U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Project Optimus – FDA's "New" Dose Optimization & Selection Paradigm in Oncology Drug Development

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Simulations Plus Webinar

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Disclaimers:
We have no conflict of interest to report. The views presented here are our personal opinions and should not be interpreted as the position of the US FDA.

Outline

1. Project Optimus—Old Question, New Emphasis—Why Now?
2. Case Study: Idelalisib
3. Dose Optimization Rather than MTD
4. MIDD Tools
5. MIDD Case Examples

OCE---Project Optimus

- **Mission:** To ensure that doses of cancer drugs are optimized to maximize efficacy as well as safety and tolerability

Specific Goals

- Communicate expectations for dose-finding and dose optimization, through Guidance, workshops, other public meetings

- Provide opportunities for and encourage drug developers to meet with FDA Oncology Review Divisions early in their development programs, well before conducting trials intended for registration, to discuss dose-finding and dose optimization.

- Develop strategies for dose finding and dose optimization that leverages nonclinical and clinical data in dose selection, including randomized evaluations of a range of doses in trials. An emphasis of such strategies will be placed on performing these studies as early as possible in the development program and as efficiently as possible to bring promising new therapies to patients.

https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus

Project Optimus: Old Question, New Emphasis

The Office of Clinical Pharmacology

"Our vision: To improve public health by building and translating knowledge of drug-response into patient-centered regulatory decisions of the highest quality.

Our mission:
1.Play a pivotal role in advancing the development of innovative new medicines by applying state-of-art scientific principles

2.Promote therapeutic optimization and individualization through best practices in research, policy development, and drug evaluation throughout the product lifecycle."—Dr. Issam Zineh, Director of OCP

"Right Dose, Right Drug, Right Patient, Right Time" Dr. Lawrence Lesko, former Director, OCP –*circa* 2005

So, What has changed? Why Now?

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-clinical-pharmacology

Lack of Dose Optimization

Oncology Drugs with PMRs/PMCs Related to Dose

2011	2012	2013	2014	2015	2016	2017
ipilimumab **vandetanib** abiraterone rivaroxaban vemurafenib brentuximab vedotin crizotinib deferiprone ruxolitinib asparaginase *Erwinia chrysanthemi*	glucarpidase axitinib vismodegib peginesatide pertuzumab **carfilzomib** ziv-aflibercept tbo-filgrastim enzalutamide bosutinib regorafenib **omacetaxine** **cabozantinib** **ponatinib**	pomalidomide **T-DM1** **radium RA-223** trametinib dabrafenib afatinib obinutuzumab ibrutinib	ofatumumab ramucirumab siltuximab **ceritinib** belinostat **idelalisib** pembrolizumab blinatumomab olaparib nivolumab	**panobinostat** palbociclib **lenvatinib** dinutuximab sonidegib trifluridine trabectedin cobimetinib osimertinib daratumumab ixazomib necitumumab **elotuzumab** alectinib	venetoclax atezolizumab olaratumab rucaparib	**ribociclib** niraparib midostaurin brigatinib durvalumab avelumab rituximab SC neratinib enasidenib **inotuzumab** tisagenlecleucel **gemtuzumab** copanlisib abemaciclib

Courtesy of Dr. Lanre Okusanya, Deputy Director, DCP I, OCP, FDA

Case Study: Idelalisib

- Granted regular approval in relapsed CLL in July 2014
  - Relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities

Study 312-0116			
Design	**Population**	**Treatment**	**Endpoint**
Randomized (1:1) Placebo-controlled	Relapsed CLL	Idelalisib + Rituximab (I + R) Placebo + Rituximab (Pbo + R)	Primary: Progression-free survival (PFS)

	I + R N = 110	**Pbo + R N = 110**
PFS Events, n (%)	25 (23)	70 (64)
Median PFS, months (95% CI)	19.4 (12.3, NR)	6.5 (4.0, 7.3)
Adjusted HR (95% CI)	0.15 (0.09, 0.24)	

Abbreviations: CI, confidence interval, CLL, chronic lymphocytic leukemia, HR, hazard ratio, NR, not reached

https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-information-april-21-22-2022-meeting-oncologic-drugs-advisory-committee-meeting-announcement

Idelalisib Approvals

- Granted accelerated approval in relapsed FL and SLL in July 2014
  - Relapsed FL and SLL in patients who have received at least two prior systemic therapies

Study 101-09				
Design	**Population**	**Treatment**	**Endpoint**	**ORR (95% CI)**
Single-arm trial	Relapsed FL (N = 72) Relapsed SLL (N = 26)	Idelalisib 150 mg orally twice daily	Primary: Overall response rate (ORR)	FL = 54% (42, 66) SLL = 58% (37, 77)

Abbreviations: FL, follicular lymphoma, SLL, small lymphocytic lymphoma

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March 2016
Three Randomized Trials Terminated Due to Increased Deaths

Study	Population & Treatment	Deaths Idelalisib	Deaths Control	Hazard Ratio (95% CI)
312-0123	• Untreated CLL • Bendamustine and rituximab ± idelalisib	**8%** (12/157)	3% (4/154)	**3.34** (1.08, 10.39)
313-0124	• Previously treated indolent NHL • Rituximab ± idelalisib	**5%** (10/191)	1% (1/95)	**4.74** (0.6, 37.12)
313-0125	• Previously treated indolent NHL • Bendamustine and rituximab ± idelalisib	**8%** (27/320)	6% (9/155)	**1.51** (0.71, 3.23)

Abbreviations: CI, confidence interval, CLL, chronic lymphocytic leukemia, NHL, non-Hodgkin lymphoma

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Difference in Toxicity Driven by PI3K-Associated Toxicities

	Study 312-0123 Untreated CLL		Study 313-0124 R/R indolent NHL		Study 313-125 R/R indolent NHL	
	I + BR N = 157	Pbo + BR N = 154	I + R N = 191	Pbo + R N = 95	I + BR N = 320	Pbo + BR N = 155
Grade ≥3 Infection	**45%**	20%	**22%**	4%	**40%**	19%
Grade ≥3 Neutropenia*	65%	64%	12%	10%	41%	37%
Grade ≥3 Diarrhea-Colitis	**9%**	3%	**19%**	2%	**13%**	0
Grade ≥3 ALT/AST increase*	**26%**	1%	**48%**	0	**27%**	<1%
Grade ≥3 Rash	**17%**	10%	**8%**	1%	**19%**	1%
Any Grade Pneumonitis	**6%**	3%	**6%**	1%	**8%**	1%

*Based on laboratory data

Abbreviations: BR, bendamustine and rituximab, CLL, chronic lymphocytic leukemia, I, idelalisib, NHL, non-Hodgkin lymphoma, Pbo, placebo, R, rituximab, R/R, relapsed or refractory

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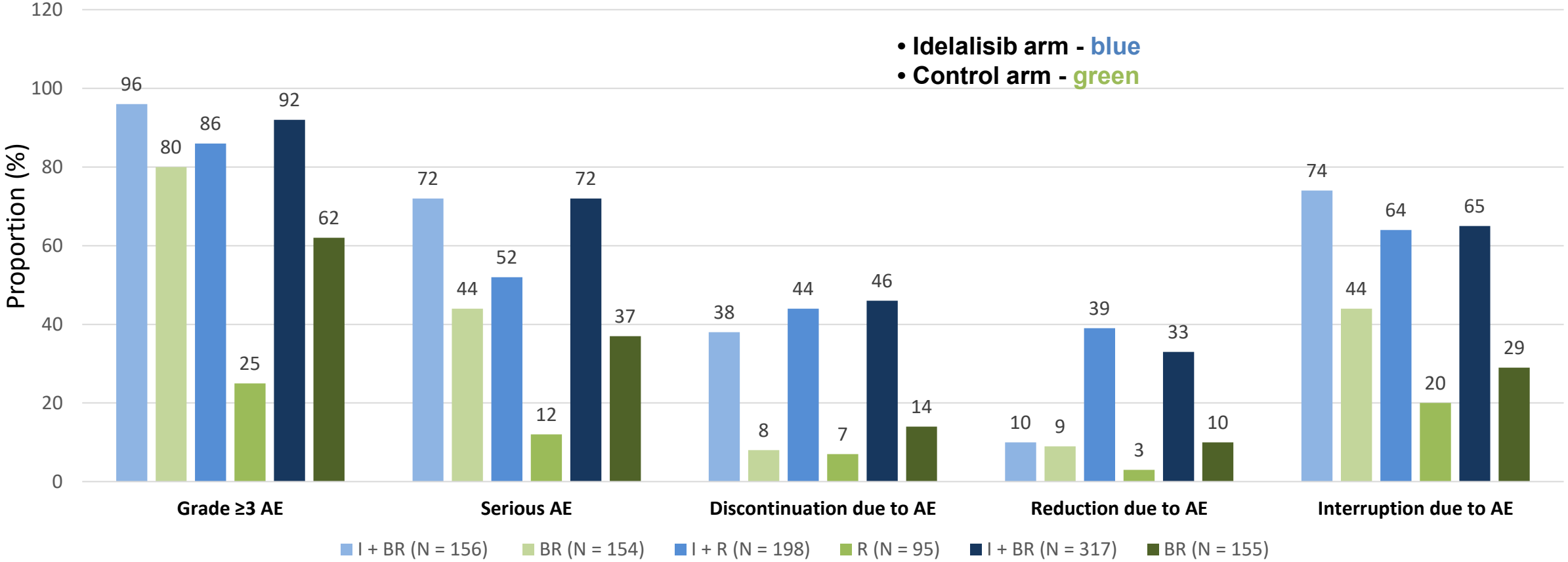
March 2016
Three Randomized Trials Demonstrated Increased Toxicity



Study 312-0123
Untreated CLL

Study 313-0124
R/R indolent NHL

Study 313-0125
R/R indolent NHL

Abbreviations: AE, adverse event, BR, bendamustine + rituximab, CLL, chronic lymphocytic leukemia, I, idelalisib, NHL, non-Hodgkin lymphoma, R, rituximab, R/R, relapsed or refractory

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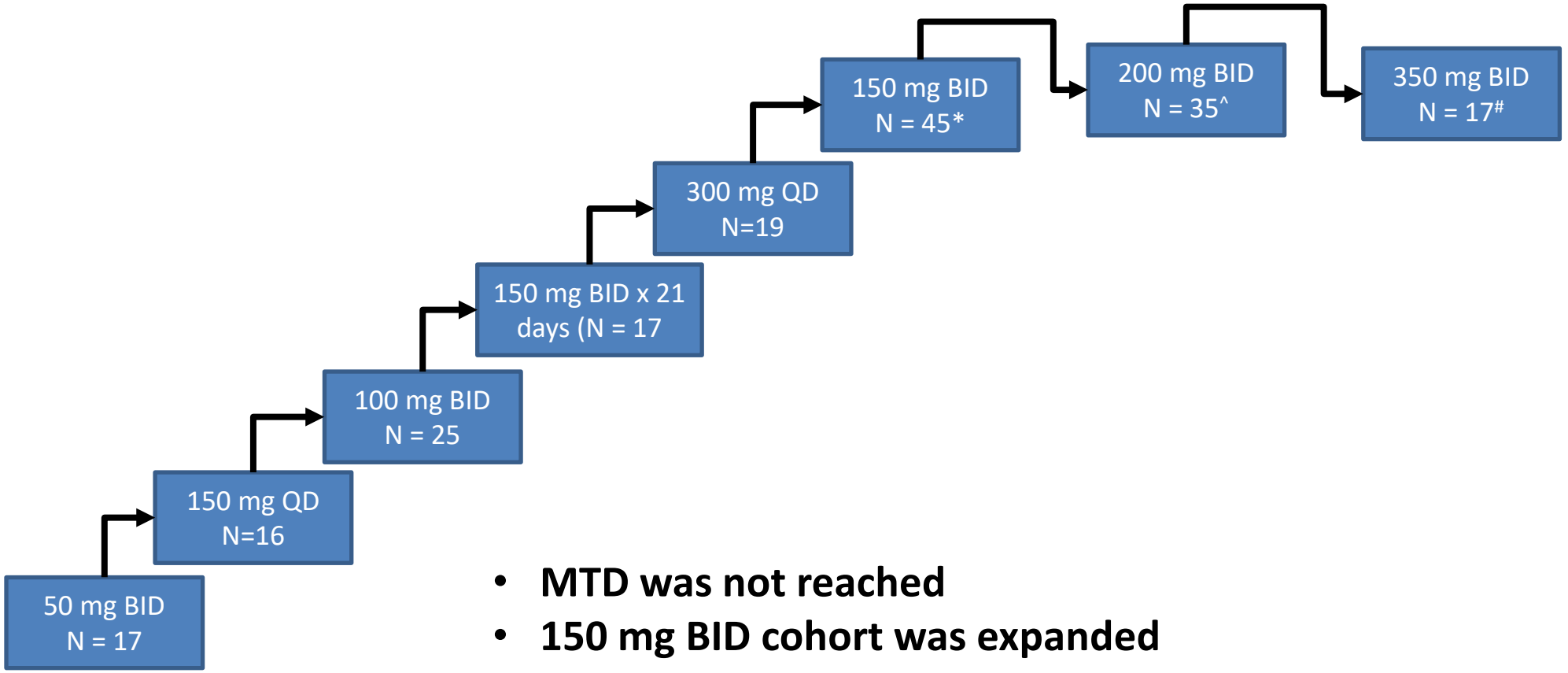
Idelalisb
(and the other PI3KI (and Other Oncology Drugs))

Where Did We Go Wrong?

Let's Go Back to the Beginning

Idelalisib Dose Finding Design



- **MTD was not reached**
- **150 mg BID cohort was expanded**
- **150 mg BID was selected as the dose for further development**

References: Study 101-02 CSR

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Idelalisib Dose Finding: Efficacy

Dose Level	MCL (n=40)		iNHL (n =64)		CLL (n=54)		DLBCL (n=9)	
	N	ORR (95% CI)	N	ORR (95% CI)	N	ORR (95% CI)	N	ORR (95% CI)
50 mg BID	5	20 (0.5, 71.6)	7	14.3 (0.4, 57.9)	5	40 (5.3, 85.3)	0	
100 mg BID	7	14.3 (0.4, 57.9)	7	85.7 (42.1, 99.6)	11	45.5 (16.7, 76.6)	0	
150 mg BID	6	50 (11.8, 88.2)	10	30 (6.7, 65.2)	11	45.5 (16.7, 76.6)	4	0 (0, 60.2)
200 mg BID	3	100 (29.2, 100)	10	60 (26.2, 87.8)	10	60 (26.2, 87.8)	3	33.3 (0.8, 90.6)
350 mg BID	3	66.7 (9.4, 99.2)	4	100 (39.8, 100)	7	71.4 (29, 96.3)	2	0 (0, 84.2)
150 mg BID × 21 days	5	20 (0.5, 71.6)	12	25 (5.5, 57.2)	0		0	
150 mg QD	7	28.6 (3.7, 71)	9	33.3 (7.5- 70.1)	0		0	
300 mg QD	4	75 (19.4, 99.4)	5	60 (14.7, 94.7)	10	60 (26.2, 87.8)	0	

Abbreviations: CI, confidence interval; MCL, mantle cell lymphoma; iNHL, indolent non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate.

References: Study 101-02 CSR

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Idelalisib Dose Finding: Safety

Dose Level	N	Grade ≥ 3 ALT n (%)	Grade ≥ 3 AST n (%)	Grade ≥ 3 ALT or AST n (%)
50 mg BID	17	2 (11.8%)	2 (11.8%)	2 (11.8%)
100 mg BID	25	2 (8.0%)	2 (8.0%)	2 (8.0%)
150 mg BID	45	5 (11.1%)	3 (6.7%)	5 (11.1%)
200 mg BID	35	7 (20.0%)	6 (17.1%)	7 (20.0%)
350 mg BID	17	3 (17.6%)	3 (17.6%)	3 (17.6%)
150 mg BID × 21 days	17	1 (5.9%)	0	1 (5.9%)
150 mg QD	16	3 (18.8%)	2 (12.5%)	3 (18.8%)
300 mg QD	19	4 (21.1%)	4 (21.1%)	4 (21.1%)
Total	191	27 (14.1%)	22 (11.5%)	27 (14.1%)

References: Study 101-02 CSR

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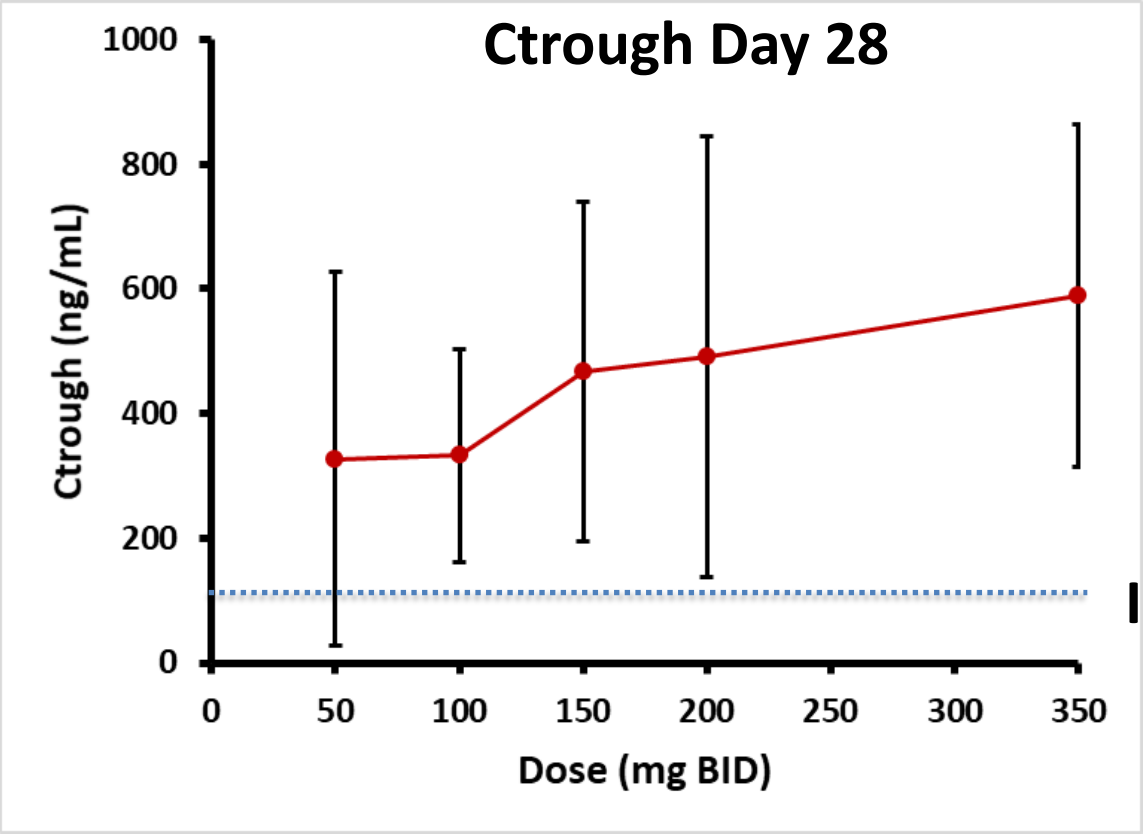
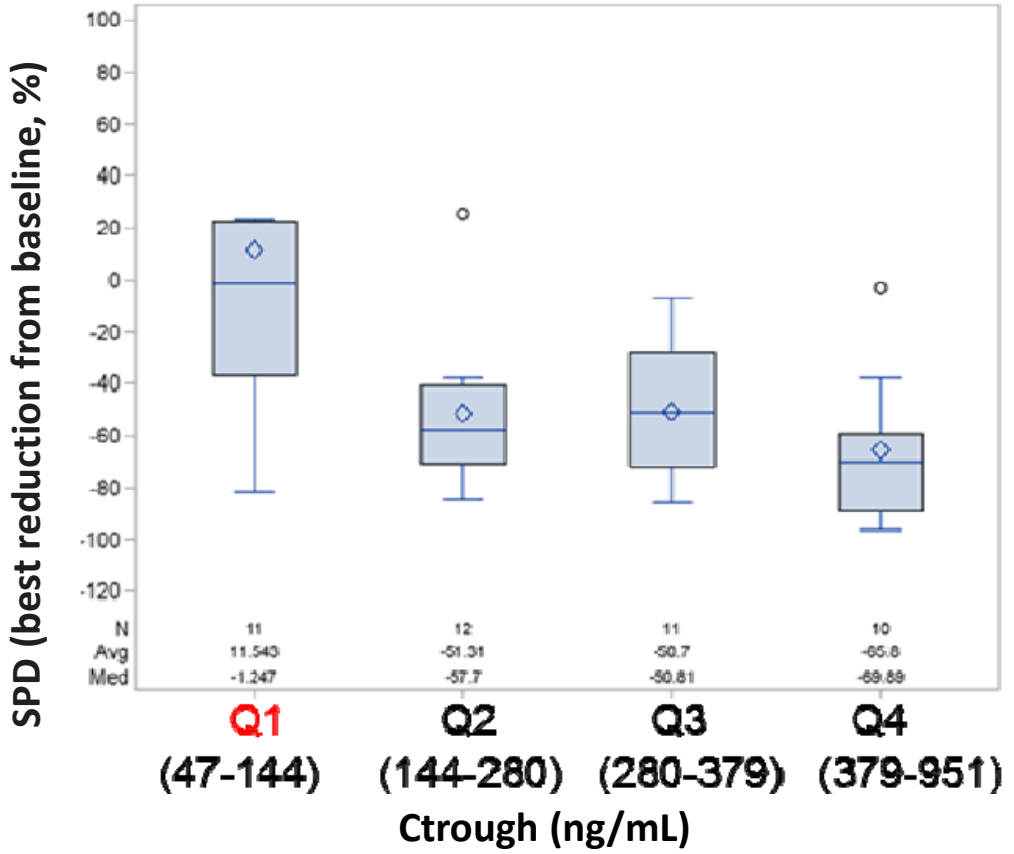
Idelalisib Dose Finding: PK/PD



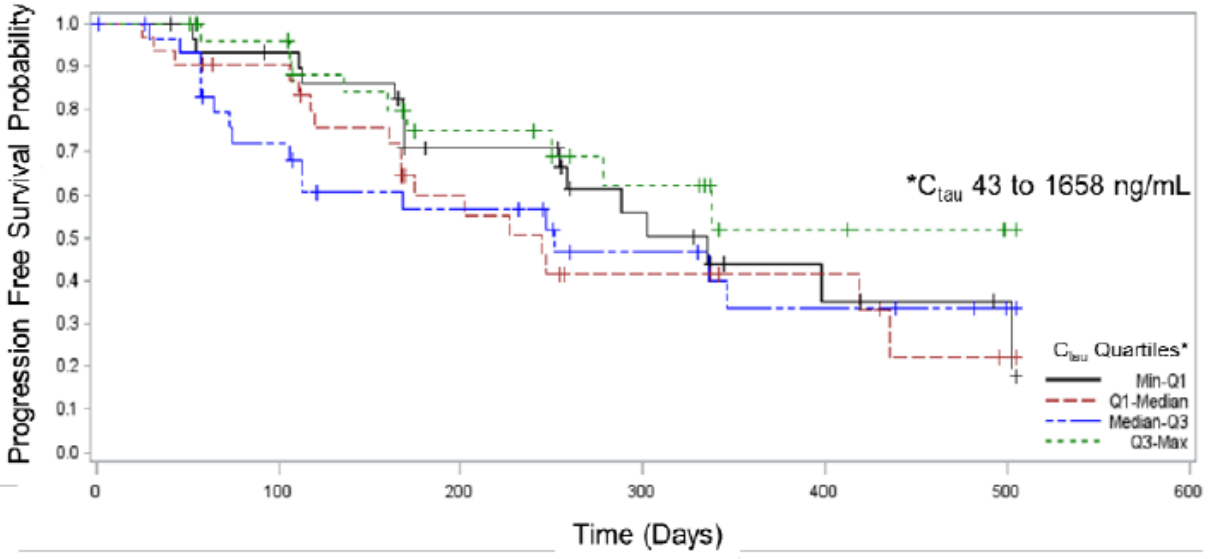


- Doses ≥100 mg BID exceeded the in vitro IC 90 for PI3Kδ in 90% of patients.

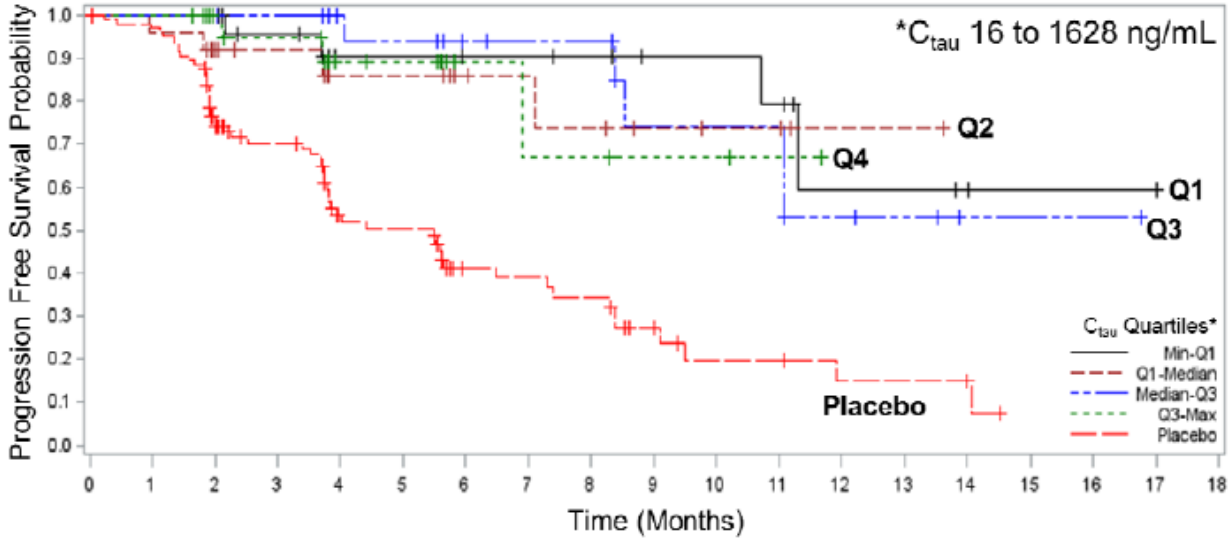
References: Based on NDA 205858 Clinical Pharmacology Review at Drugs@FDA

Idelalisib: E-R for Efficacy

iNHL (Study 101-09)



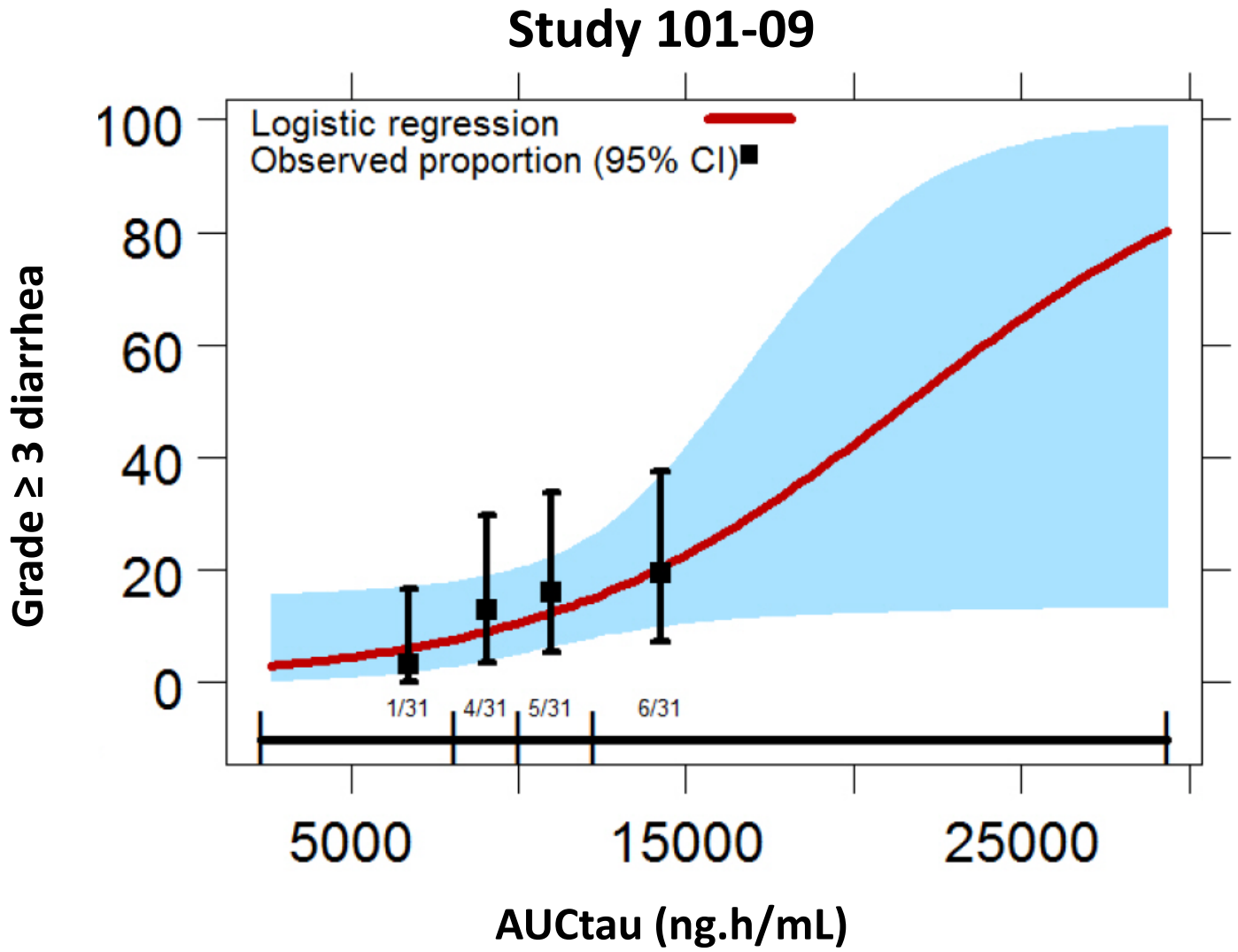
CLL (Study GS-US-312-0116)



- No exposure response relationship for efficacy was identified, due to the limited data available from the one dose level (150 mg BID).

References: NDA 205858 Clinical Pharmacology Review at Drugs@FDA

Idelalisib: E-R for Safety



References: NDA 205858 Clinical Pharmacology Review at Drugs@FDA

Idelalisib Dosing Considerations

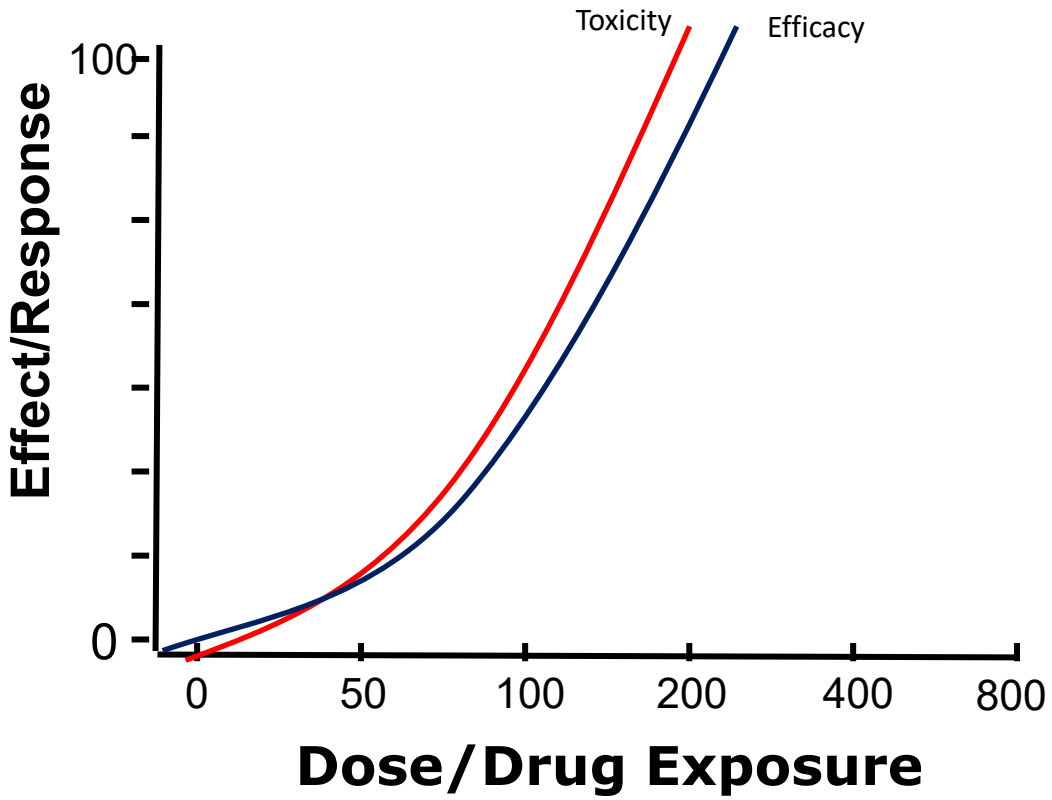
Idelalisib – approved dose 150 mg BID

- Monotherapy
  - **Maximum tolerated dose (MTD) not reached**
  - Exposure-response for efficacy plateaued at 150 mg BID
  - Higher exposure associated with increased risk of toxicity
  - High rates of treatment modifications due to toxicity
  - Lower doses (e.g., 100 mg BID) may be efficacious and tolerable

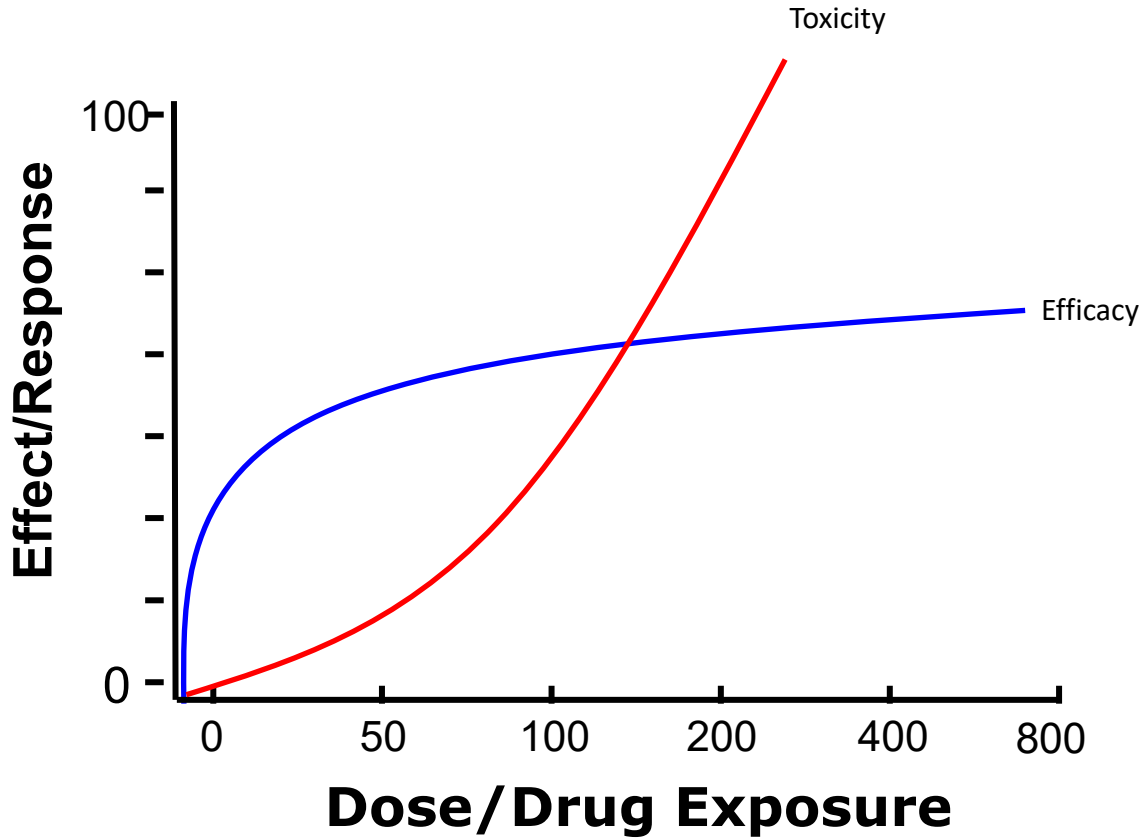
Abbreviations: E-R, exposure-response, PK, pharmacokinetic

Dose Selection for Oncology
Dose Optimization Rather Than MTD

Cytotoxic Chemotherapy



Targeted Therapies



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Take Home Messages

1. Dose Optimization, Not MTD
   - MTD blinds us to better dosing choices
2. Maximize the Use of Knowledge Generated During Development
   - Make greater use of PK/PD, biomarker data, outcomes, Modeling & Simulation tools

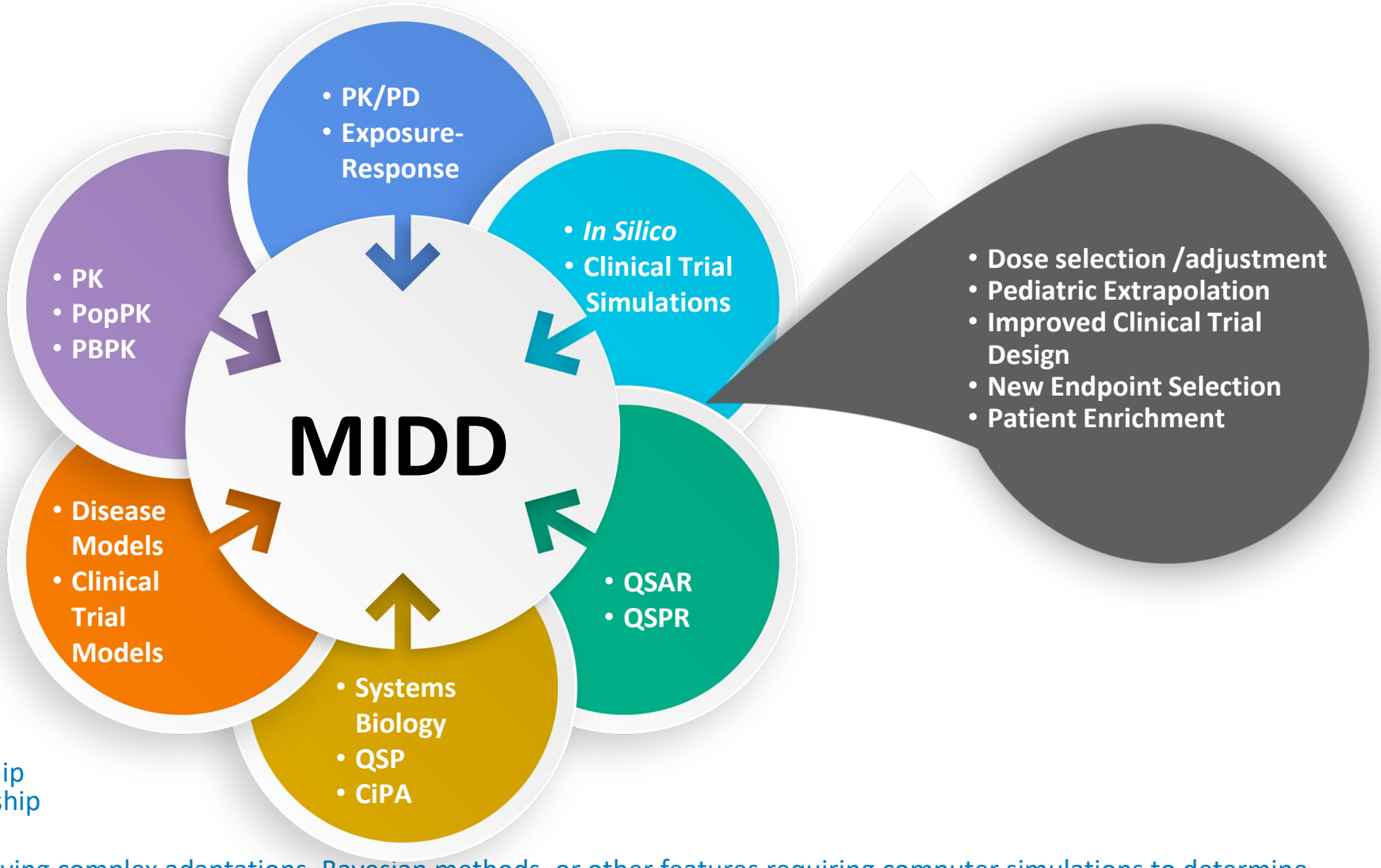
Dose Optimization Strategies

- The MTD is not the goal to strive for—consider doses that better optimize efficacy/toxicity
- Give consideration to nonclinical data including in vitro/in vivo receptor occupancy/target engagement data
- Enroll sufficient patients to characterize the PK (e.g., linearity, absorption, elimination) of the drug after multiple doses
- Consider PK/PD relationships with biomarkers and study outcomes
- Utilize modeling and simulation to predict outcomes by dose level-MIDD
- At the dose levels being considered, expansion of several dose cohorts may be necessary to assess activity and tolerability at other dose levels
- Randomized, parallel dose response trials may be an appropriate strategy to assess doses when feasible
- Multiple doses may be compared prior to or as a part of registration trial(s) by adding an additional dosage arm

Model Informed Drug Development for Oncological Product Development

Model-Informed Drug Development

Development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources to address drug development or regulatory issues*



QSAR: Quantitative structure–activity relationship
QSPR: Quantitative structure–property relationship

* From PDUFA 6; Excludes statistical designs involving complex adaptations, Bayesian methods, or other features requiring computer simulations to determine the operating characteristics of a confirmatory clinical trial.

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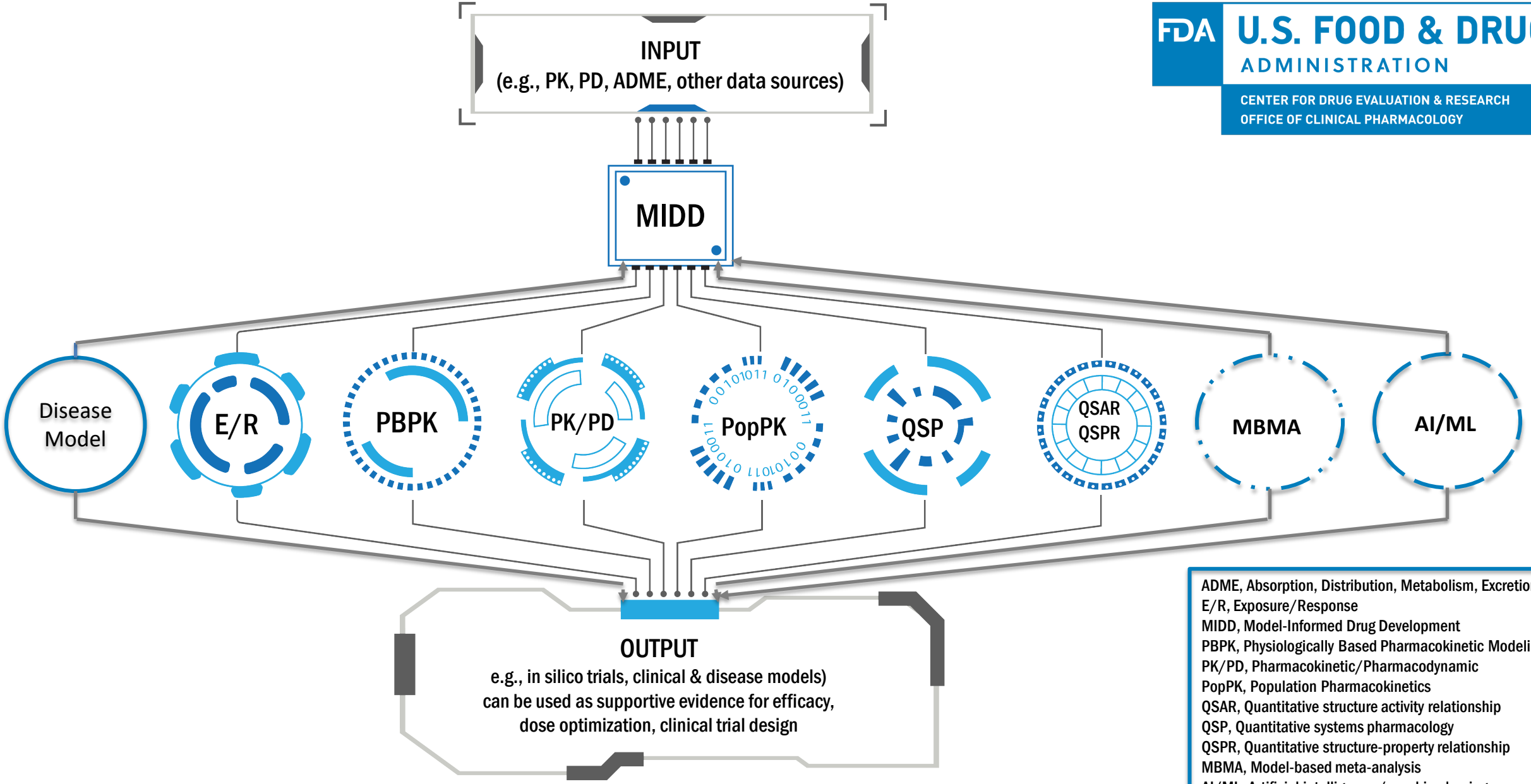
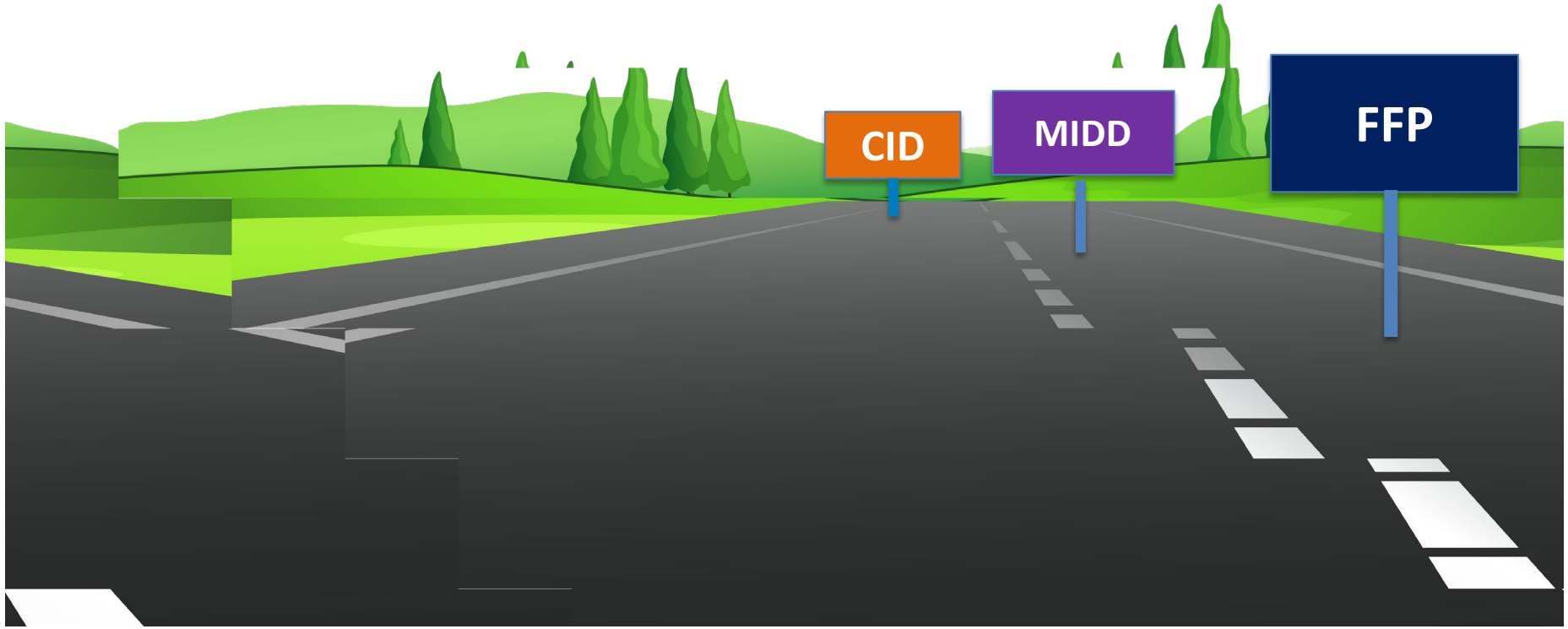


ADME, Absorption, Distribution, Metabolism, Excretion
E/R, Exposure/Response
MIDD, Model-Informed Drug Development
PBPK, Physiologically Based Pharmacokinetic Modeling
PK/PD, Pharmacokinetic/Pharmacodynamic
PopPK, Population Pharmacokinetics
QSAR, Quantitative structure activity relationship
QSP, Quantitative systems pharmacology
QSPR, Quantitative structure-property relationship
MBMA, Model-based meta-analysis
AI/ML; Artificial intelligence / machine learing

Courtesy by Dr. Kimberly Bergman

Avenues for Regulatory Interaction



- To enhance interactions among stake holders in new drug development
- To support Project Optimus

Fit for Purpose (FFP) Initiative

- The Fit-for-Purpose (FFP) Initiative provides a pathway for regulatory acceptance of dynamic tools for use in drug development programs.
- A designation of 'fit-for-purpose' (FFP) will be established based on a thorough evaluation of the information provided.

Disease Area	Submitter	Tool	Trial Component
Multiple	Janssen Pharmaceuticals & Novartis Pharmaceuticals	Statistical model: MCP-Mod	Dose finding
Multiple	Ying Yuan, PhD University of Texas, MD Anderson	Statistical Method: Bayesian Optimal Interval (BOIN) design	Dose Finding
Multiple	Pfizer	Empirical Bayesian Emax model	Dose Finding

Link to the FDA FPP initiative:
<https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative>

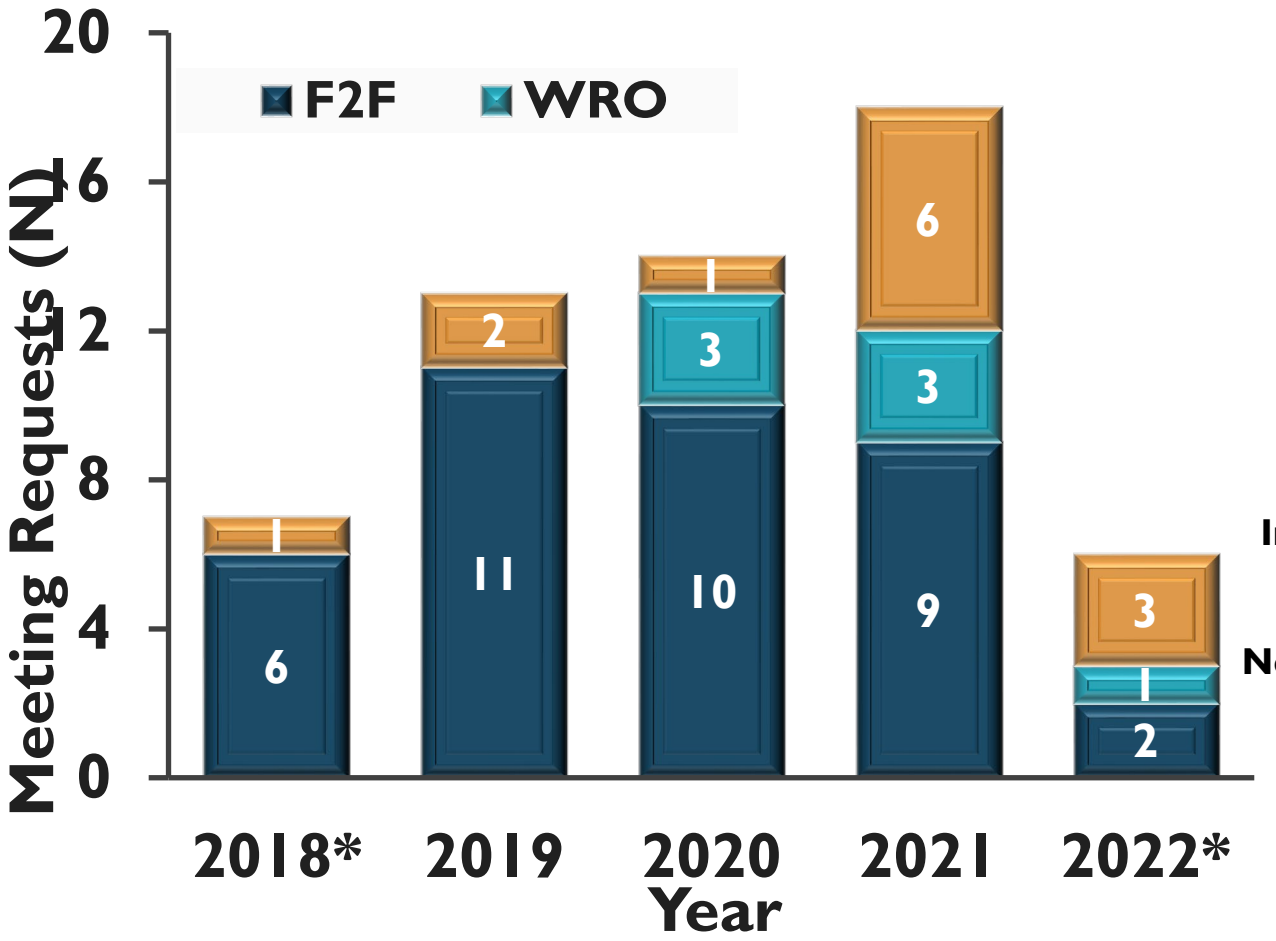
MIDD Paired Meeting Program

- This program is jointly administered by CDER and CBER.
- OCP is the point of contact.
- The sponsor should be a drug or a biologics developer.
- The product should be registered under an U.S. IND/NDA/BLA.
- FDA accepts requests on a continuous basis.
- FDA expects to grant 2-4 submissions on a quarterly basis.
- Expect to continue in PDUFA VII as a formal program.

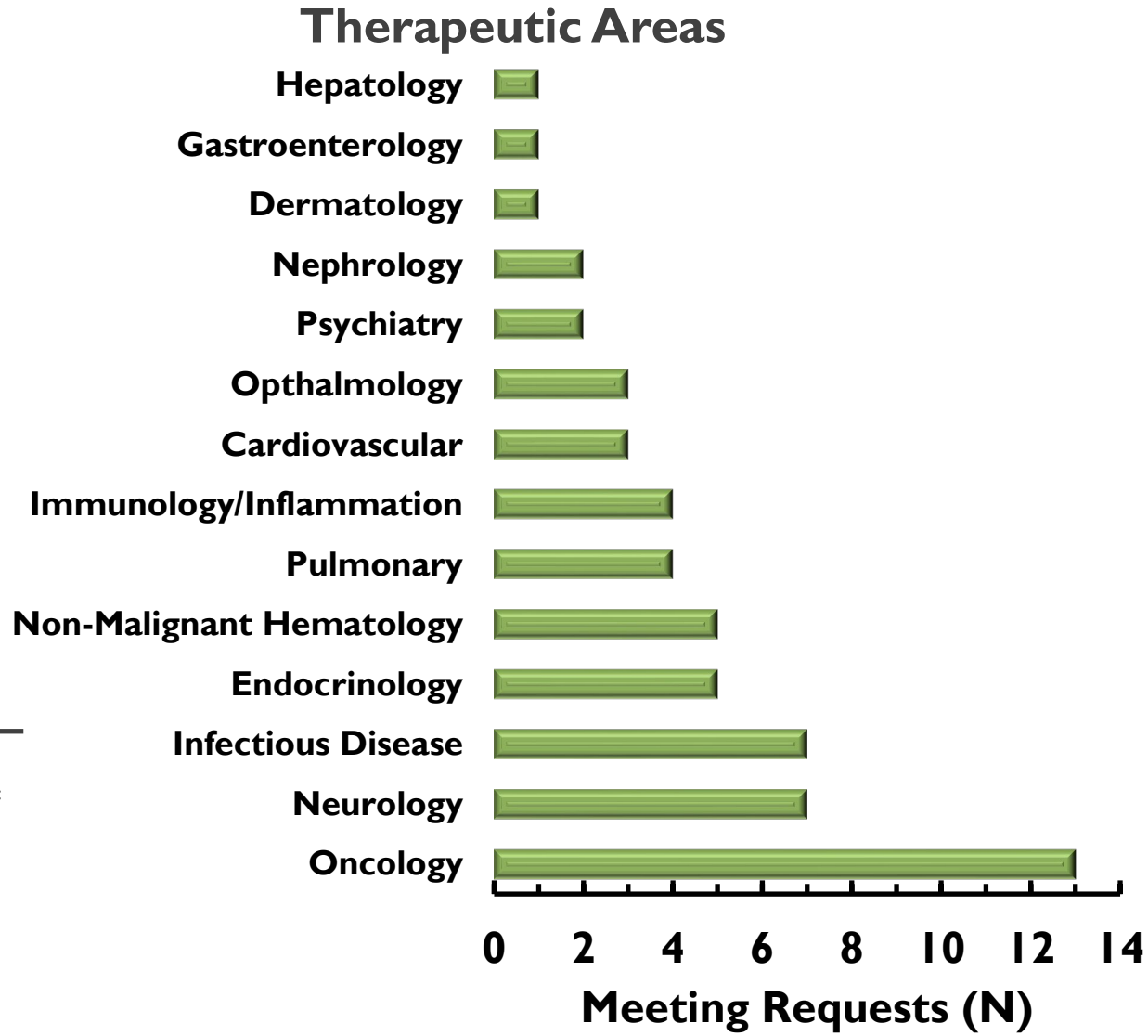
Joint effort for:
(1) all stake holders
(2) multi-disciplinary review team members

Link to the FDA MIDD Program:
<https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program>

Clear Demand for the Program and Increasing



*: Incomplete summary for 2022.



** Partial year #s*

¤ Conducted as of Dec 31, 2021

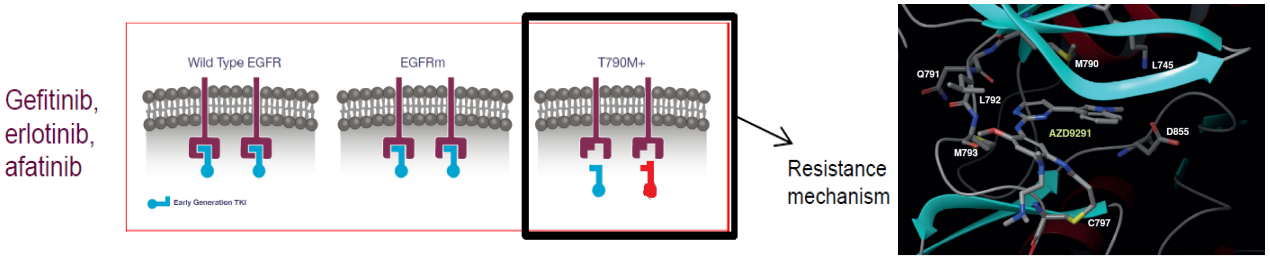
Case Example 1: Osimertinib

Background Information

- 3rd generation EGFR kinase inhibitor for NSCLC:
  - with **metastatic EGFR T790M mutation** (after previous EGFR TKI therapy)
  - with exon 19 deletions or exon 21 L858R mutations (as adjuvant therapy or first-line treatment for metastatic cancer)
- Approved Dosage
  - **80 mg** orally once daily (QD) with or without food
- Drug Discovery Initiation -> (4 ys) FIH -> First FDA AA approval (2.5 ys, OR) -> FDA regular approval (1.5 ys., OR)

Drug Development Was Supported by Robust Non-Clinical Platforms

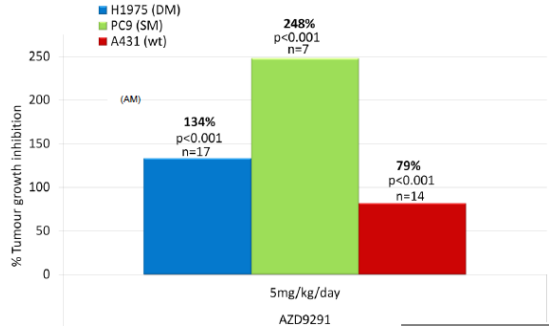
- Specific chemistry design (target & mechanism)



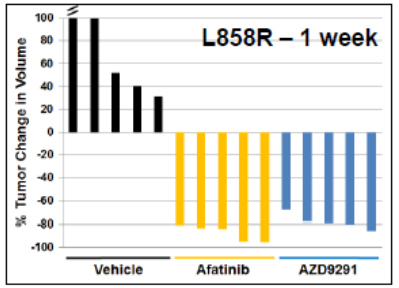
- Specific cell line models

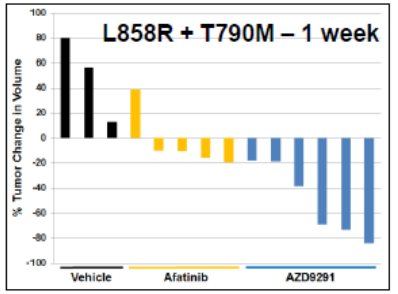
Clinical EGFR mutation	Cell line model
Exon 19 del	PC-9, H1650, HCC827, (HCC4006)*
L858R	H3255, (11-18)*
Ex19del/ T790M	PC-9VanR
L858R/ T790M	H1975
Wild-type EGFR	A431, H2073, LoVo

- Xenograft disease models

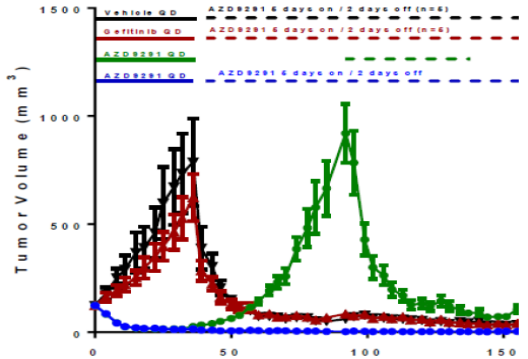


- Transgenic mouse models





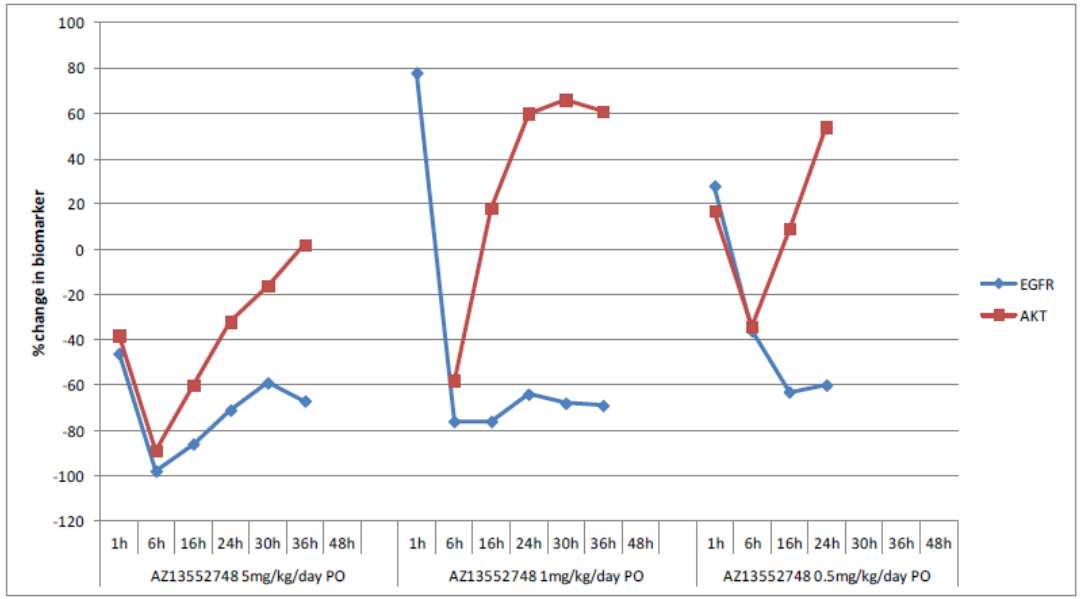
- Patient derived explant models



Darren Cross, 2016 FDA-AACR Workshop

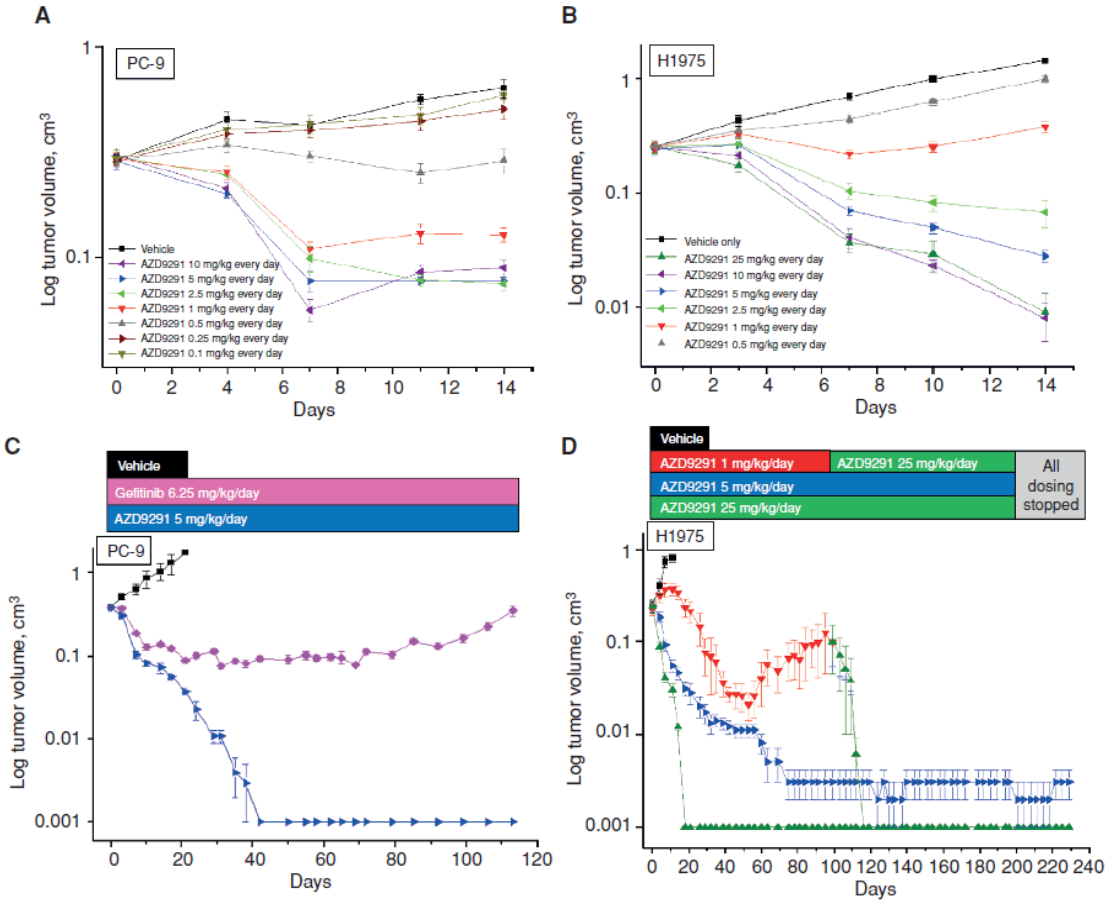
Solid Non-Clinical Dose-Activity Evaluation

- Pharmacodynamic data



% change in phospho/total ratios for EGFR and Akt in response to osimertinib (AZ13552748) in H1975 xenograft model

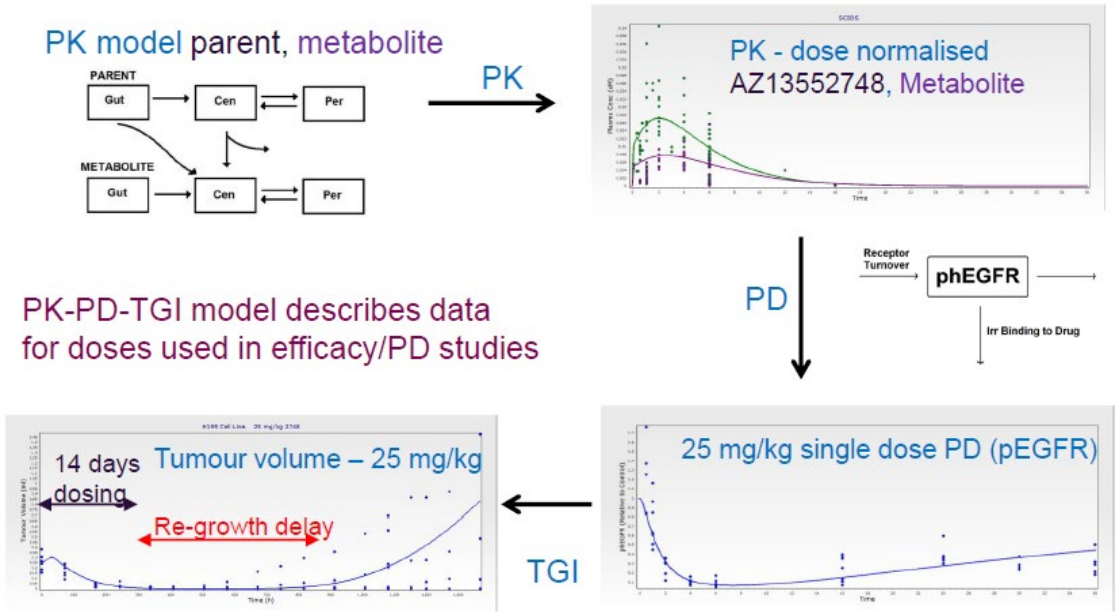
- Antitumor activity

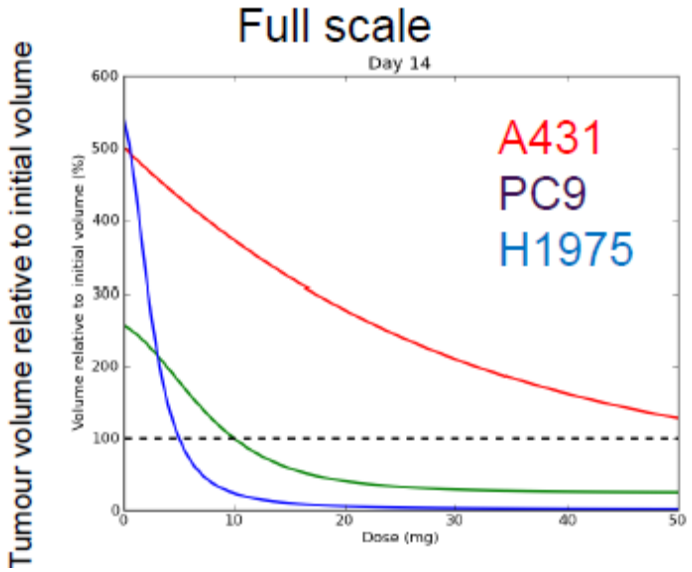


Darren Cross, 2016 FDA-AACR Workshop

Cross et al. (2014) Cancer Discovery, 4, 1046-1061

Strong Predictive Modeling for Forward Translation and Dose Finding

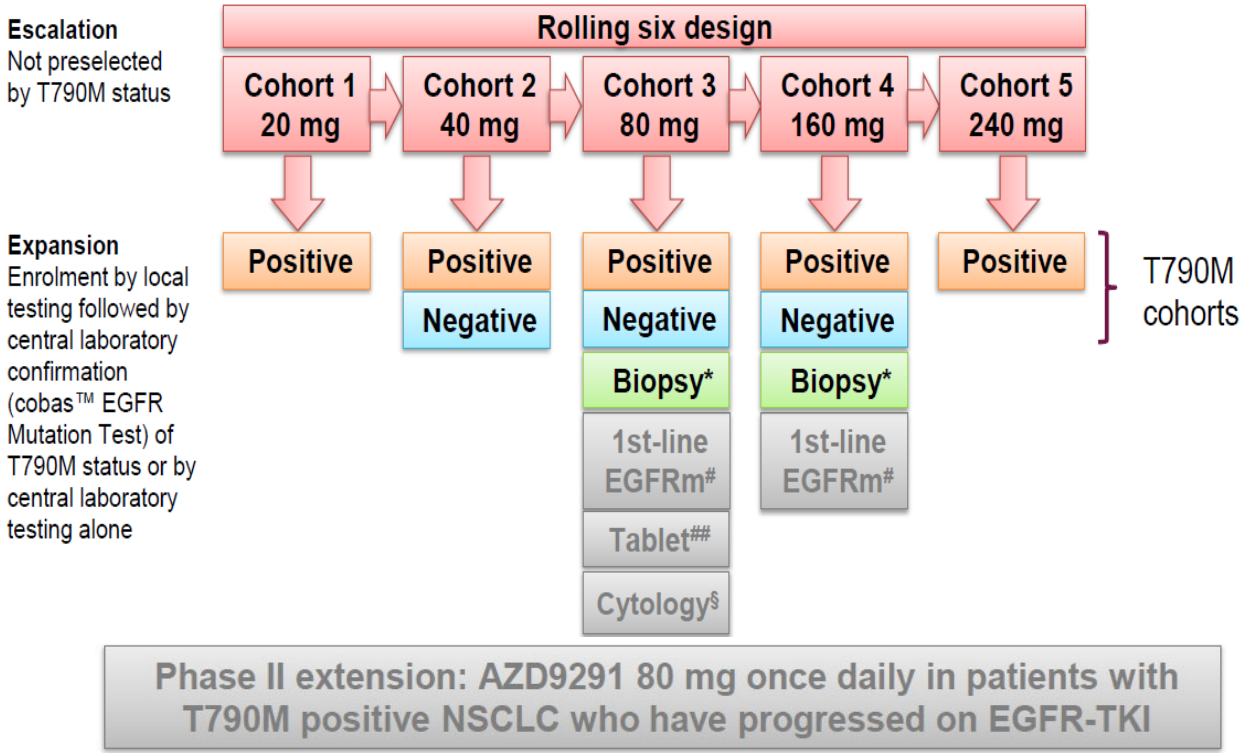


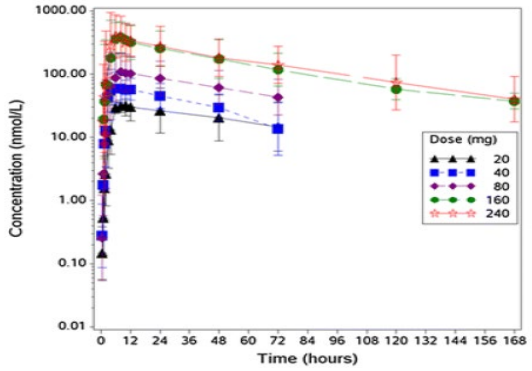


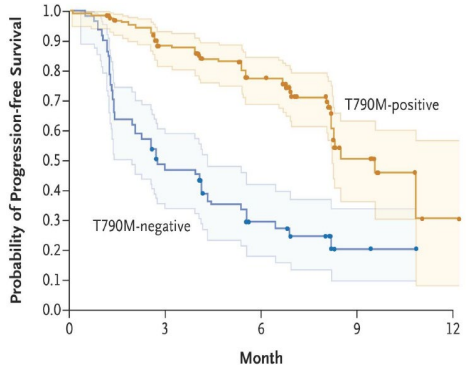
Modeling support taking drug into clinic and predict the first dose of 20 mg in human should provide antitumor activity

Darren Cross, 2016 FDA-AACR Workshop

AURA Phase I Trial

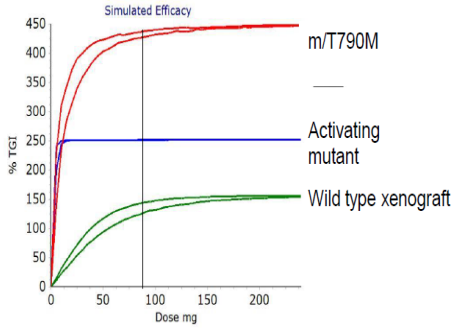






Response rate in T790M positive cohorts

	20 mg	40 mg	80 mg	160 mg	240 mg	Total
N (157)	10	32	61	41	13	157
ORR (95% CI)	50% (19, 81)	59% (41, 76)	66% (52, 77)	51% (35, 67)	54% (25, 81)	59% (51, 66)



AZD9291 appeared less tolerable at doses above 80 mg with more incidence of:

- Skin disorders, nail effects and diarrhea (~doubling)
- Severe grade 3+ AE
- Dose reductions due to AE

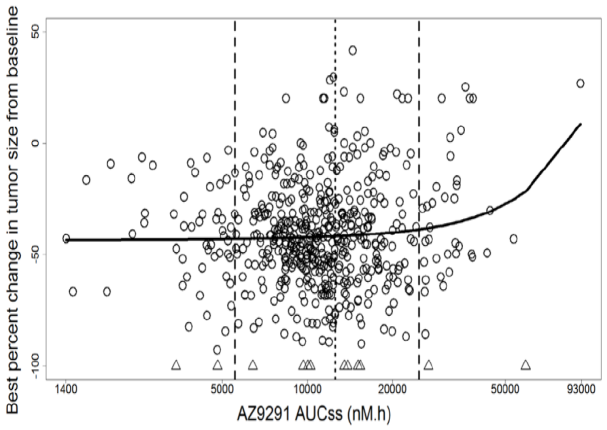
Pasi Janne, 2016 FDA-AACR Workshop

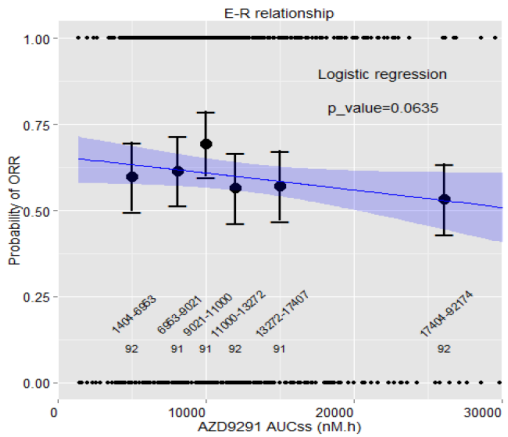
Darren Cross, 2016 FDA-AACR Workshop

AURA and AURA 2 Phase II Trial (T790M+)

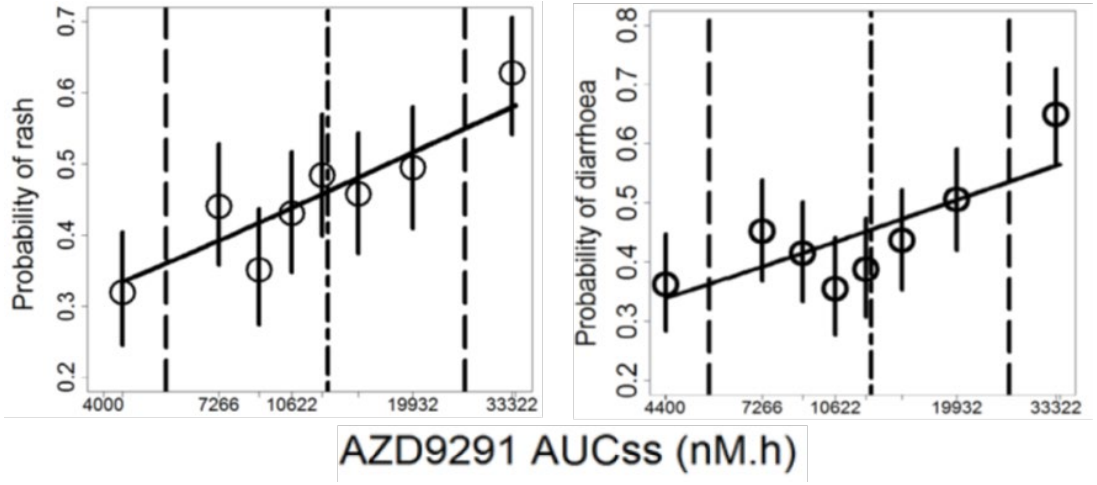
Efficacy Measure (BICR)	Aura Extension (n=201)	AURA2 (n=210)	Pooled (n=411)
Confirmed Objective Response Rate	57%	61%	59%
(95% CI)	(50, 64)	(54, 68)	(54, 64)
Complete Response	0	1%	0.5%
Partial Response	57%	60%	59%

ER for Efficacy





ER for Safety



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AURA3 Phase III Trial vs. Chemo (T790M+) Initiated Before AA

Locally Advanced/Metastatic NSCLC with EGFR T790M mutation (after previous EGFR TKI therapy) (n=419)

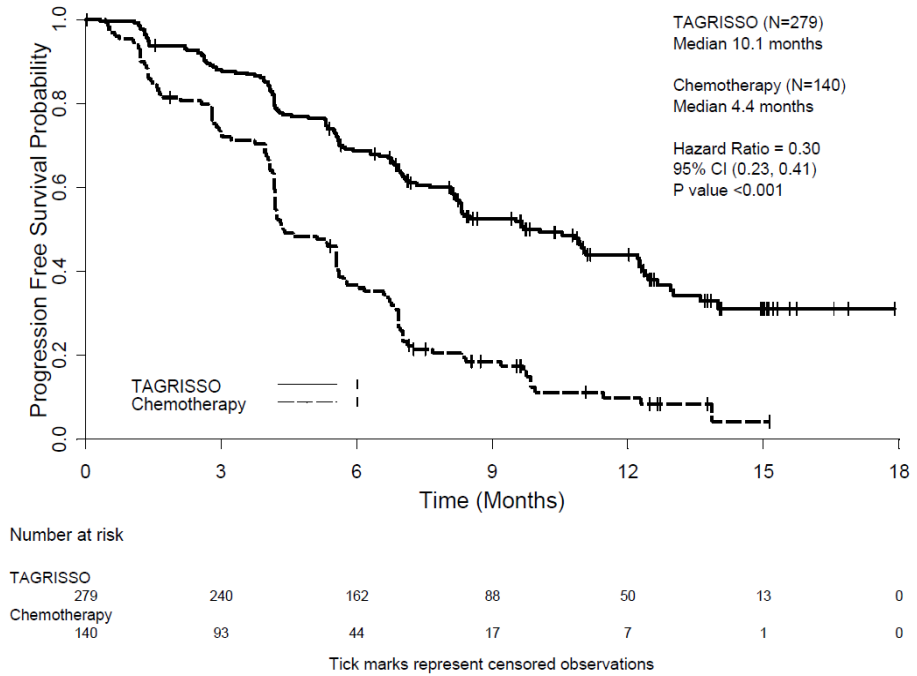
R

2 → **Osimertinib (80 mg QD)**

1 → **Platinum–Pemetrexed**

Primary: PFS
Secondary:
- ORR, DOR, DCR,
- Tumor Shrinkage
- OS

Other: PRO, TFST, TSST



Efficacy Parameter	TAGRISSO (N=279)	Chemotherapy (N=140)
Objective Response Rate[e]		
Objective Response Rate	65%	29%
(95% CI)[b, f]	(59%, 70%)	(21%, 37%)
Complete response	1%	1%
Partial response	63%	27%
P-value	<0.001	
Duration of Response (DoR)		
Median Duration of Response in months (95% CI)	11.0 (8.6, 12.6)	4.2 (3.0, 5.9)

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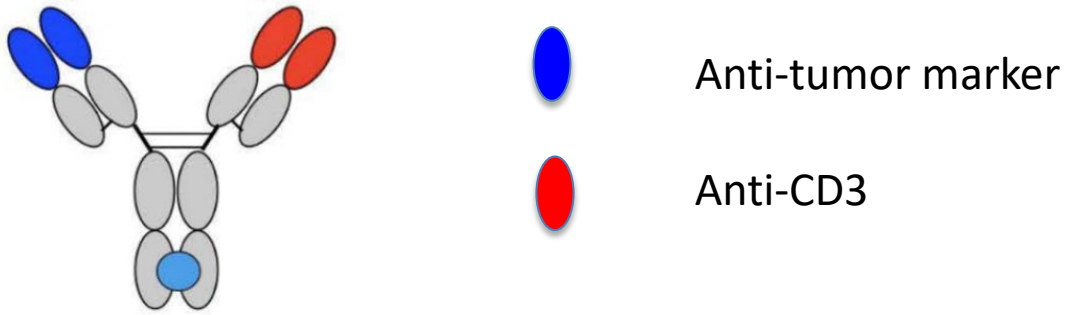
Osimertinib – Summary of Dose Finding/Optimization

Non-clinical/PD	From specific structure-based chemistry design to various robust assay platforms enabled rapid mechanistic activity and dosing evaluation
Predictive Modeling	Integrated Dose-PK-PD-Clinical Response information for forward translation and dose finding
Multiple Doses	Sufficient data in the expansion study provided robust dose-response evaluation and targeted population identification
Continual Optimization	Integrated up-to-date inform using predictive modeling and exposure-response analyses to support subsequent development program for first-line and adjuvant indications

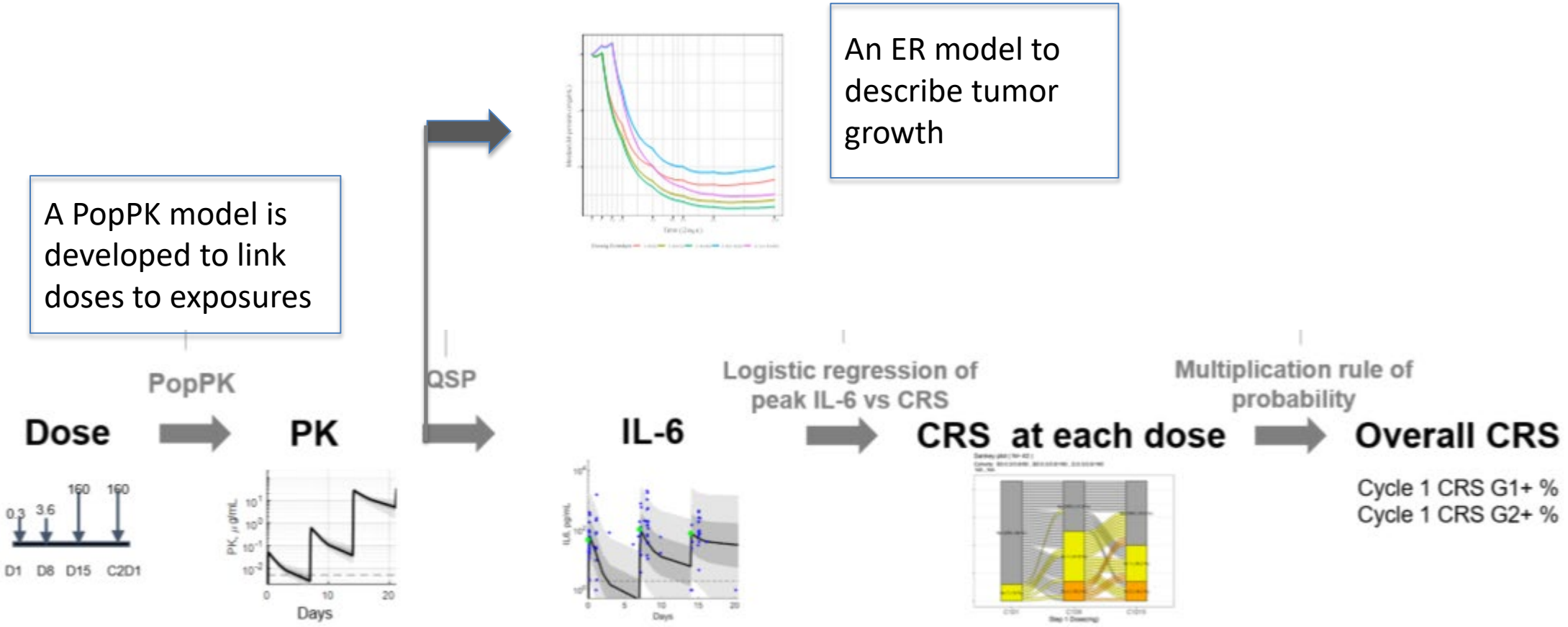
Case Example 2: Drug X

Background Information

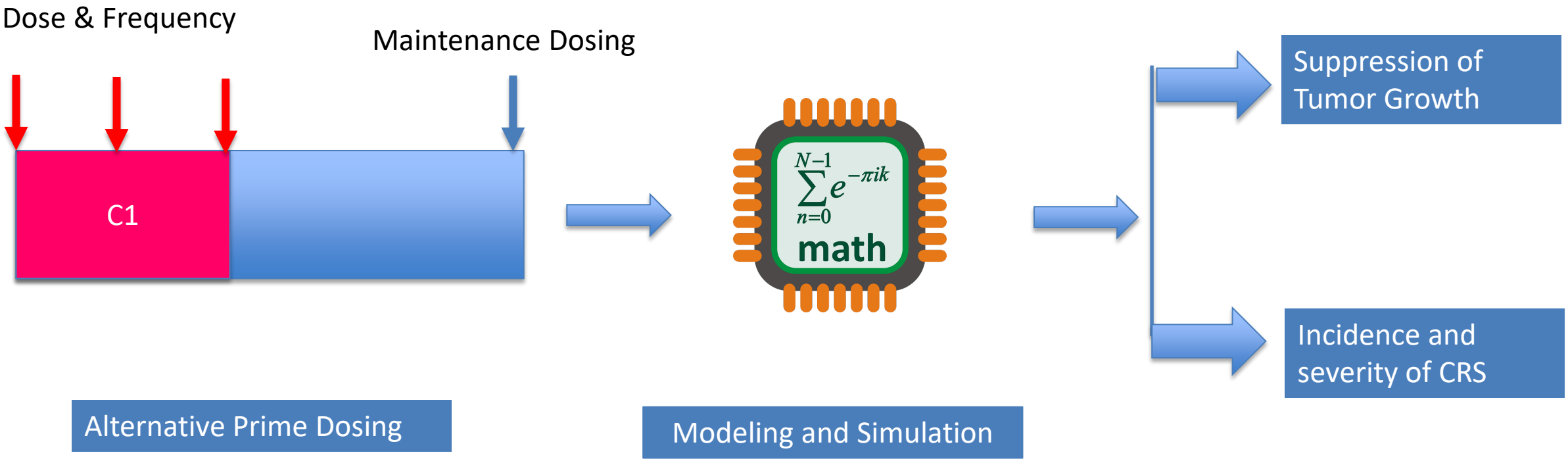
Drug X is a bispecific antibody under clinical development for the treatment of demagogical malignancy.



The sponsor is planning a Phase 3 clinical trial. Modeling approach is used to identify appropriate prime dosing to minimize the risks of developing cytokine release syndrome (CRS) in patients initiating the treatment.

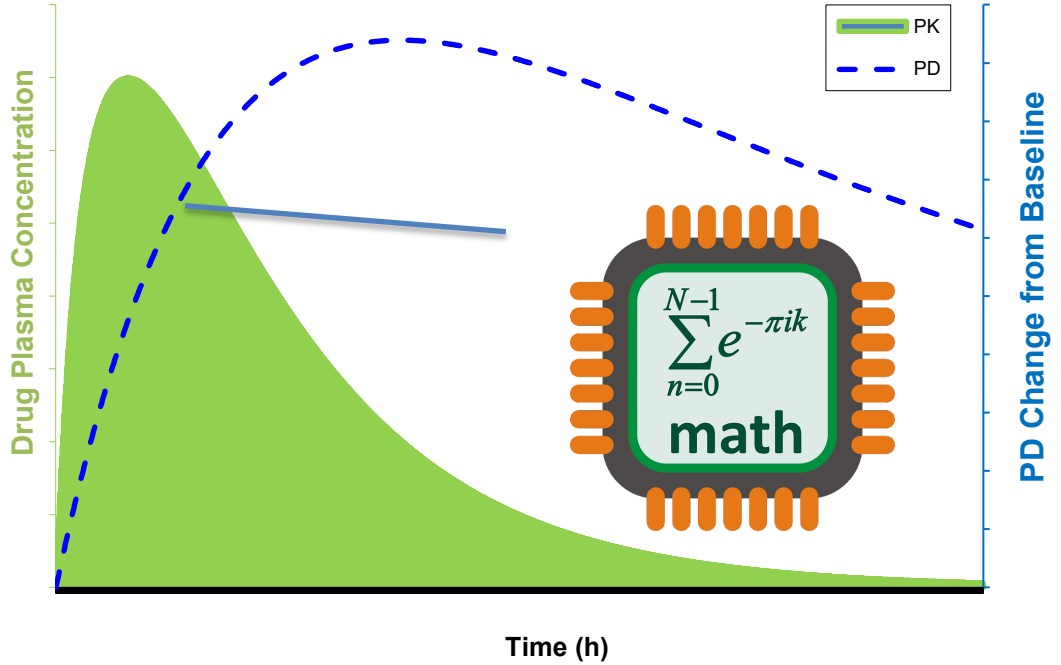

A PopPK model is developed to link doses to exposures
PopPK
Dose
0.3
3.6
160
160
D1
D8
D15
C2D1
PK
Days
QSP
IL-6
Days
An ER model to describe tumor growth
Logistic regression of peak IL-6 vs CRS
CRS at each dose
Multiplication rule of probability
Overall CRS
Cycle 1 CRS G1+ %
Cycle 1 CRS G2+ %
A QSP model is developed to describe IL-6 change following the exposure change of Drug X
An ER model further links the IL-6 level to the incidence of CRS.
The overall incidence of CRS is calculated

Trial Simulation for Alternative Prime Dosing



Take Home Messages

- Dose optimization is critical in new drug development for oncological products.
- Project Optimus, in combination with other programs, such as MIDD and FFP, provide an essential pathway for early interactions with drug developers to improve dose selection.
- Quantitative clinical pharmacology tools can be broadly used to support dose optimization in new cancer therapy development.



MIDD: Dose-Exposure-PD-response -> Benefit/Risk

Thank Yous

OCP

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