standard 7+3 Therapy



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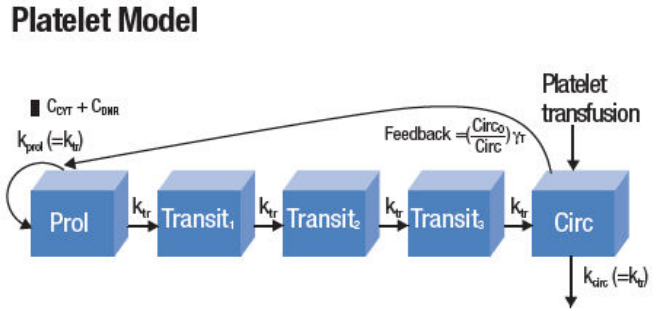
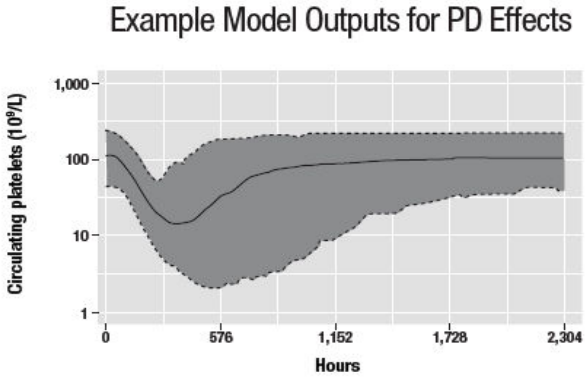


Friberg LE, et al. J Clin Oncol. 2002;20(24):4713-4721.



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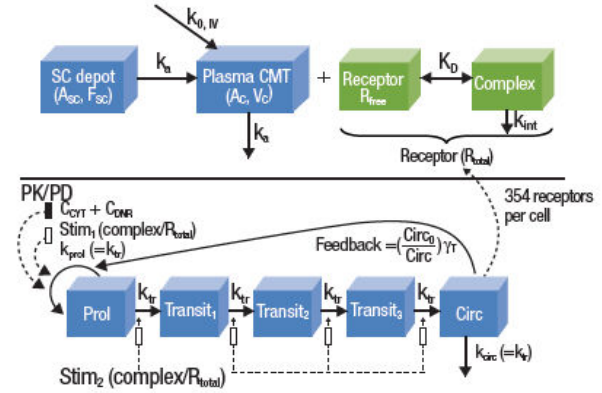
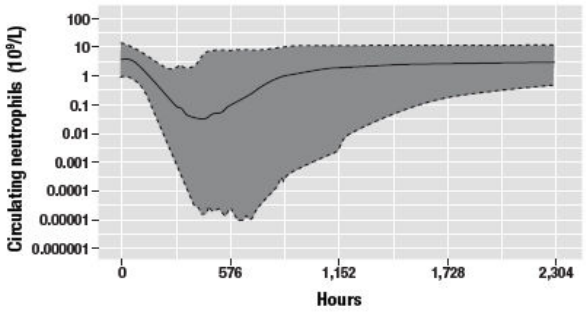


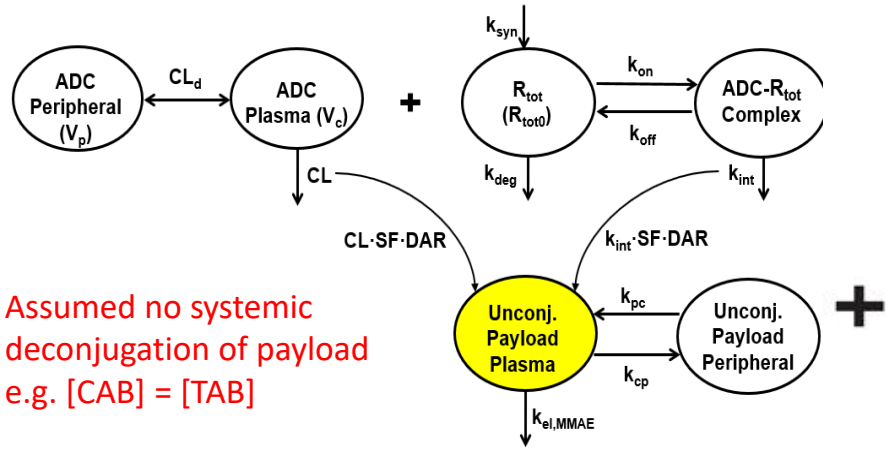
Melhem M, et al. Br J Clin Pharmacol. 2018;84(5):911-925.



Wang Q et al. S. Population PK-PD modeling of myelosuppression in patients with hematologic malignancies for CPX-351 and standard-of-care 7+3 therapy. Poster presented at 60th ASH meeting, 2018.

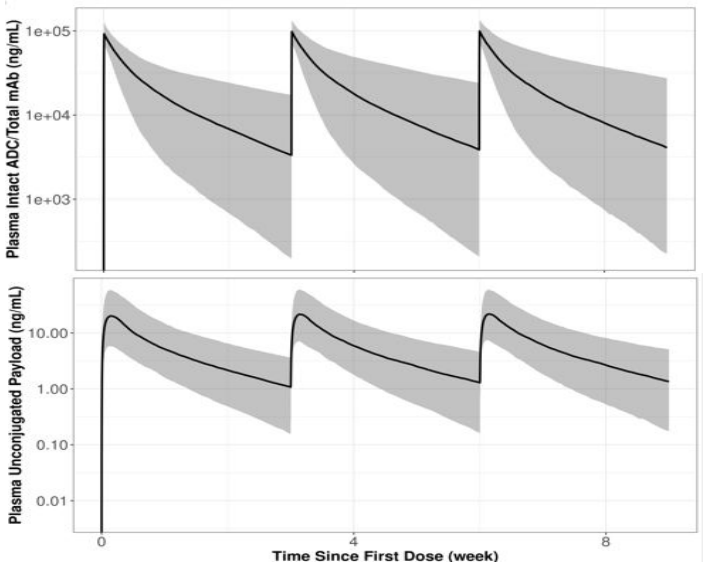
Cook S et al. Population PK-PD modeling of chemotherapy-induced neutropenia and thrombocytopenia in patients treated with CPX-351. Poster presented at ACoP9 meeting, 2018.

Application of PK-PD Models for Myelosuppression to an ADC



Assumed no systemic deconjugation of payload
e.g. [CAB] = [TAB]

ADC dosed Q3W x 3



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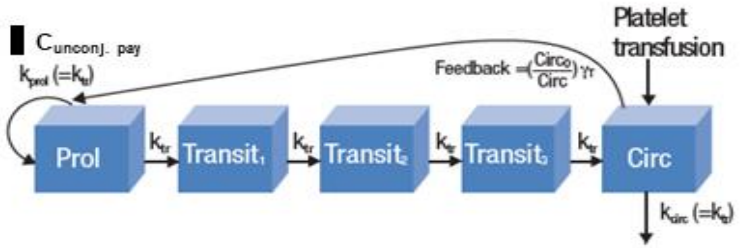
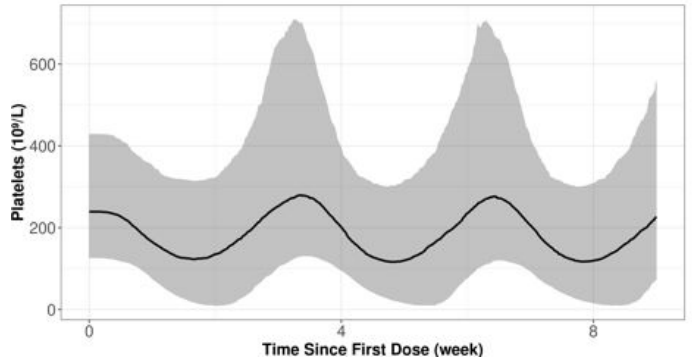
Platelet Model



ADC dosed Q3W x 3



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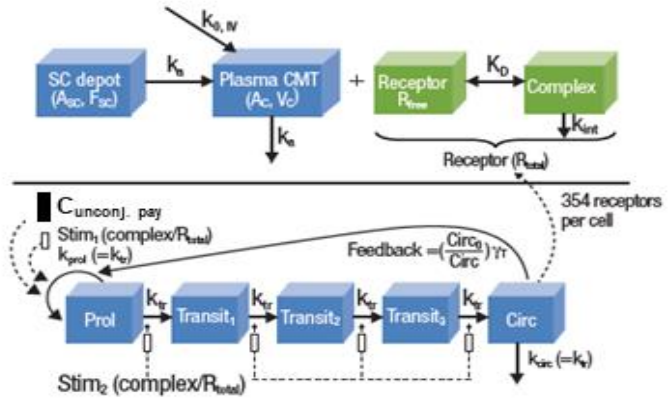
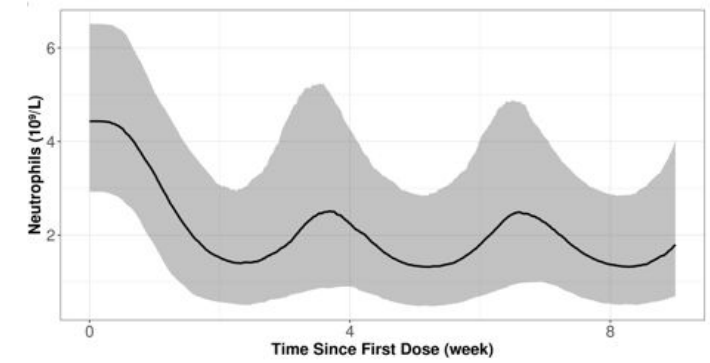
Neutrophil Model

GCSF PK with target-mediated disposition

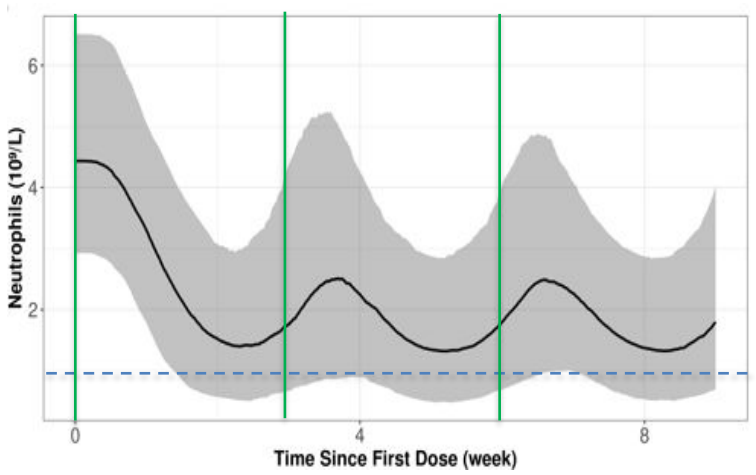


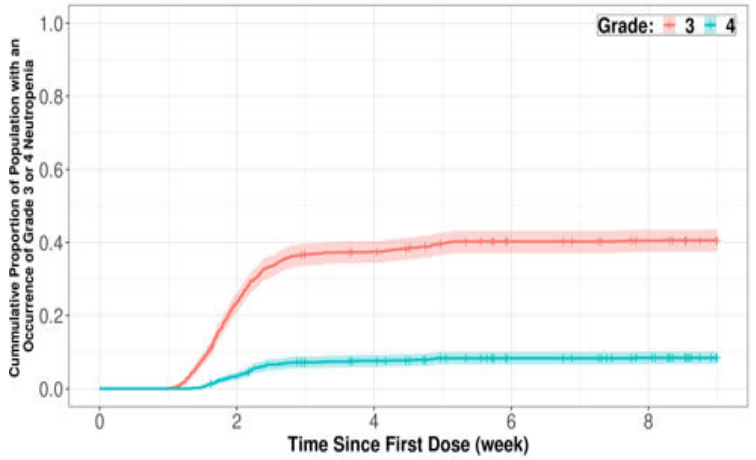
ADC dosed Q3W x 3



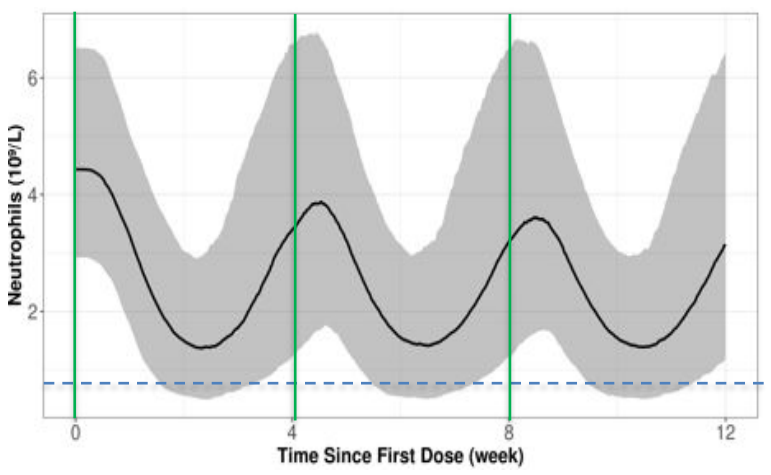
Simulations for Impact of Dose Interval and GCSF on ADC Dosing Regimen

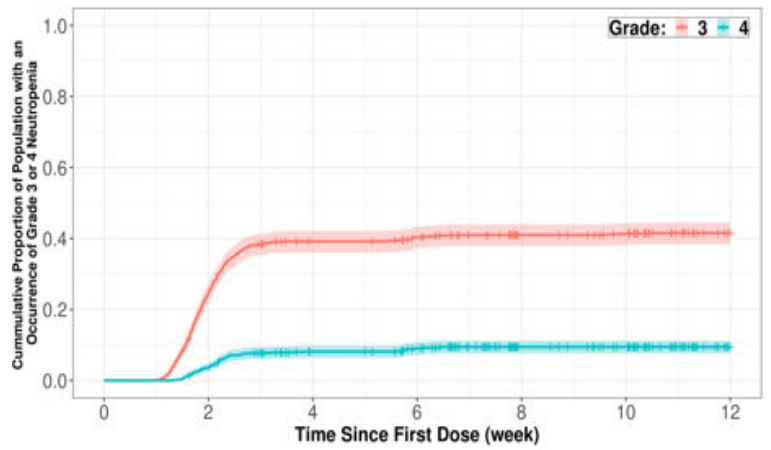
ADC dosed Q3W x 3



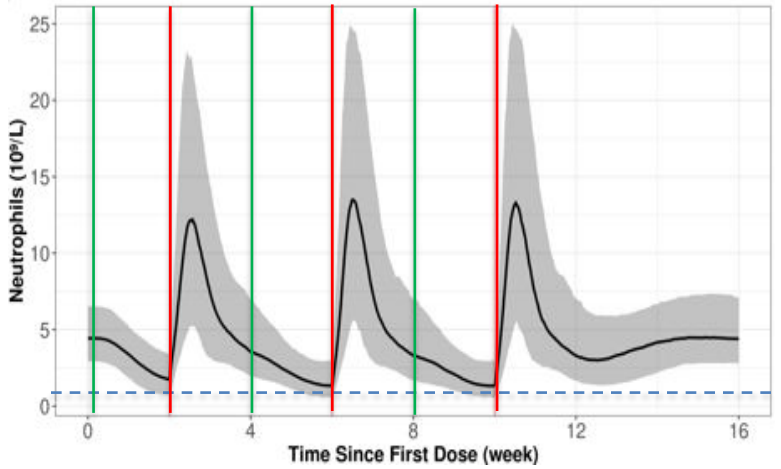


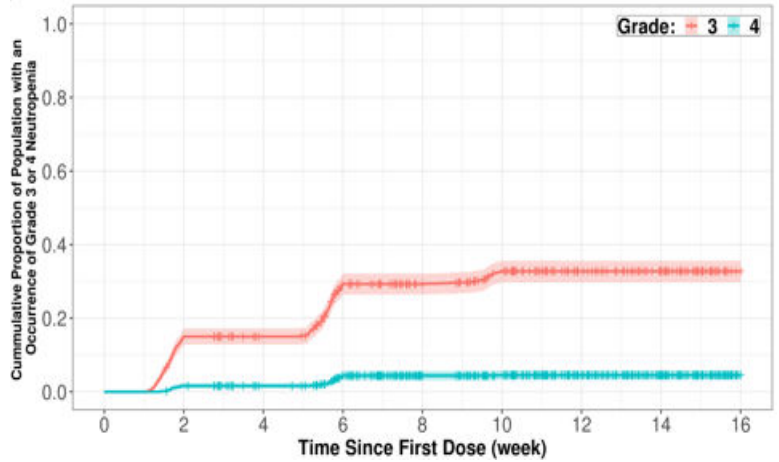
ADC dosed Q4W x 3





ADC dosed Q4W x 3, with 6 mg SC
Pegfilgrastim 2 weeks after each ADC dose





Example 3:

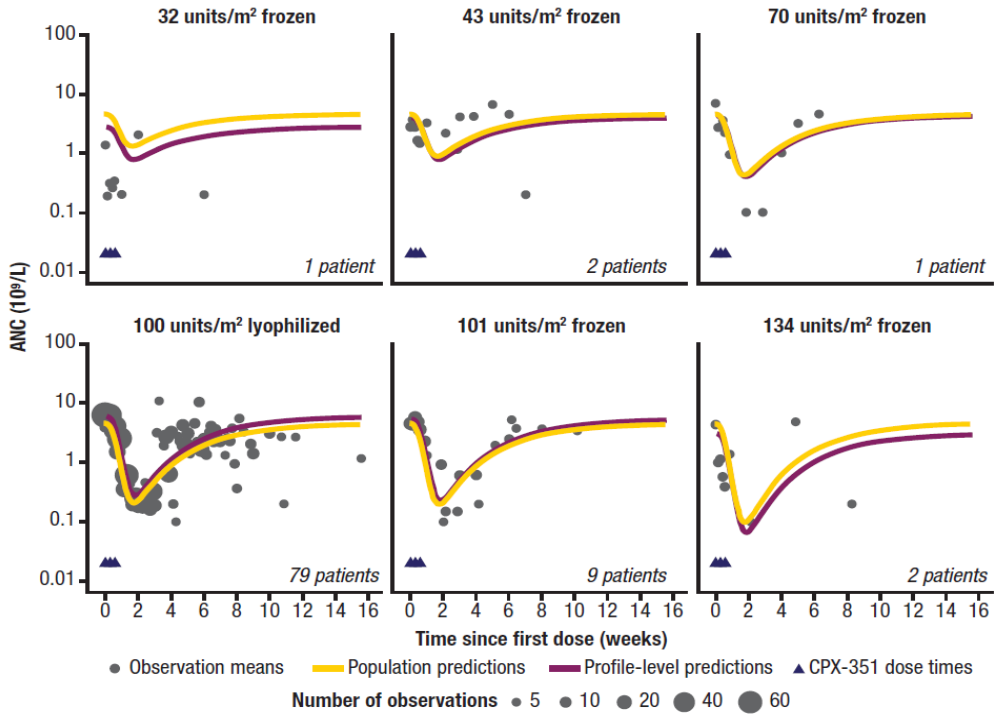
Predicting the Impact of Combination Therapy on Myelosuppression to Select Starting Dose for Clinical Trials

Impact of Combination Vyxeos® and Venetoclax on Myelosuppression

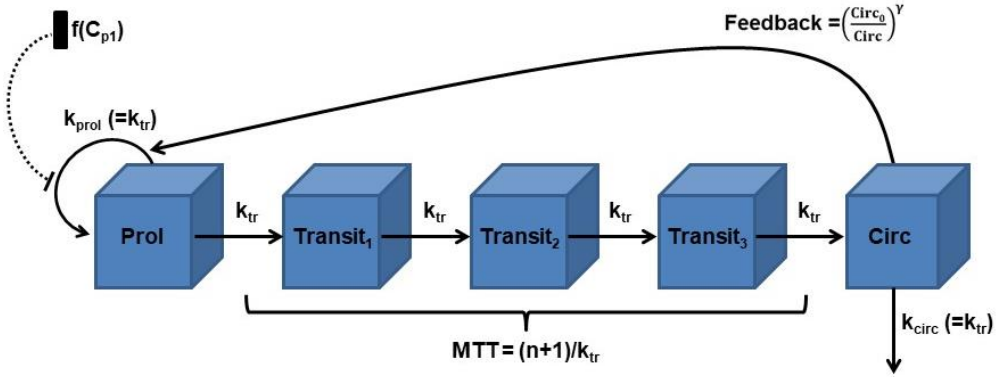
- Venetoclax (B-cell lymphoma 2 inhibitor) is approved in combination with low-dose cytarabine for patients with AML who are ineligible for IC
- Semi-mechanistic PK-PD models for both ANC and platelet counts were developed to characterize the myelosuppressive effects of Vyxeos® and venetoclax monotherapy
  - Vyxeos® pop PK model was used along with mean PD data for first induction cycle from 3 clinical studies conducted in AML patients
  - Venetoclax pop PK model and mean PD data were obtained from literature
- Goal was to predict the safety profile and to recommend starting dose for low-intensity therapy of Vyxeos® plus venetoclax

Impact of Combination Vyxeos® and Venetoclax on Myelosuppression

PK-PD Model Fitting for CPX-351



Each unit of CPX-351 contains 1 mg cytarabine and 0.44 mg daunorubicin.
ANC, absolute neutrophil count.



Parameter	ANC		Platelet	
	Final Estimate	RSE (%)	Final Estimate	RSE (%)
$Circ_0$ (10^9/L)	4.45	8.9	203	12.6
MTT (h)	66.6	5.0	87.2	9.0
γ	0.0278	8.1	0.258	18.5
I_{max}	1	fixed	0.313	11.2
IC_{50} for CPX-351 (μM)	295	8.96	0.0109	50.2
IC_{50} for Venetoclax (μM)	120	18.0	16.5	8.7

Liang Y, Cook SF et al. Population PK-PD Modeling of Neutrophil and Platelet Count for Lower-Intensity Therapy of CPX-351 Combined With Venetoclax in Acute Myeloid Leukemia. Poster presented at ASH Meeting, 2023.

Simulations to Select Starting Vyxeos® Dose for Phase 1b Study

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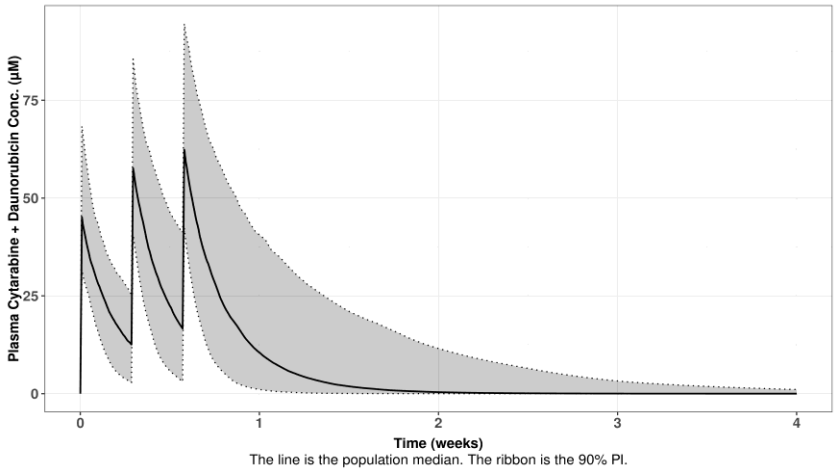
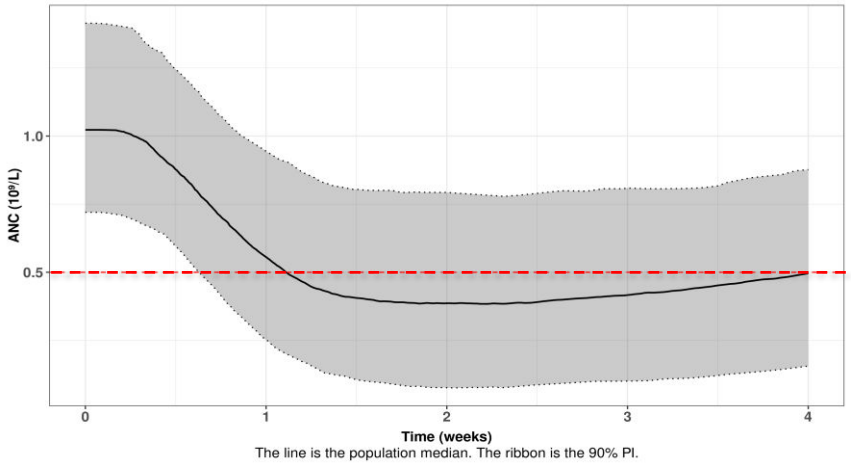
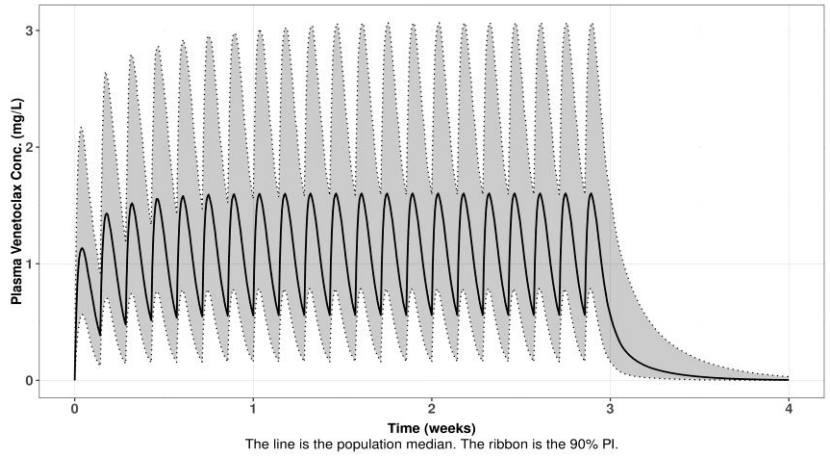
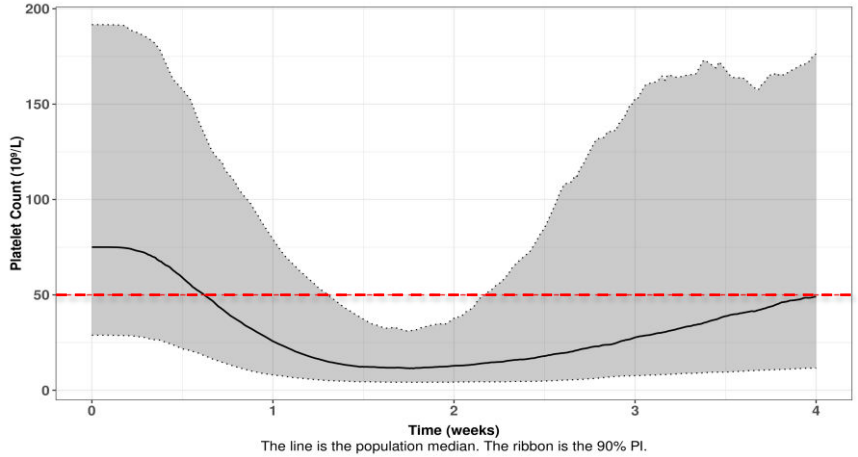
20 units/m² Vyxeos® on Days 1 and 3; 400 mg Venetoclax QD until Day 21









- Simulations used to determine starting dose for LiT of Vyxeos®/venetoclax for Ph 1b study in newly diagnosed AML patients unfit for IC
- Targeted ≥ 50% of patients to recover above Grade 4 at end of 28-day cycle

Liang Y, Cook SF et al. Population PK-PD Modeling of Neutrophil and Platelet Count for LiT of CPX-351 Combined With Venetoclax in AML. Poster at ASH Meeting, 2023.

Summary

- These examples illustrate how PK-PD modeling and simulation can be used to support dose optimization and inform the design of clinical trials
- A wide range of PK-PD modeling approaches can be used to characterize safety AE data and the same data can in fact be modeled multiple ways (e.g., categorical vs. continuous time-course models)
- Innovative approaches leveraging literature data or other published PK-PD models can provide tremendous value during drug development to help improve patient outcomes

SESSION 3A: CONSIDERING THE TOTALITY OF EFFICACY AND SAFETY DATA TO AIDE REGISTRATIONAL TRIAL DESIGNS

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MODERATOR

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

INTRODUCTORY SPEAKER

Jin Y. Jin, PhD
Genentech

INTRODUCTORY SPEAKER

Scott Van Wart, PhD
Enhanced Pharmacodynamics

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Cara Rabik, MD, PhD
U.S. Food and Drug Administration

W. Douglas Figg, PharmD
National Cancer Institute

Julia Maues
Patient Centered Dosing Initiative