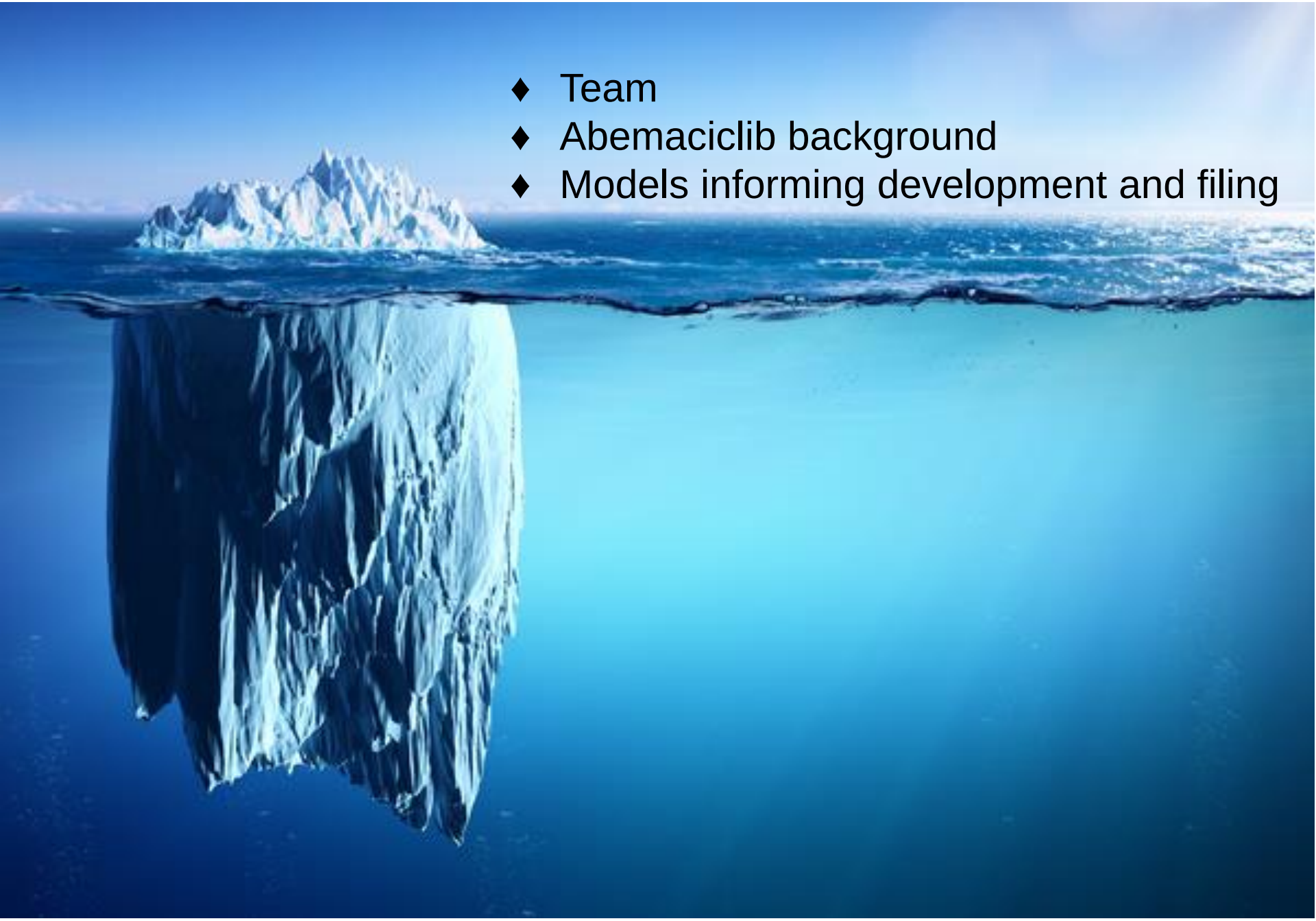
Model Informed Development of Abemaciclib: Collaboration, Computation, and Communication

FDA-ISoP Public Workshop: Model Informed Drug Development (MIDD) for Oncology Products

1 February 2018

Kellie Turner, Pharm.D., Ph.D.

Lilly


Team
Abemaciclib background
Models informing development and filing

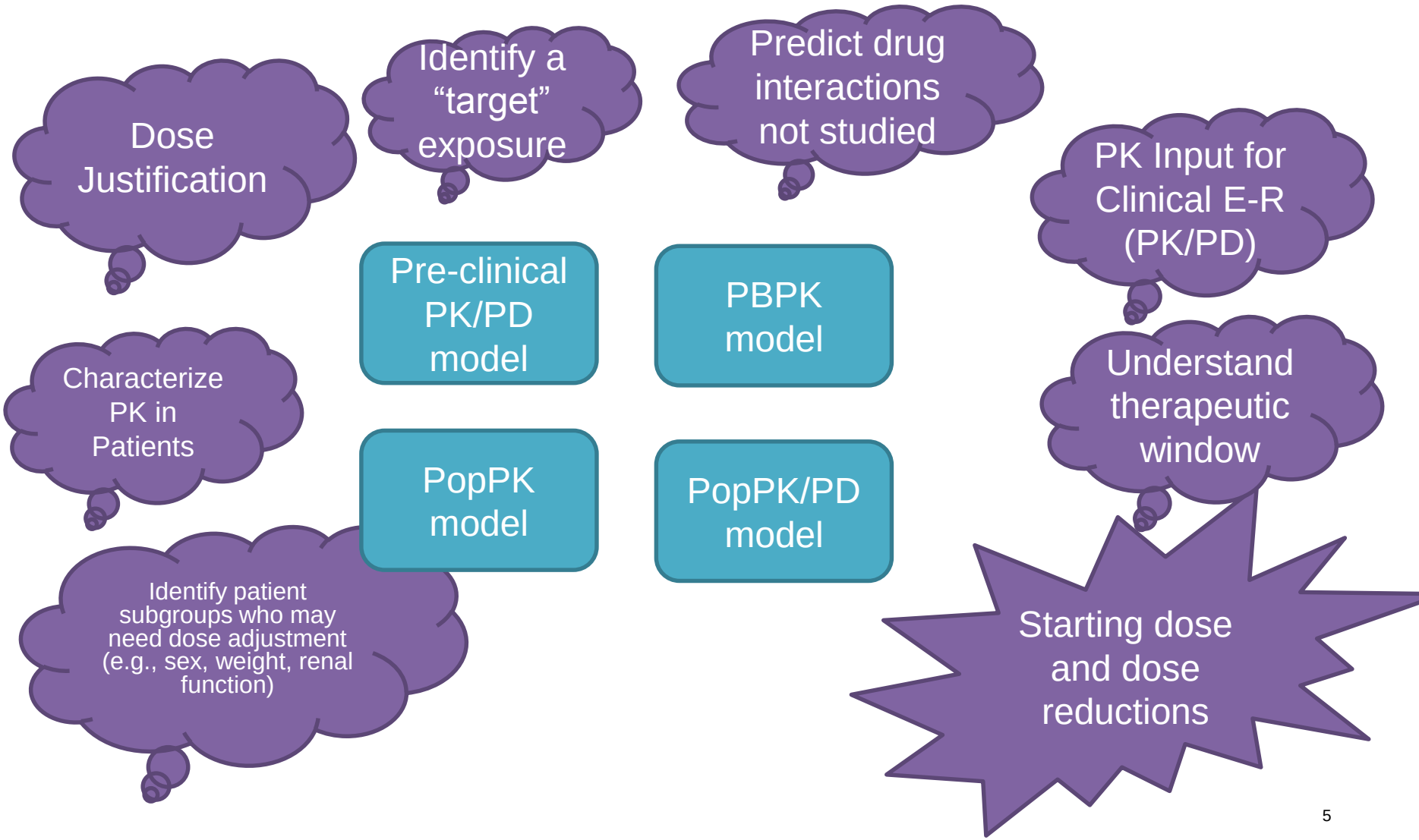
Collaborators

- PK/PD/Pharmacometrics
  - Emmanuel Chigutsa
  - Jan-Stefan van der Walt
  - Siva Rama Prasad Kambhampati
  - Damien Cronier
  - Sonya Tate
  - Amanda Sykes
  - Lisa Ferguson-Sells
- ADME
  - Maria Posada
  - Gemma Dickinson
  - Steve Hall
  - Palaniappan Kulanthaivel
- Clinical Pharmacology
  - Jill Chappell
- Dataset creation
  - Gordon Morrow
  - Jin Su
- CMC
  - Stephen Stamatis
  - John Rose
- Statistics
  - Martin Frenzel
  - Yong Lin
  - Tammy Forrester
- Medical
  - Ian Smith
- Special Thanks to Study Participants!

Abemaciclib

- CDK 4 & 6 inhibitor approved in HR+ HER2- advanced/metastatic breast cancer based on MONARCH 1 and MONARCH 2
- CYP3A4 substrate
- Active metabolites equipotent to parent and represent ~45% of plasma exposure
- 200 mg orally twice daily (single agent)
- 150 mg orally twice daily (with fulvestrant)
- Dose reductions for individual tolerability in 50 mg units to 50 mg twice daily

Models with a purpose



Pre-Clinical PK/PD Model to Identify Potentially Effective Clinical Dose Range

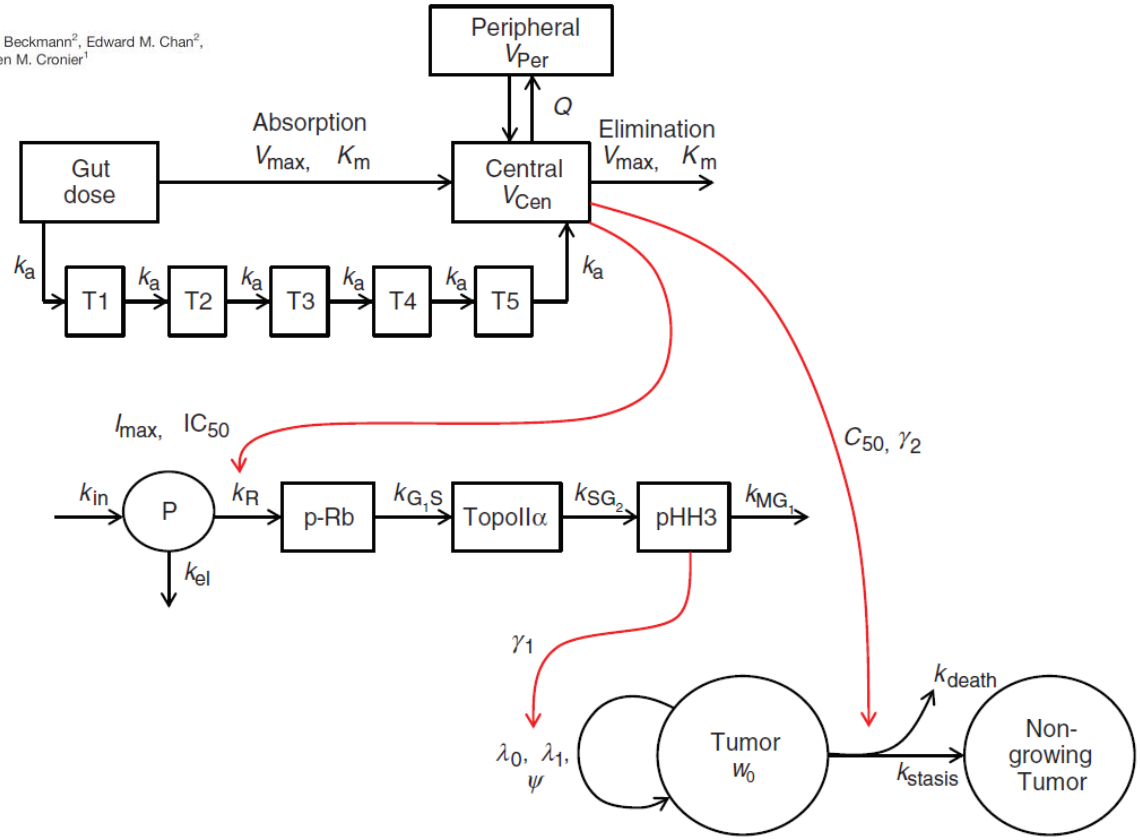
Published OnlineFirst May 21, 2014; DOI: 10.1158/1078-0432.CCR-13-2846

Clinical Cancer Research

Cancer Therapy: Preclinical

Semi-Mechanistic Pharmacokinetic/Pharmacodynamic Modeling of the Antitumor Activity of LY2835219, a New Cyclin-Dependent Kinase 4/6 Inhibitor, in Mice Bearing Human Tumor Xenografts

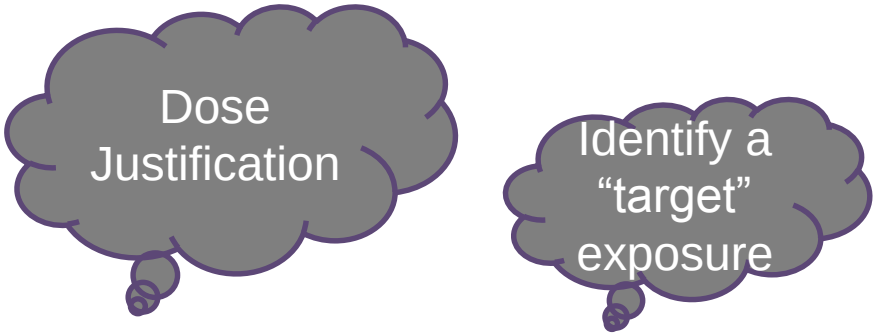
Sonya C. Tate[1], Shufen Cai[2], Rose T. Ajamie[2], Teresa Burke[2], Richard P. Beckmann[2], Edward M. Chan[2], Alfonso De Dios[2], Graham N. Wishart[1], Lawrence M. Gelbert[2], and Damien M. Cronier[1]



Tate Clin Cancer Res 2014

Preclinical PK/PD Model Impact

- Sustained inhibition of CDK4/6 required for durable cell cycle arrest
- Supports a chronic dosing strategy
- Selection of a PD biomarker
- Identified a target $C_{min,ss}$ needed to maintain durable cell cycle arrest



Target Exposure and Maximal Target inhibition Achieved at 150 and 200 mg Q12H

Clin Pharmacokinet
DOI 10.1007/s40262-017-0559-8

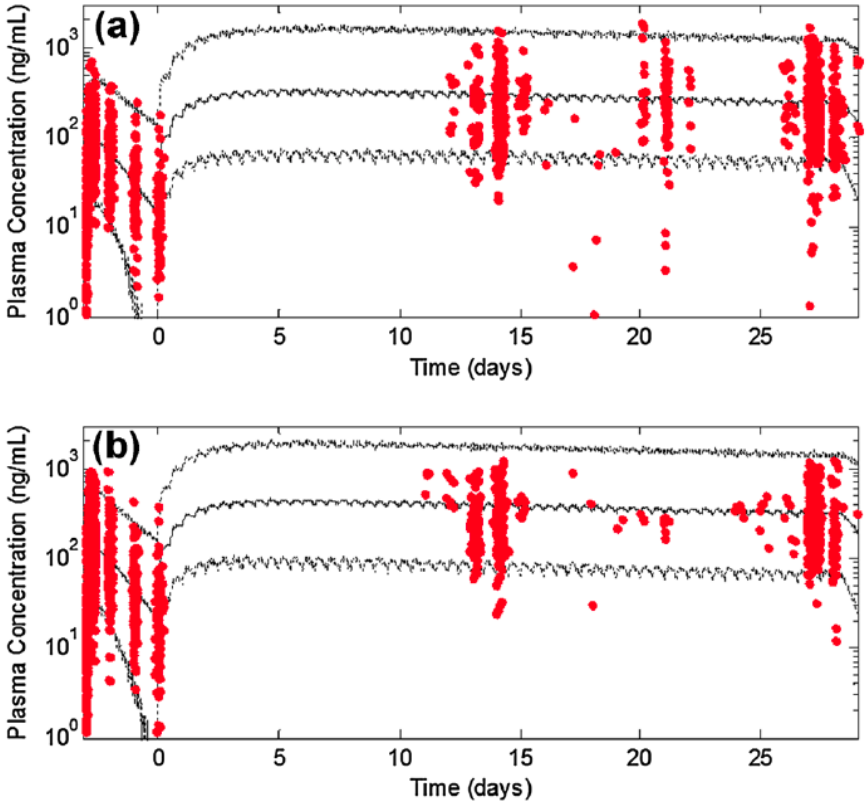
ORIGINAL RESEARCH ARTICLE

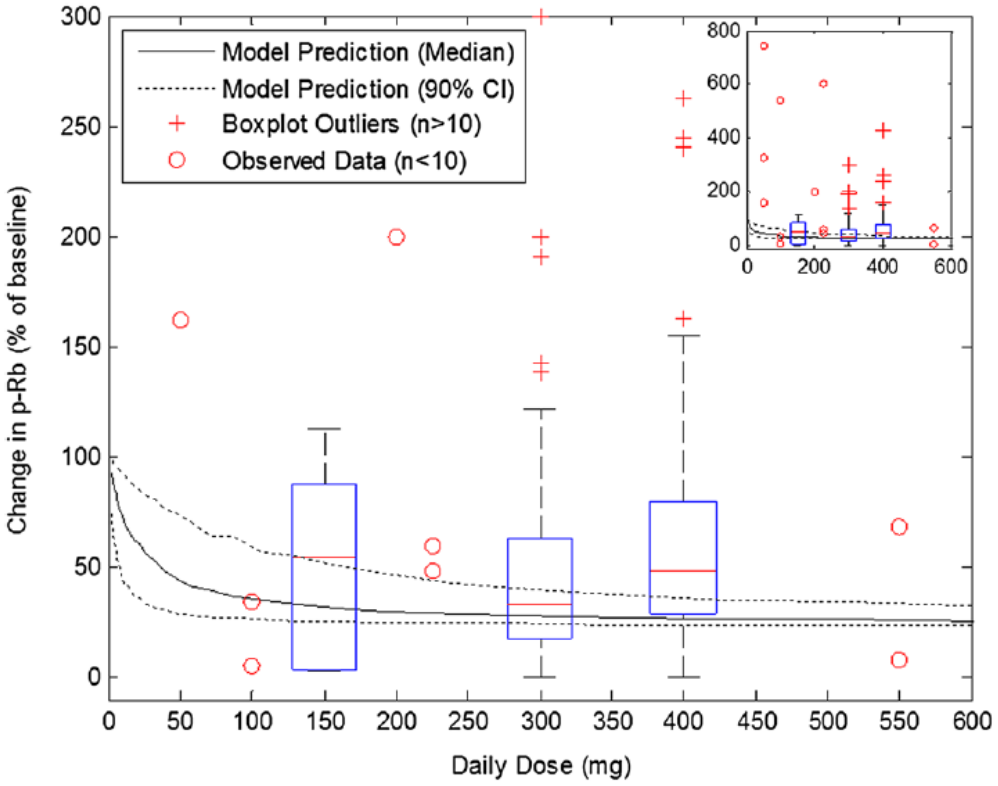
A Population Pharmacokinetic and Pharmacodynamic Analysis of Abemaciclib in a Phase I Clinical Trial in Cancer Patients

Sonya C. Tate[1] · Amanda K. Sykes[1] · Palaniappan Kulanthaivel[2] · Edward M. Chan[2] · P. Kellie Turner[2] · Damien M. Cronier[1]

Dose Justification

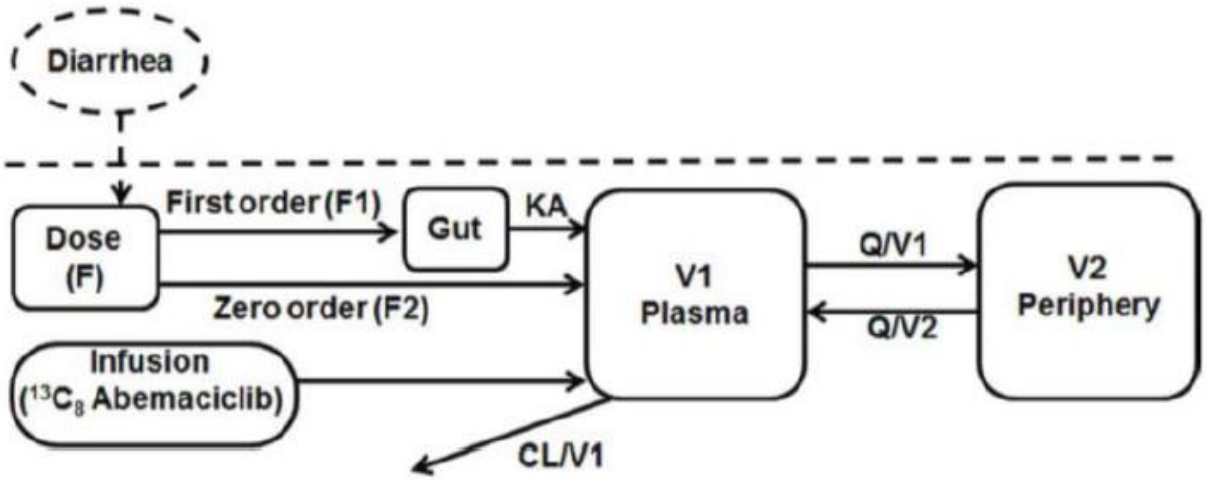
Identify a "target" exposure





Tate Clin Pharmacokinet 2017

How can we model PK data from multiple studies and manage computational intensity of covariate screen?

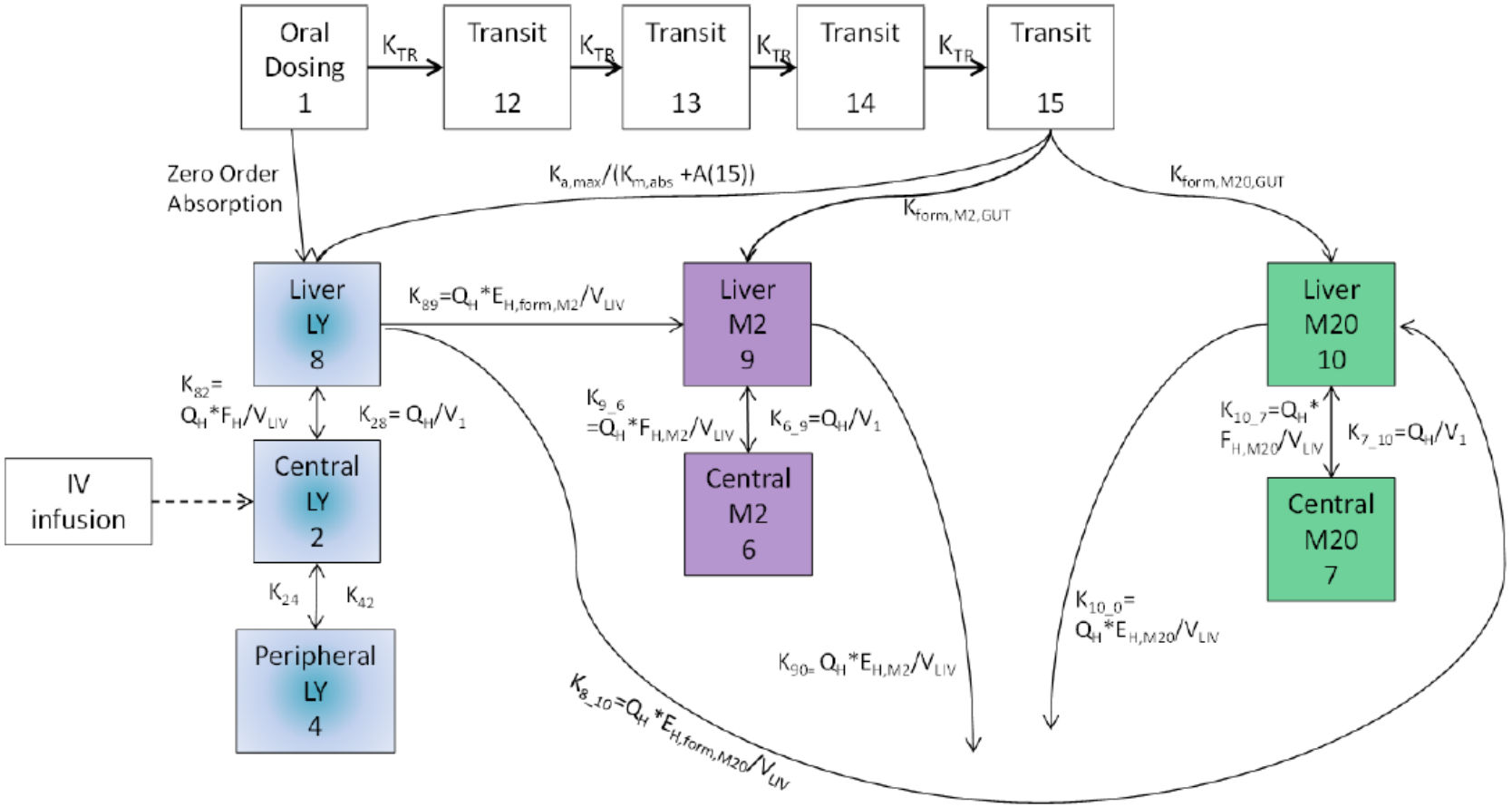


- Precursor to mechanistic model that included parent and 2 active metabolites, eased computational burden of covariate screening

Identify patient subgroups who may need dose adjustment (e.g., sex, weight, renal function)

Kambhampati et al ACoP 2017

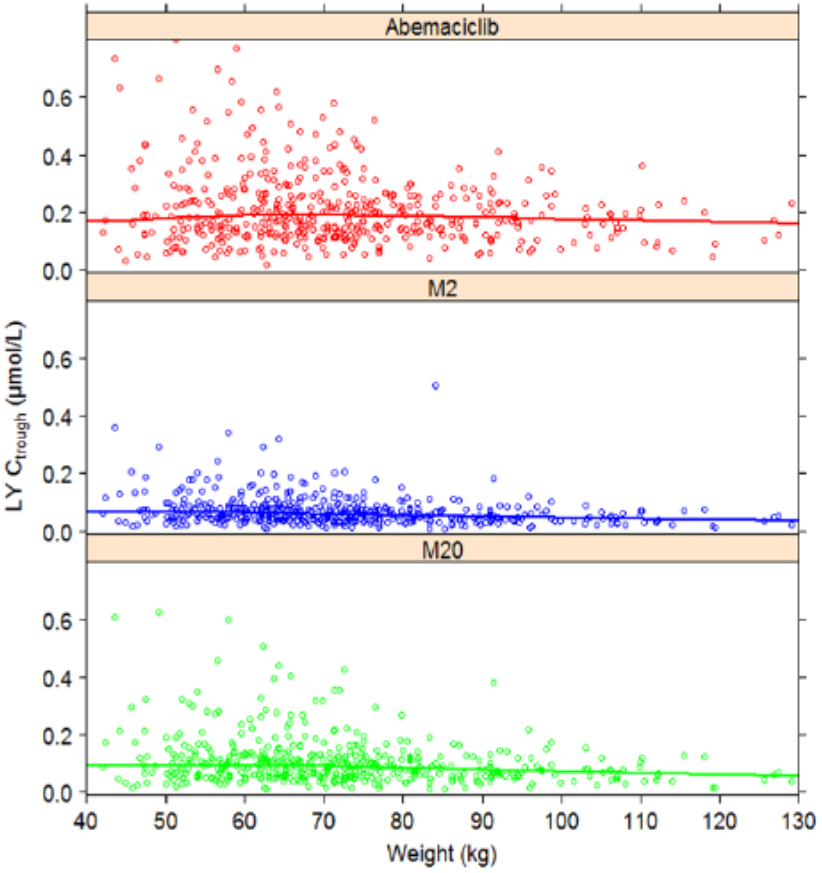
What Mechanism Describes Abemaciclib PK and Active Metabolite Formation for E-R Analysis/Modeling?



Chigutsa et al ACoP 2017

Mechanistic PopPK Model Impact

- Described the disposition of parent and 2 active metabolites
- Useful as input to exposure-response analysis that could help to understand relative contribution of parent and metabolites to response endpoints
- Determination of covariate effects that could impact dose



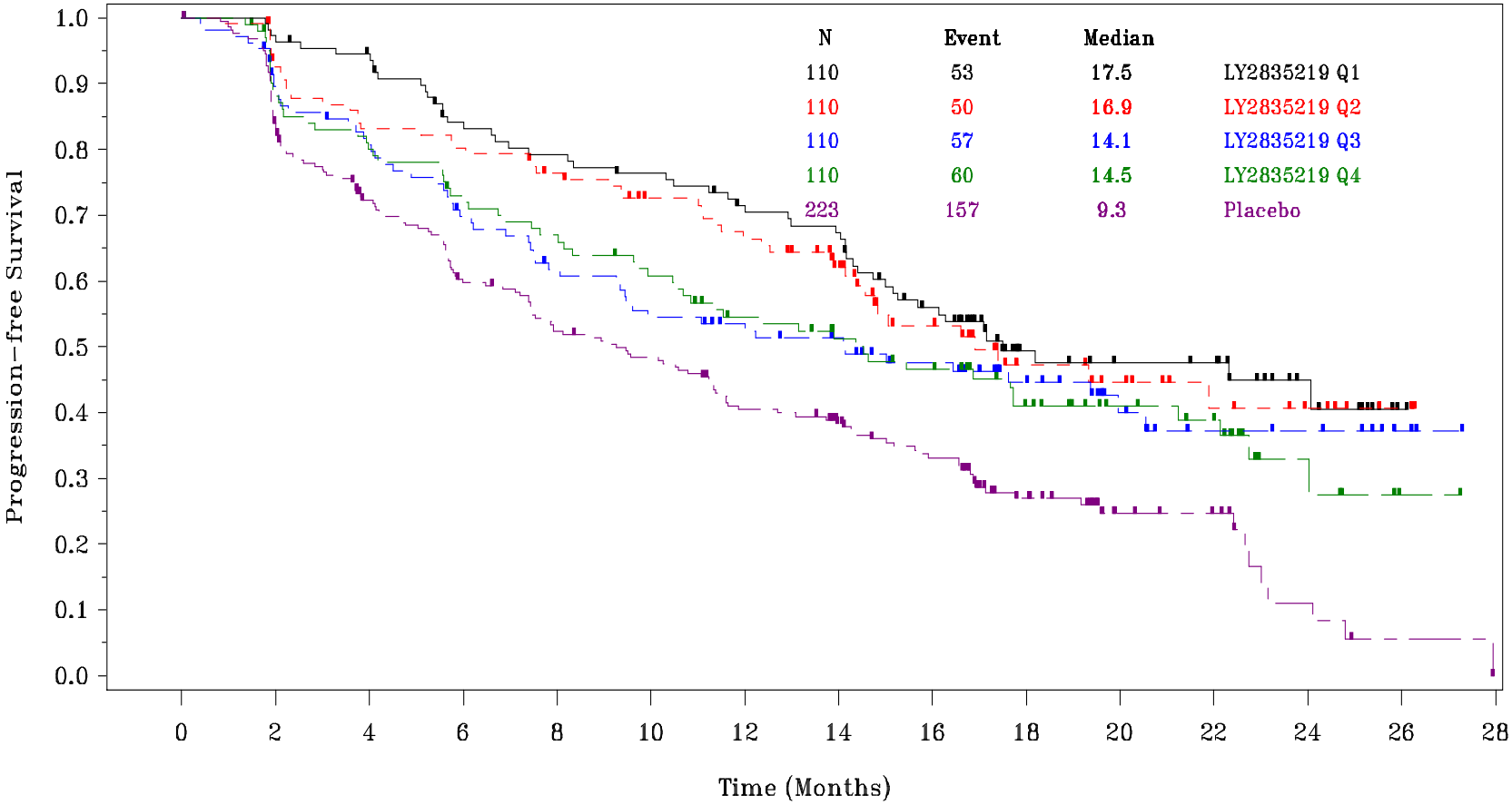
Characterize PK in Patients

Identify patient subgroups who may need dose adjustment (e.g., sex, weight, renal function)

Input for Clinical E-R (PK/PD)

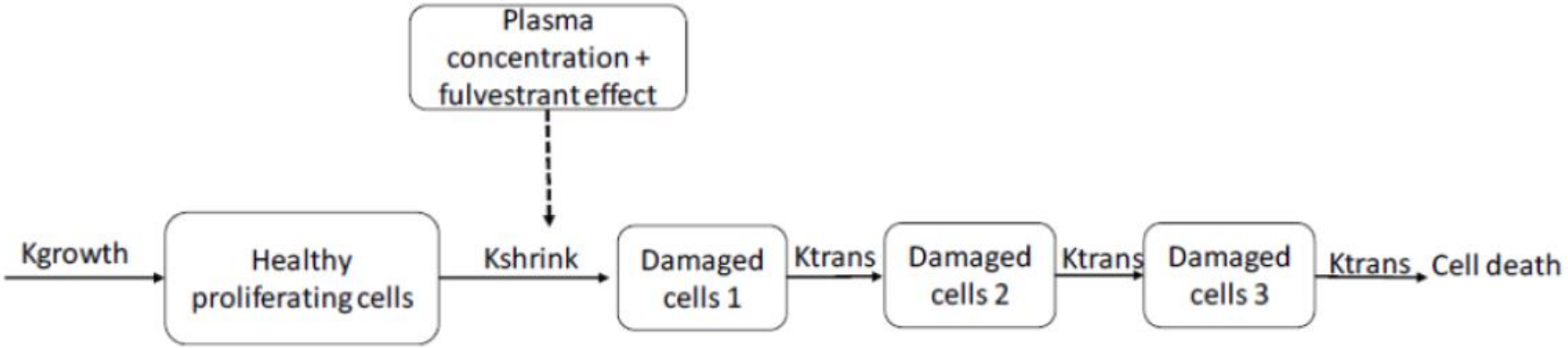
Chigutsa et al ACoP 2017

Conundrum: Exposure-Response Static Analysis in MONARCH 2

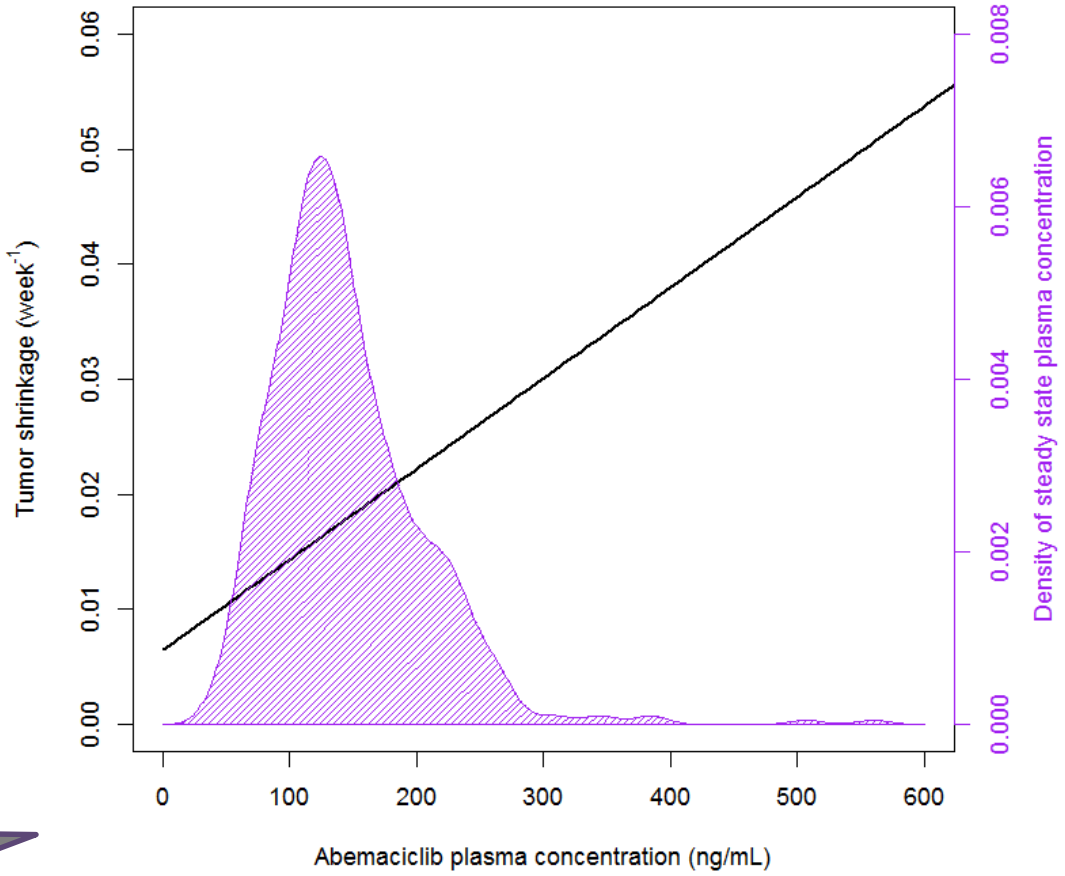


At Risk														
LY2835219 Q1	110	106	101	87	82	78	70	67	51	27	22	21	10	1	0
LY2835219 Q2	110	98	88	85	79	71	65	50	33	19	15	10	7	3	0
LY2835219 Q3	110	92	82	69	60	53	48	43	36	26	15	9	8	3	0
LY2835219 Q4	110	89	80	71	66	59	50	44	39	28	21	17	6	1	0
Placebo	223	182	150	123	107	98	80	68	56	32	15	12	4	1	0

How did abemaciclib concentration affect tumor size change in MONARCH 2?



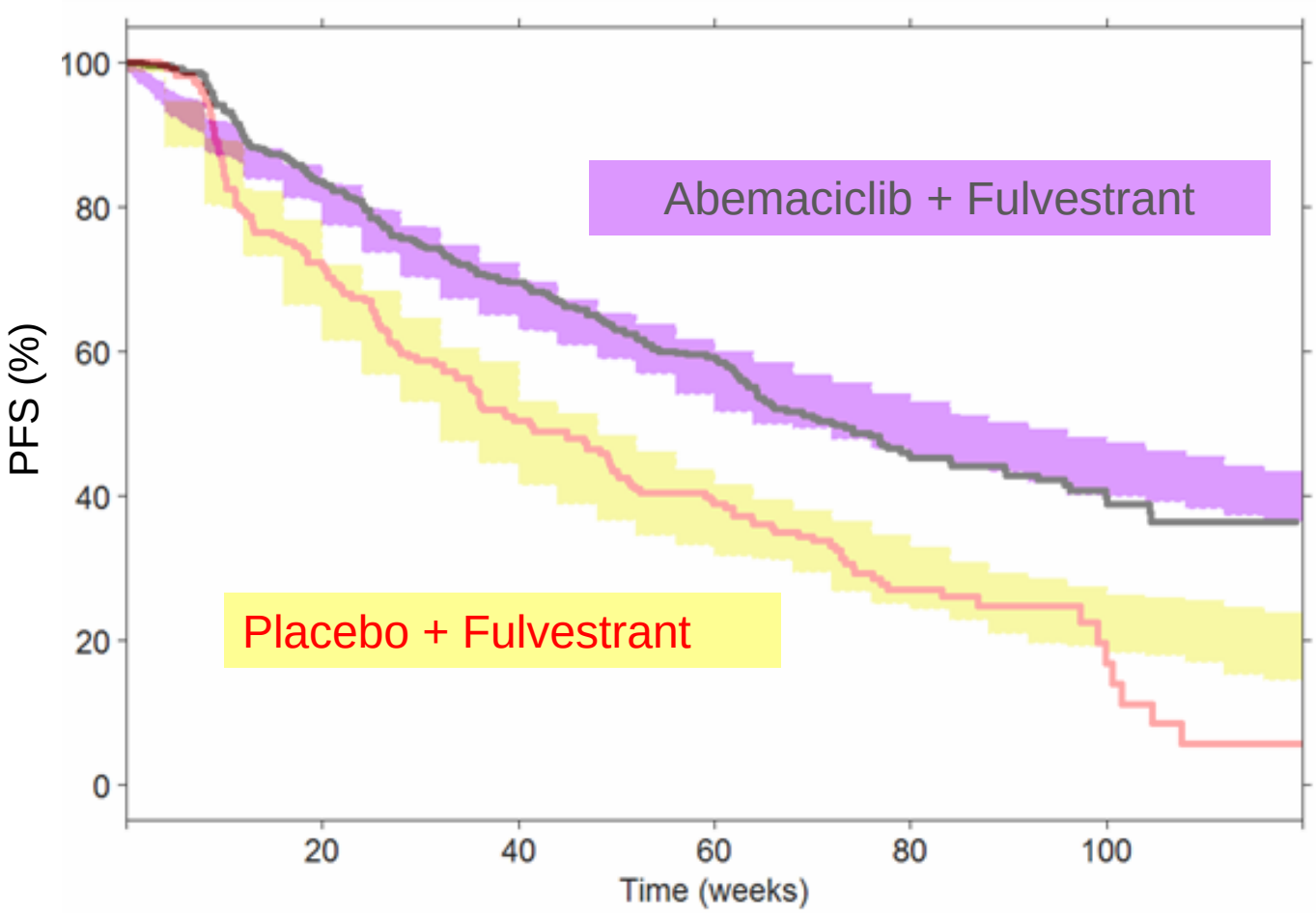
Positive Relationship between Exposure and Response (Tumor Shrinkage) in MONARCH 2



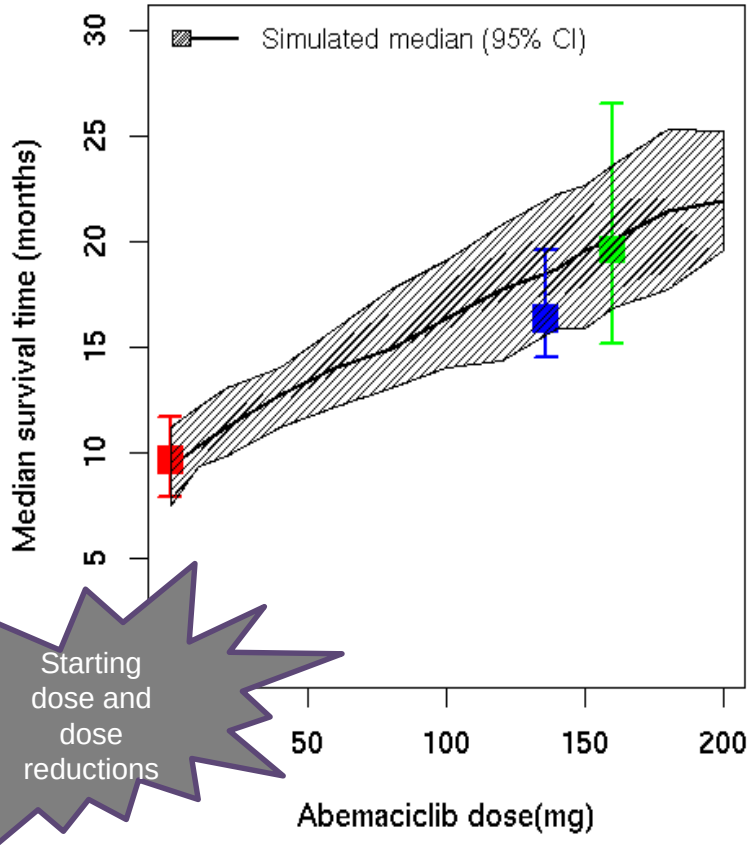
Starting dose and dose reductions

MONARCH 2 PopPK/PD Model Showed Higher Abemaciclib Concentrations Reduced Hazard of Progression

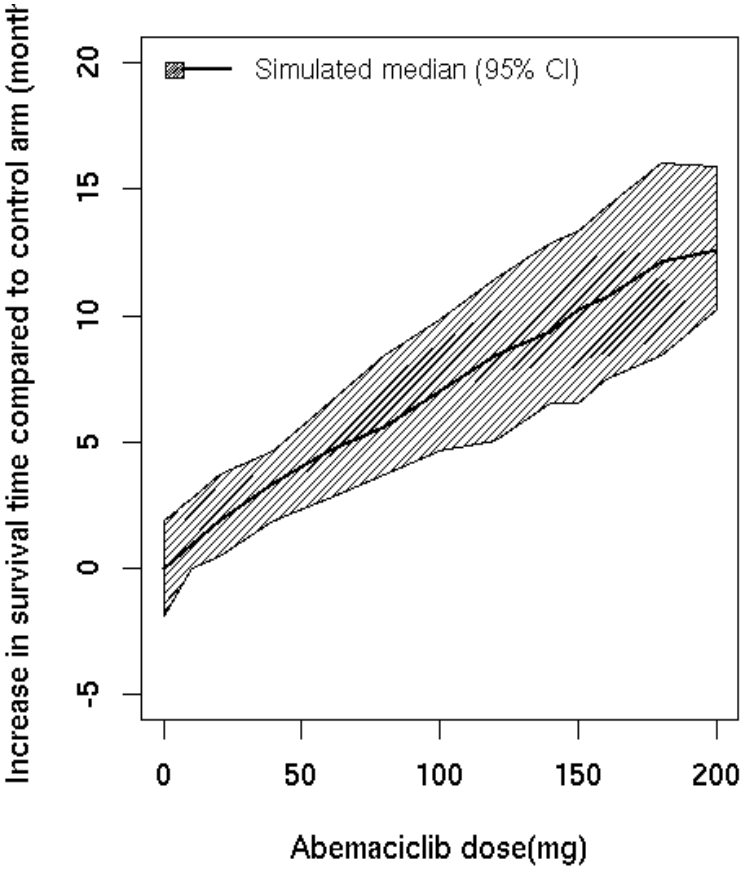
$$\frac{dHaz}{dt} = HBASE \times e^{CFB \times THAZ - SLOPE \times CONC \times e^{-DECAY \times t}}$$



Positive Relationship Between Dose and Response (PFS) in MONARCH 2

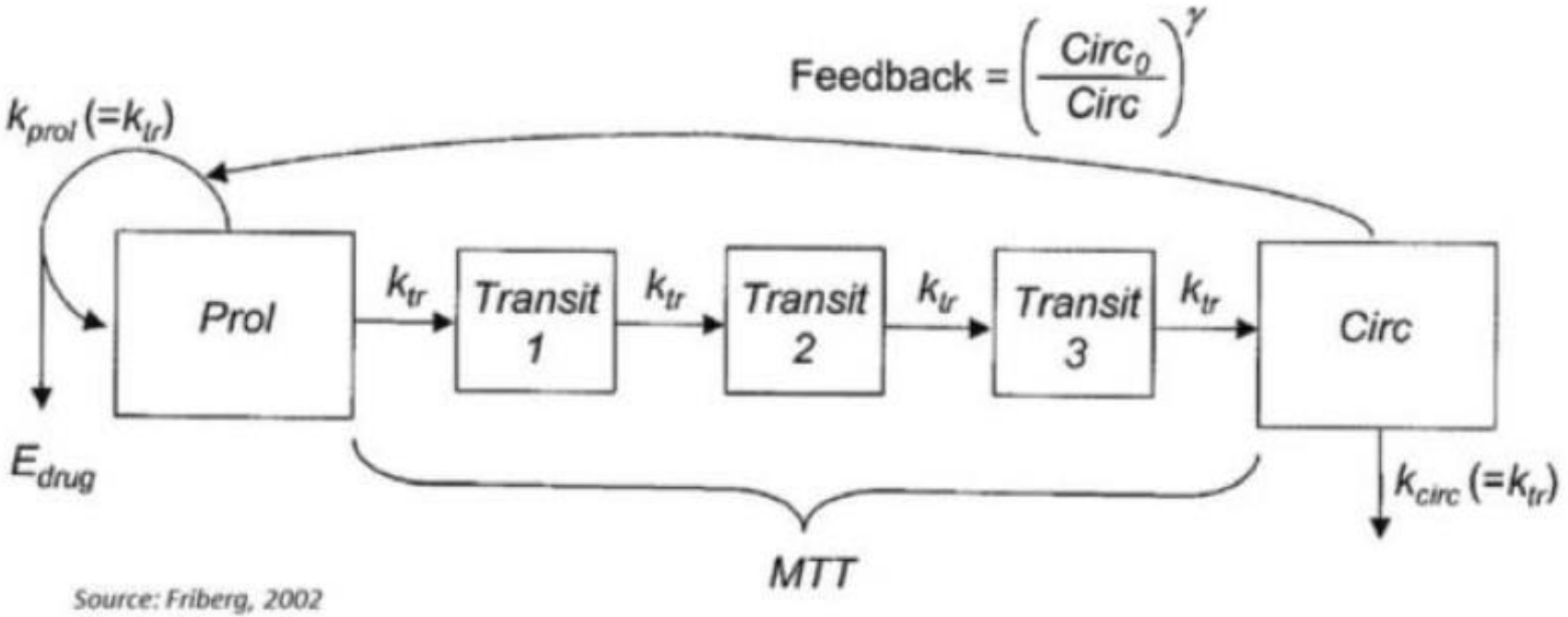


Starting dose and dose reductions



- Confirmed appropriateness of starting dose and dose reductions used in registration study in light of the results from the static analysis
- Defined the efficacy portion of the therapeutic window, which could be used to evaluate scenarios such as impact of food effect and drug interactions

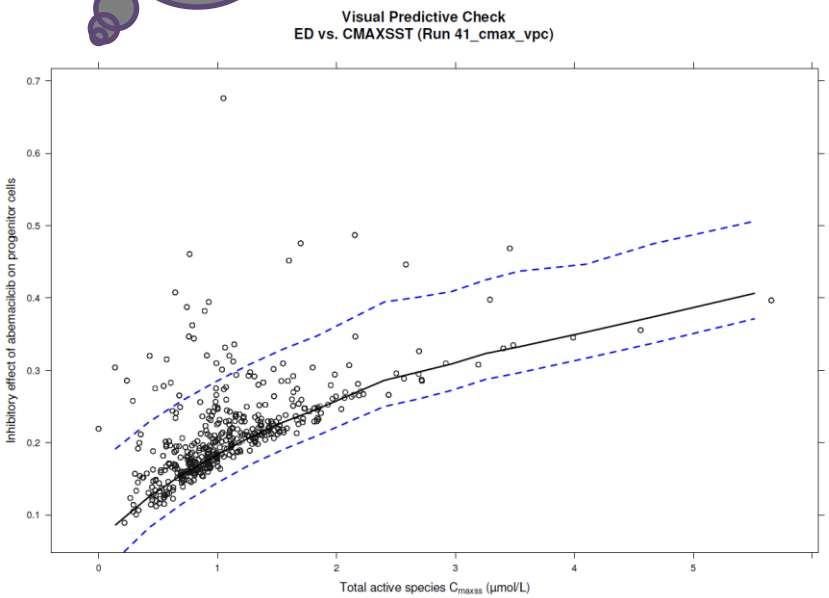
What was the relationship between abemaciclib exposure and neutropenia in MONARCH 2?



Source: Friberg, 2002

Exposure-Response Relationship for Neutrophil Progenitors in MONARCH 2

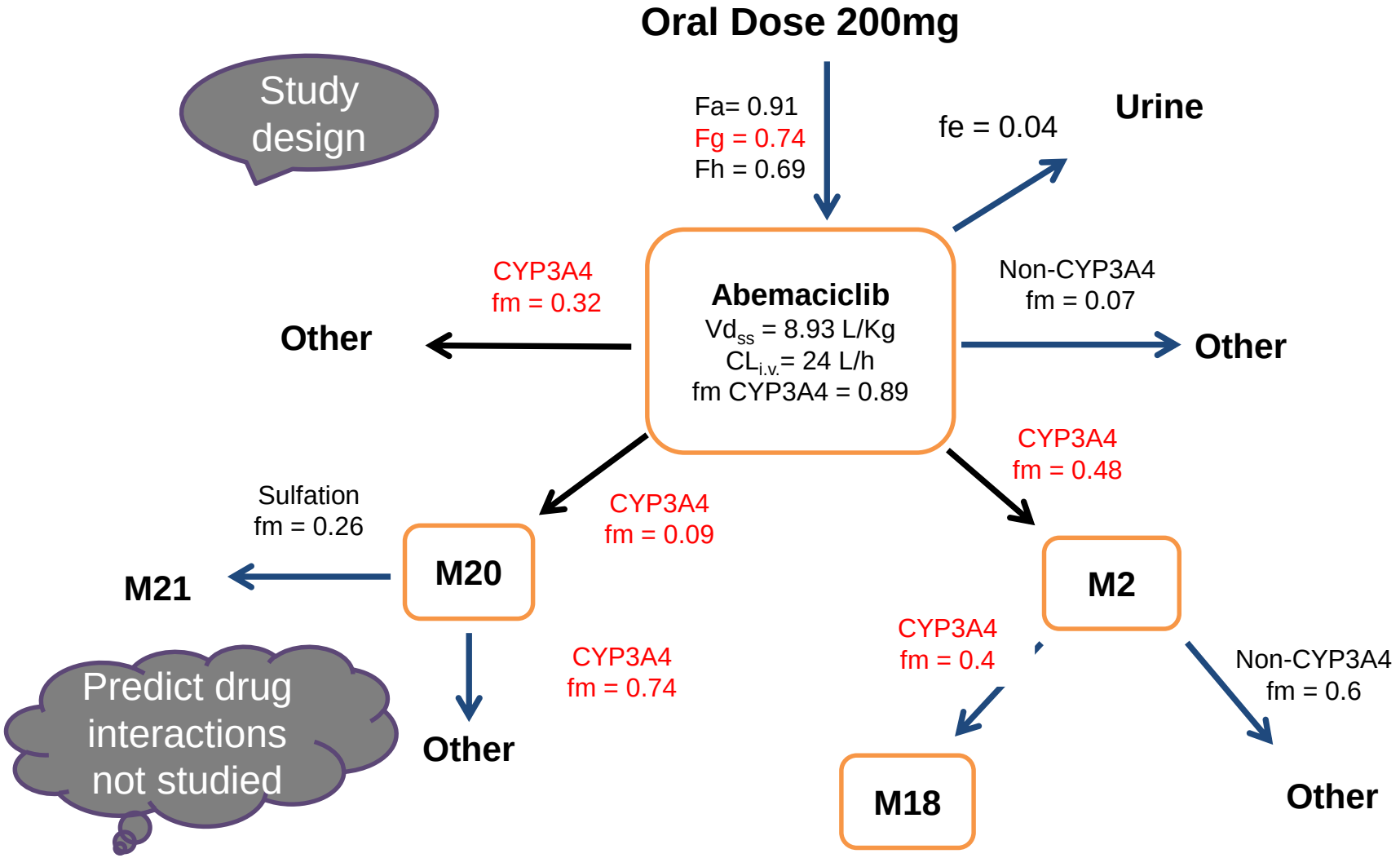
Understand therapeutic window



- Confirmed understanding of the frequency of this adverse event
- Defined an aspect of the safety side of the therapeutic window, which could be used to evaluate scenarios such as impact of food effect and drug interactions

$$Drug_{effect} = \theta_{Fulvestrant} + \theta_{Abemaciclib} \cdot (1 - MT) \cdot \left(\theta_{C_{max,ss,total}} \cdot \log(1 + C_{max,ss,total})\right)$$

PBPK Model to Predict Effect of Unstudied Scenarios on Total Active Species PK Impacted Label



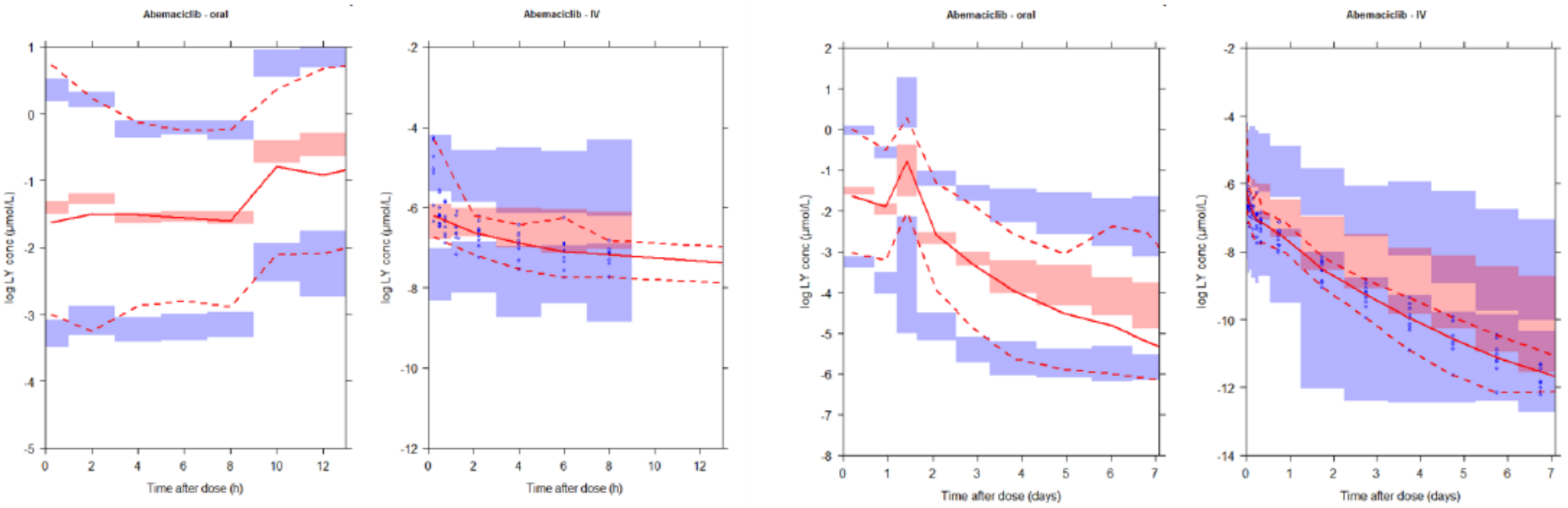
Posada et al ASCPT 2017

Models Informed Abemaciclib Drug Development

	Pre-Clinical PK/PD	PopPK	PopPK/PD	PBPK
Continuous, twice daily dosing	✓		✓	
Identification/confirmation of a target systemic exposure	✓	✓	✓	
Biomarker selection to demonstrate target engagement in patients	✓			
Covariate evaluation, no dose adjustment needed for weight, etc.		✓	✓	
Acceptability of starting dose and dose adjustments for tolerability			✓	
Understanding the risk for adverse events associated with changes in exposure			✓	
Dose adjustment recommendations for drug interactions not studied				✓

Backups

Pred-corrected VPC of Empiric PK model



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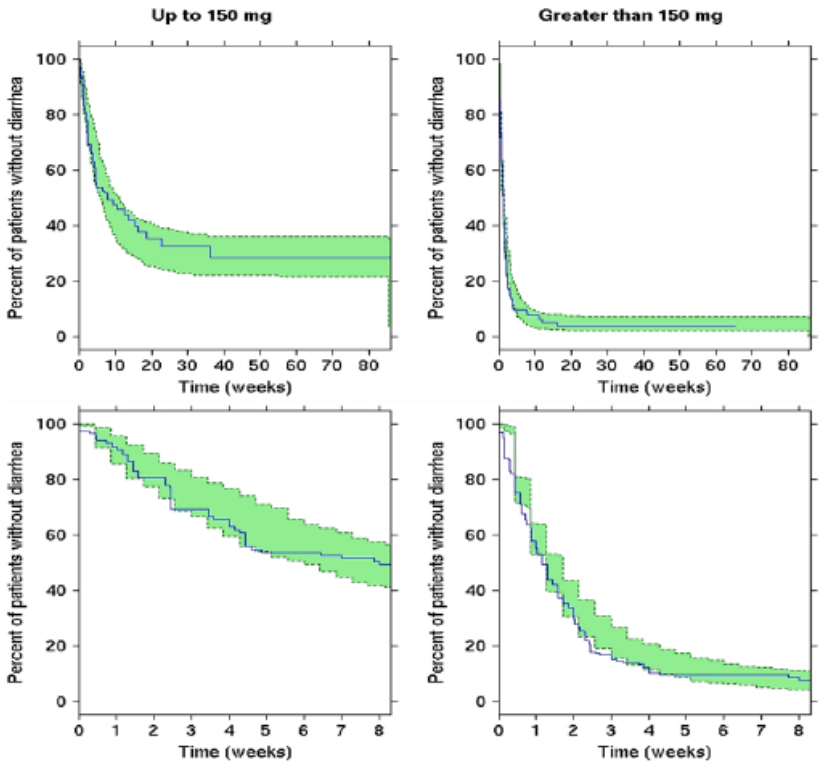
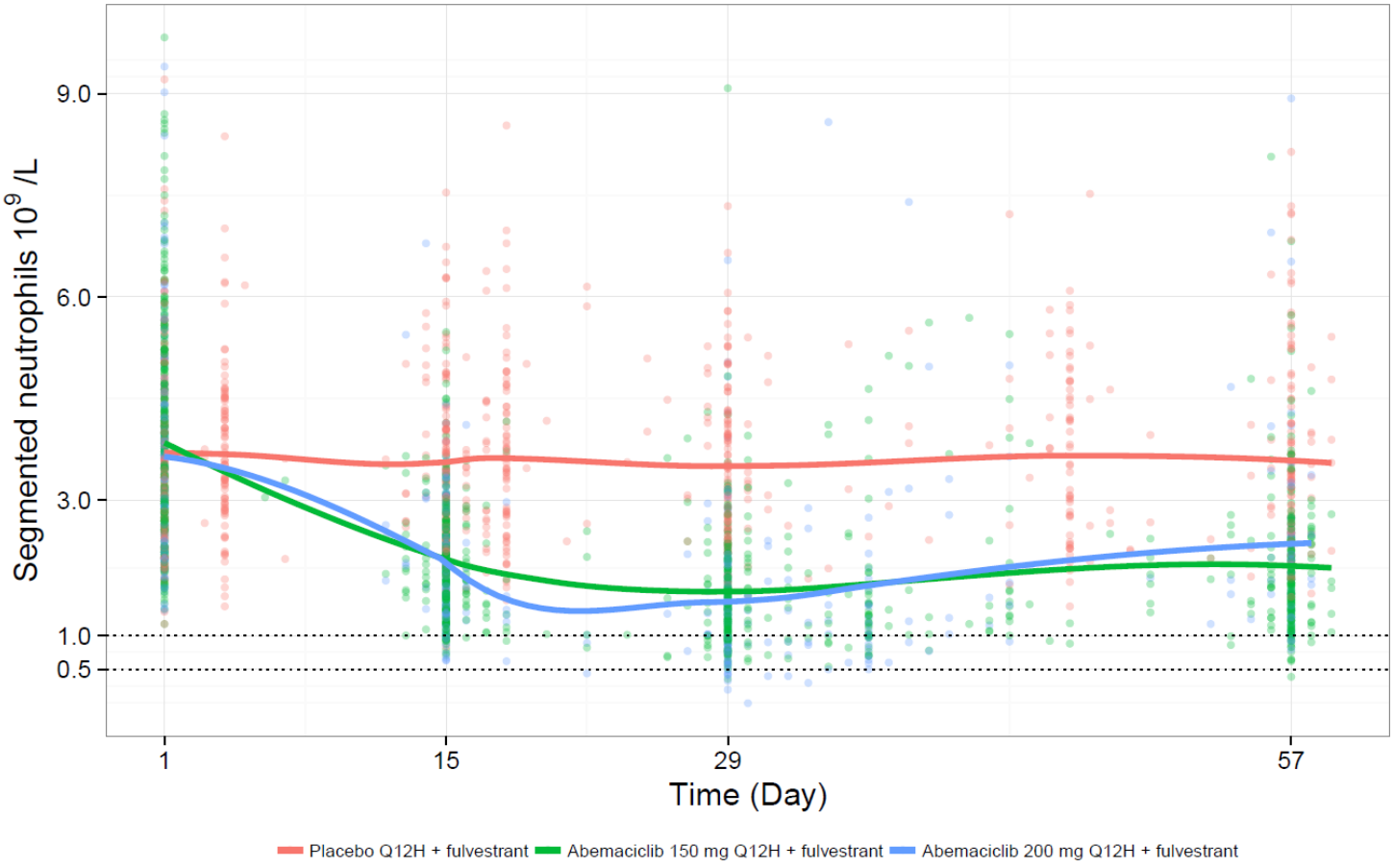
Diarrhea Time to Event Model



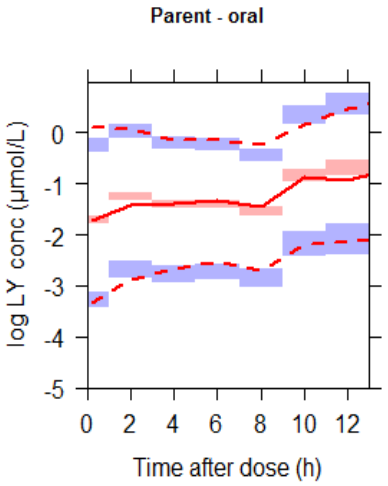
- Parameterized the observed slight reduction in exposure over time as the effect of diarrhea on PK
- Demonstrated that the risk of diarrhea was higher for doses ≥ 200 mg
- As precursor to mechanistic model that included parent and 2 active metabolites, eased computational burden of covariate screening

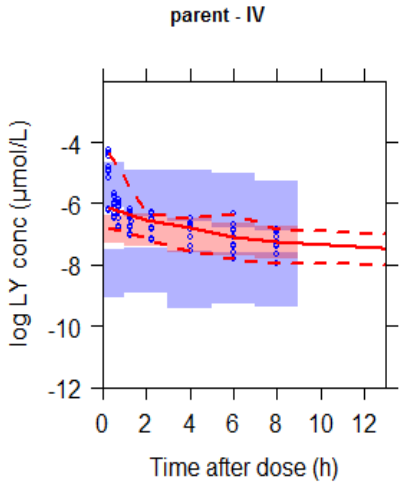
Kambhampati et al ACoP 2017

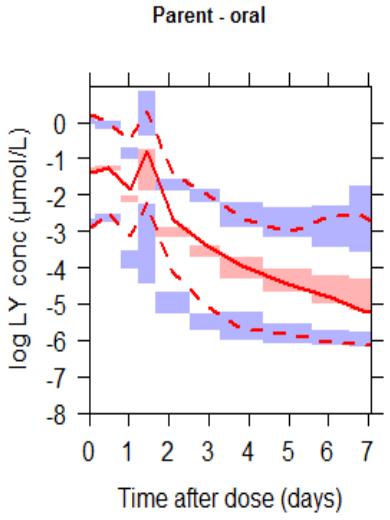
Neutrophil observations in MONARCH 2

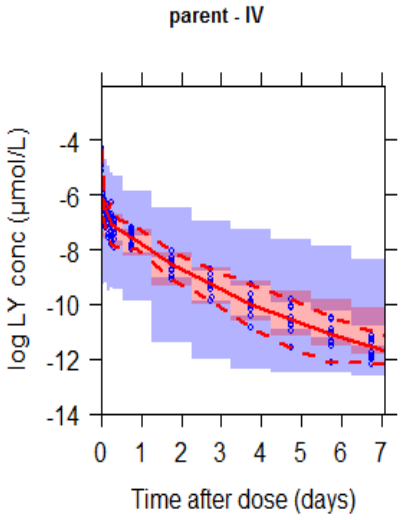


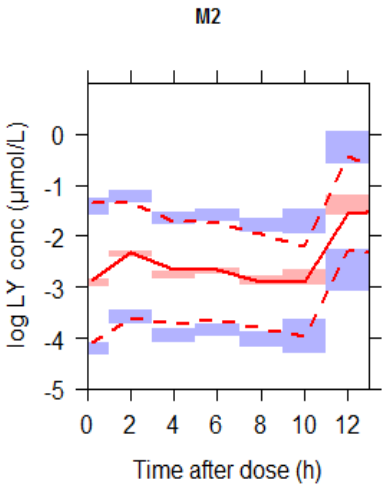
Pred-corrected VPC of Mechanistic PK Model

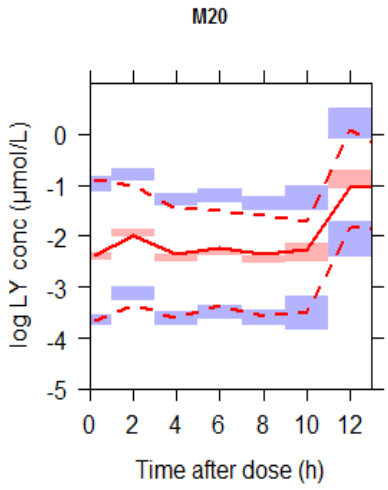


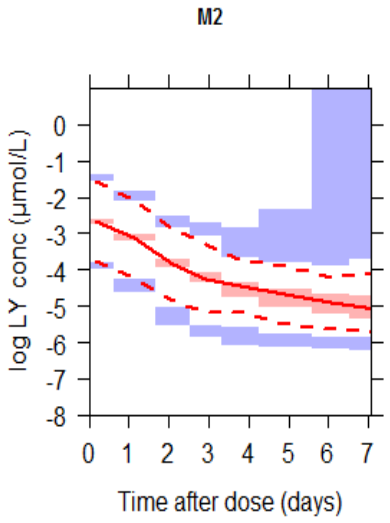


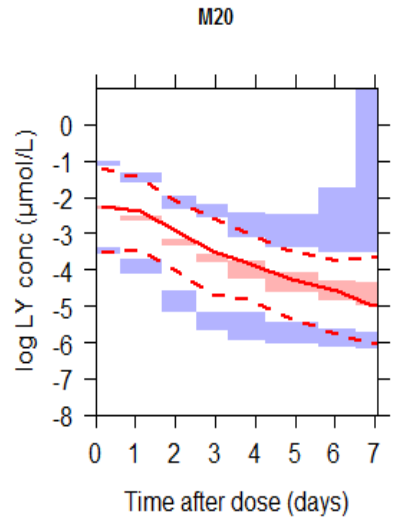












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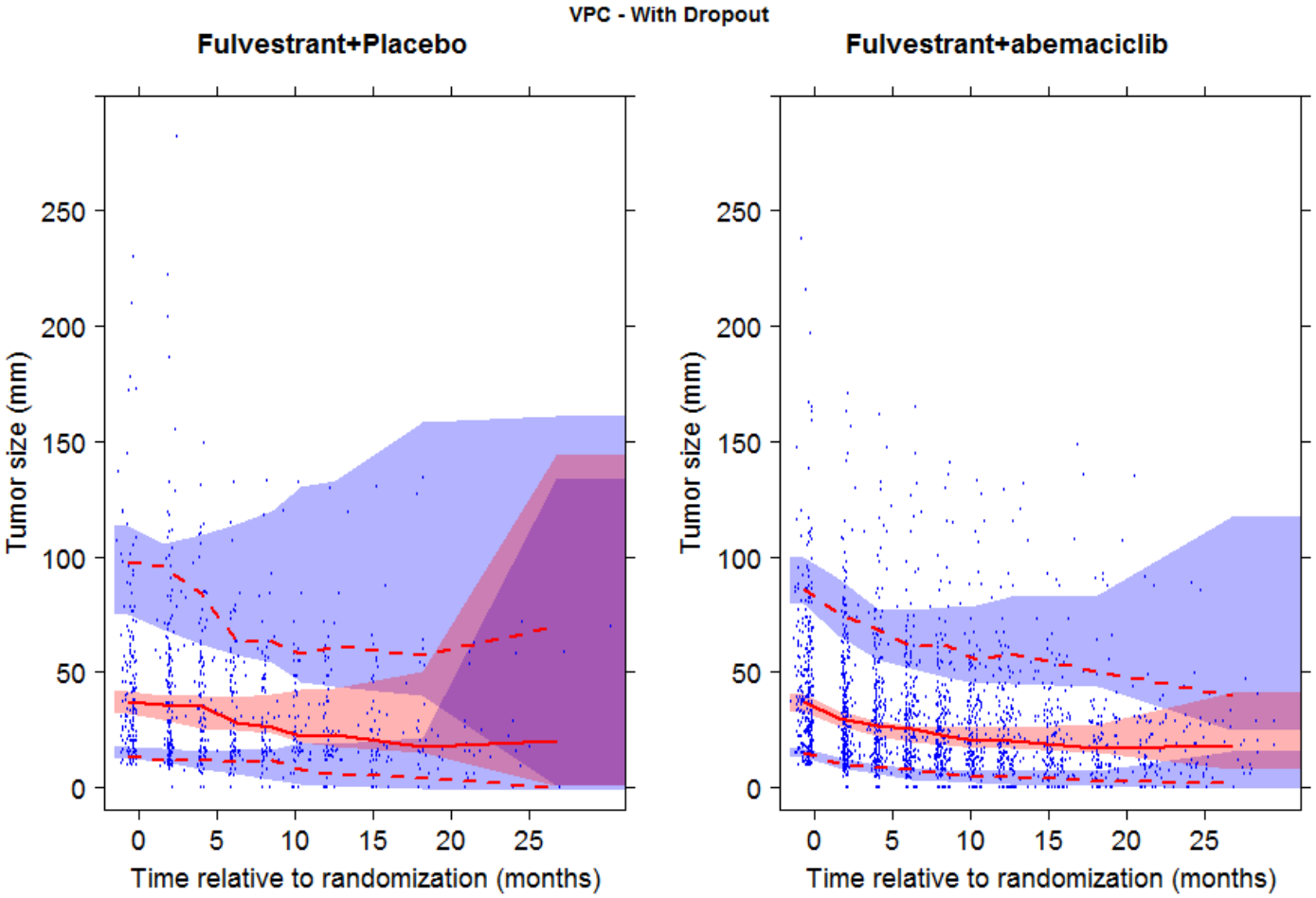
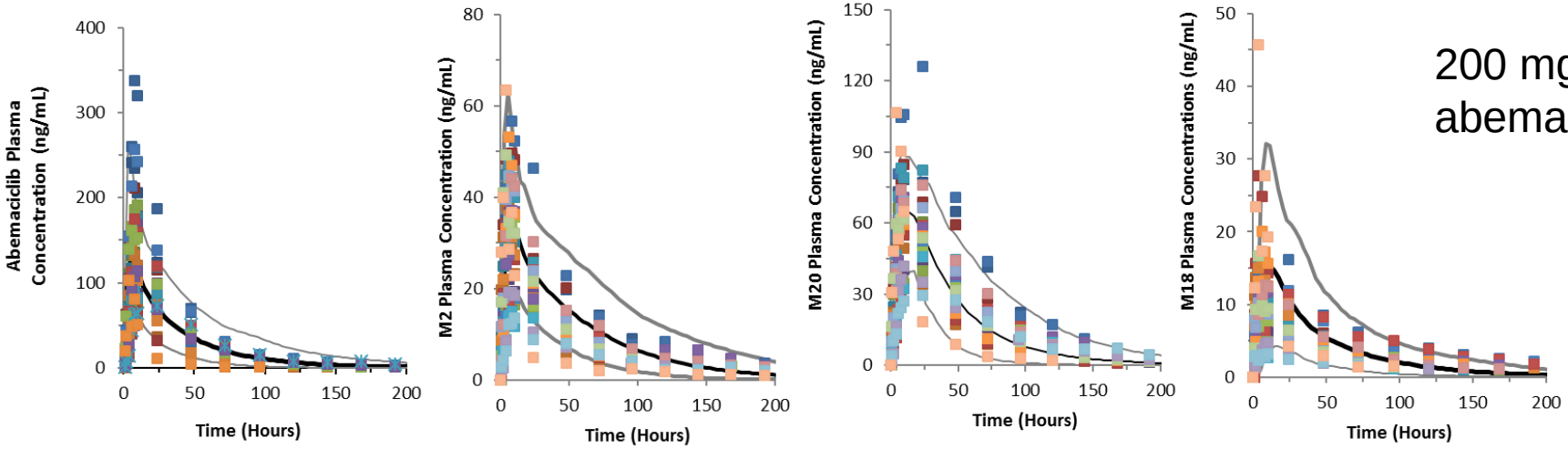
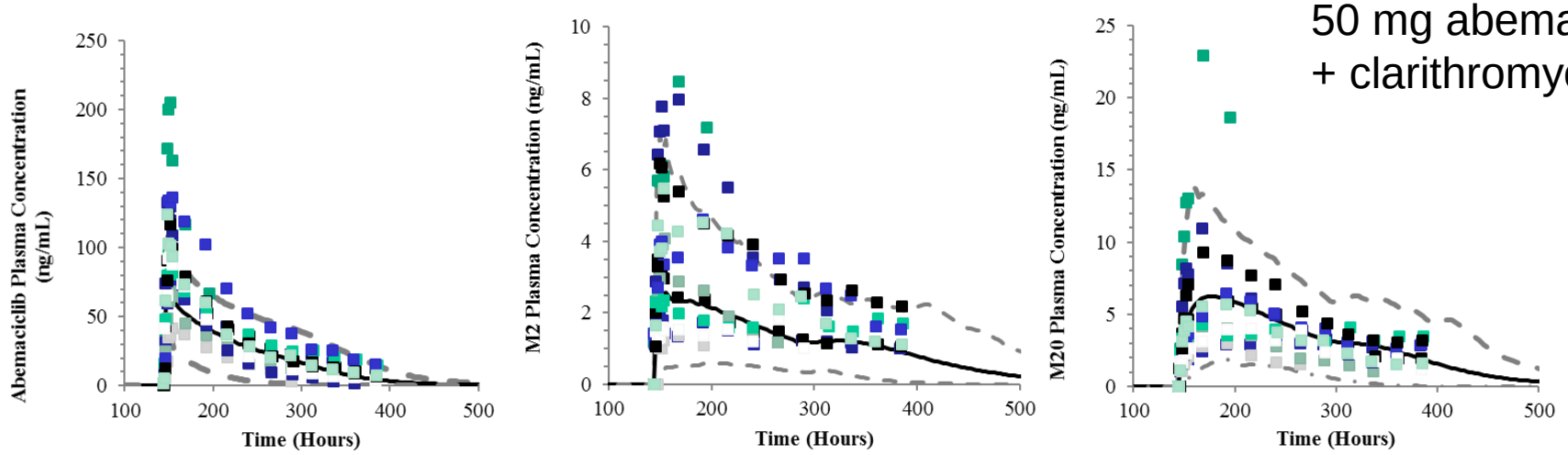
VPC of Final Tumor Size Model with Dropout in MONARCH 2



Abemaciclib and Metabolite Observations and Predictions



200 mg abemaciclib



50 mg abemaciclib + clarithromycin

Posada et al ASCPT 2017

CYP3A4 Inhibition Predictions

Analyte	Parameter	Inhibitor				
		Verapamil	Diltiazem	Clarithromycin	Itraconazole	Ketoconazole
Abemaciclib	$AUC_{0\text{-}inf}$ ratio Geo mean (90%CI)	2.28 (2.10,2.48)	3.95 (3.71, 4.2)	4.95 (4.54,5.39)	7.15 (6.86,7.45)	15.7 (14.2,17.3)
	C_{max} ratio Geo mean (90%CI)	1.64 (1.57,1.70)	1.92 (1.85, 1.98)	2.09 (2.01,2.17)	2.19 (2.11,2.27)	2.5 (2.37,2.60)
M2	$AUC_{0\text{-}inf}$ ratio Geo mean (90%CI)	1.06 (1.04,1.09)	1.05 (1.00, 1.09)	0.89 (0.84,0.94)	0.87 (0.81,0.93)	0
	C_{max} ratio Geo mean (90%CI)	0.61 (0.57, 0.66)	0.42 (0.39, 0.45)	0.29 (0.26,0.32)	0.25 (0.23,0.26)	0
M20	$AUC_{0\text{-}inf}$ ratio Geo mean (90%CI)	1.30 (1.25,1.36)	1.53 (1.46, 1.60)	1.33 (1.25,1.42)	1.60 (1.46,1.74)	0
	C_{max} ratio Geo mean (90%CI)	0.74 (0.71,0.77)	0.56 (0.52,0.60)	0.41 (0.37,0.45)	0.37 (0.35,0.39)	0
M18	$AUC_{0\text{-}inf}$ ratio Geo mean (90%CI)	0.6 (0.55, 0.65)	0.34 (0.31,0.36)	0.29 (0.27,0.32)	0.09 (0.08,0.10)	0
	C_{max} ratio Geo mean (90%CI)	0.33 (0.29, 0.39)	0.12 (0.10 ,0.14)	0.10 (0.09,0.12)	0.03 (0.025,0.028)	0
Active Species	$AUC_{0\text{-}inf}$ ratio Geo mean	1.63	2.41	2.76	3.78	6.87

Posada et al ASCPT 2017