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OFFICE OF CLINICAL PHARMACOLOGY

# Pragmatic and Holistic Approach for Dose Finding and Optimization in Oncology Drug Development – A Clinical Pharmacology Point of View

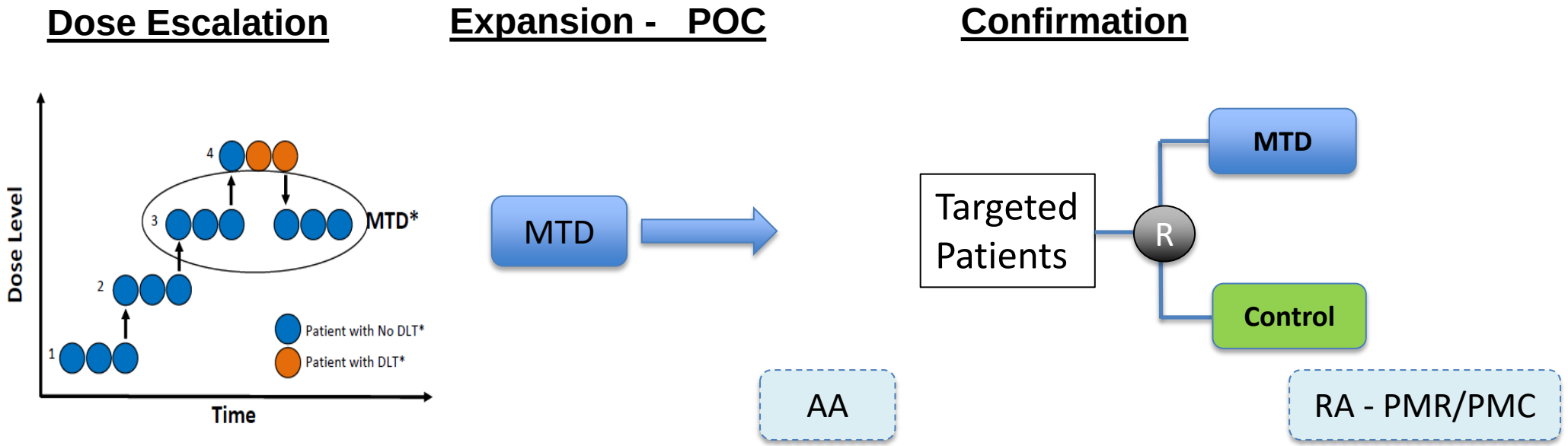
Jiang Liu, Ph.D.,
Associate Director for Therapeutic Review
Division of Pharmacometrics
OCP/OTS/CDER/FDA

Disclaimer:
1. I have no conflict of interest to report.
2. The views presented here are my personal opinions and should not be interpreted as the position of the US FDA.

# Outlines

- Current paradigm of oncology drug dose finding/optimization and the concerns
- Factors affecting dose finding/optimization
- Case studies: from lab to lifecycle
- Holistic approach with totality of evidence
- Summary

# Current Oncology Dose finding/optimization paradigm




- Dose selection is mainly driven by toxicity (assuming “more is better” for efficacy)
- MTD determined with few patients and short duration
- DLTs may not reflect chronic tolerability/other safety

# Consequences for Patients

| Why? | Consequences for patients |
| --- | --- |
| Landscape shift:<br>• Cytotoxic agents -> MTA -> IO, BsAbs<br>  ▪ Different dose-response: more is not always better<br>• Longer duration of therapy<br>  ▪ DLT may not reflect actual (long term) toxicity/tolerability<br>Not efficient:<br>• Not using all information of **dose-exposure-response** from nonclinical, historic data, clinical data from each patient | • Experience preventable toxicity<br>• Impact quality-of-life<br>• Impact ability to remain on a drug and ability to receive future therapies<br>• Treatment is not optimized for an actual patient |

# Consequences for Drug Development

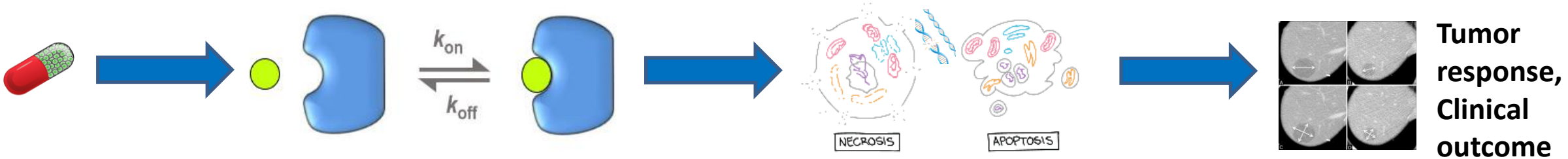
- Drug not being used in clinical practice or withdrawl (e.g., recent PI3K ODAC) - Built your house on quicksand
- Postmarketing Study

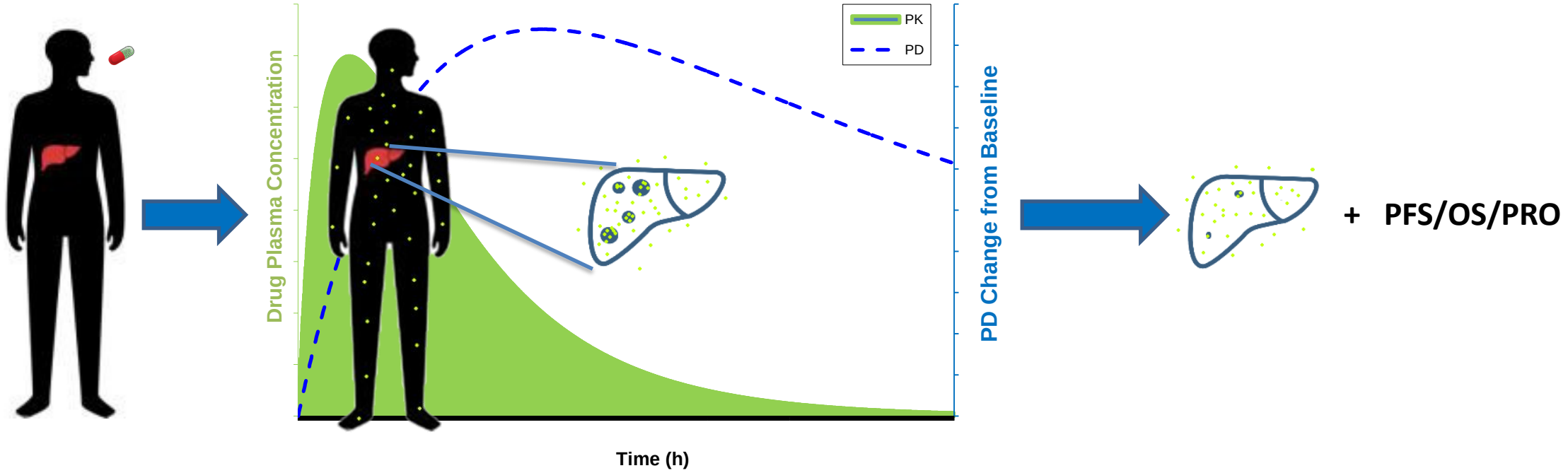
| 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|
| **ipilimumab** | glucarpidase | pomalidomide | ofatumumab | **panobinostat** | venetoclax | **ribociclib** |
| **vandetanib** | axitinib | **T-DM1** | ramucirumab | palbociclib | atezolizumab | niraparib |
| abiraterone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

# Premarket Dose Optimization Is Preferred

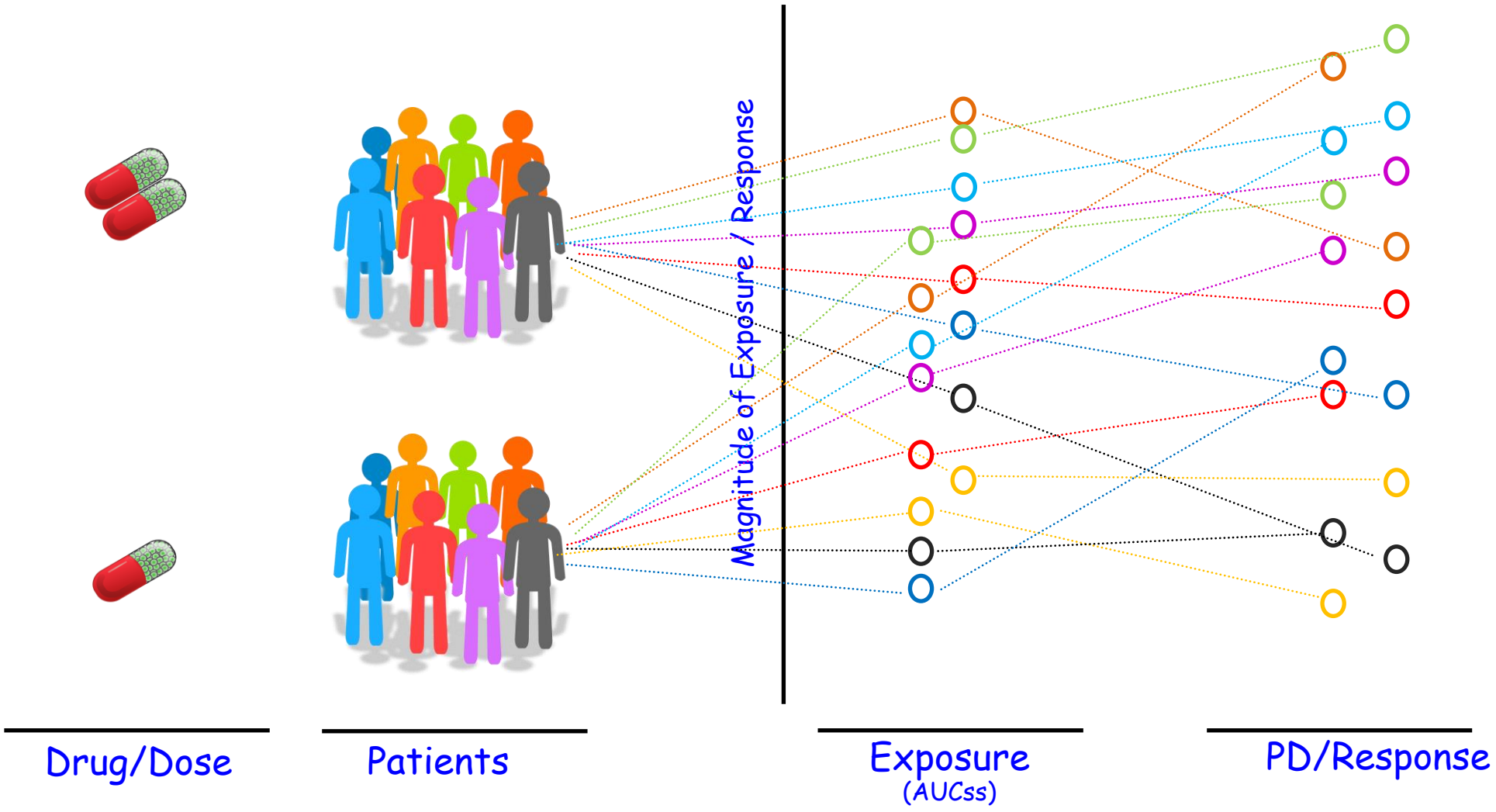
- Prevents large number of patients from experiencing avoidable toxicity
- More efficient to evaluate multiple doses early in development
  - Challenging to conduct dose optimization trials post-approval
- Earlier understanding of dose-exposure-response allows for
  - More rapid expansion to new indications
  - Development of combination regimens
- Increases the likelihood of successfully bringing a drug to market

# Drug Action: Dose-Exposure-(PD)-Outcomes

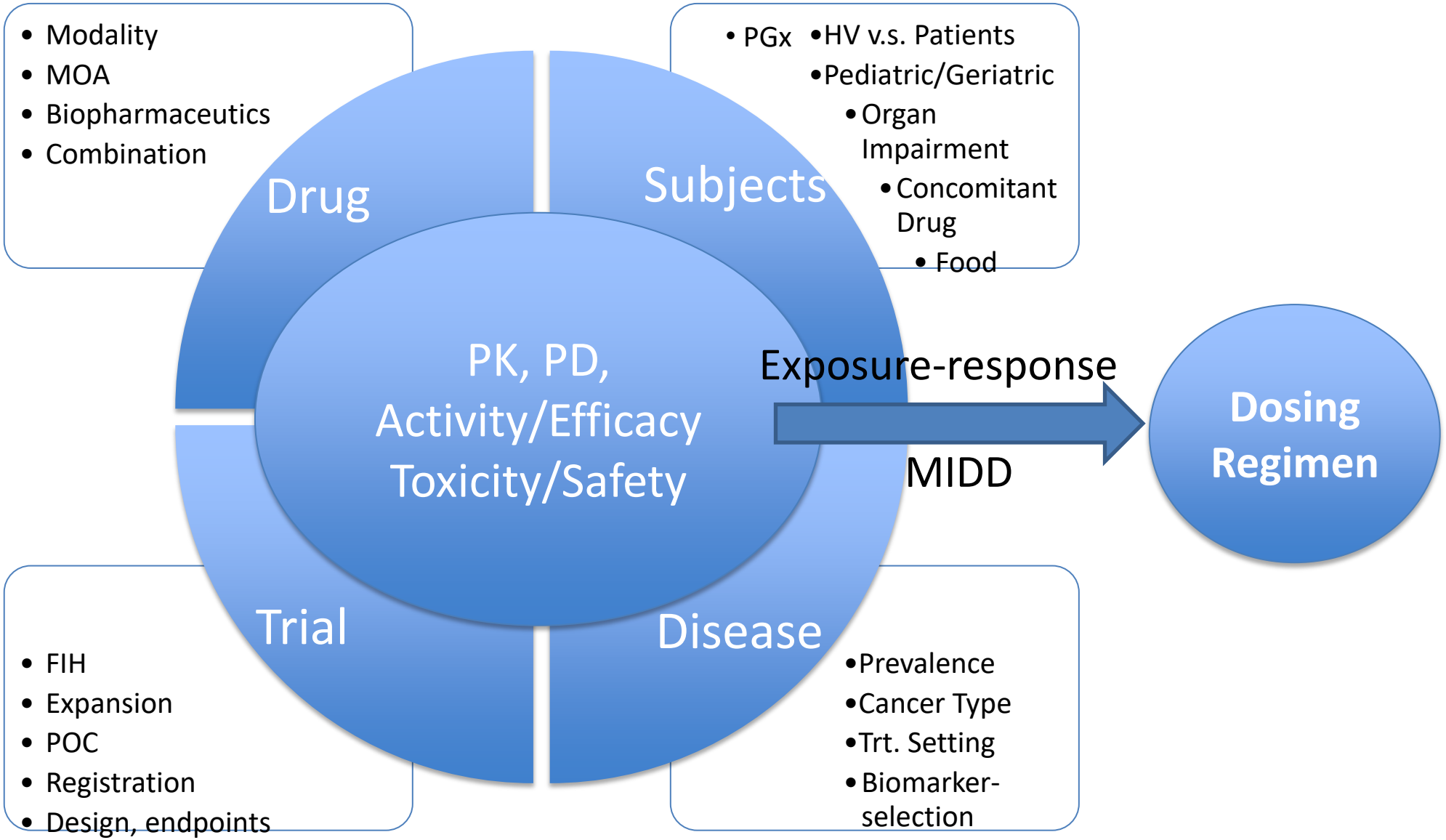


# Source of Variability

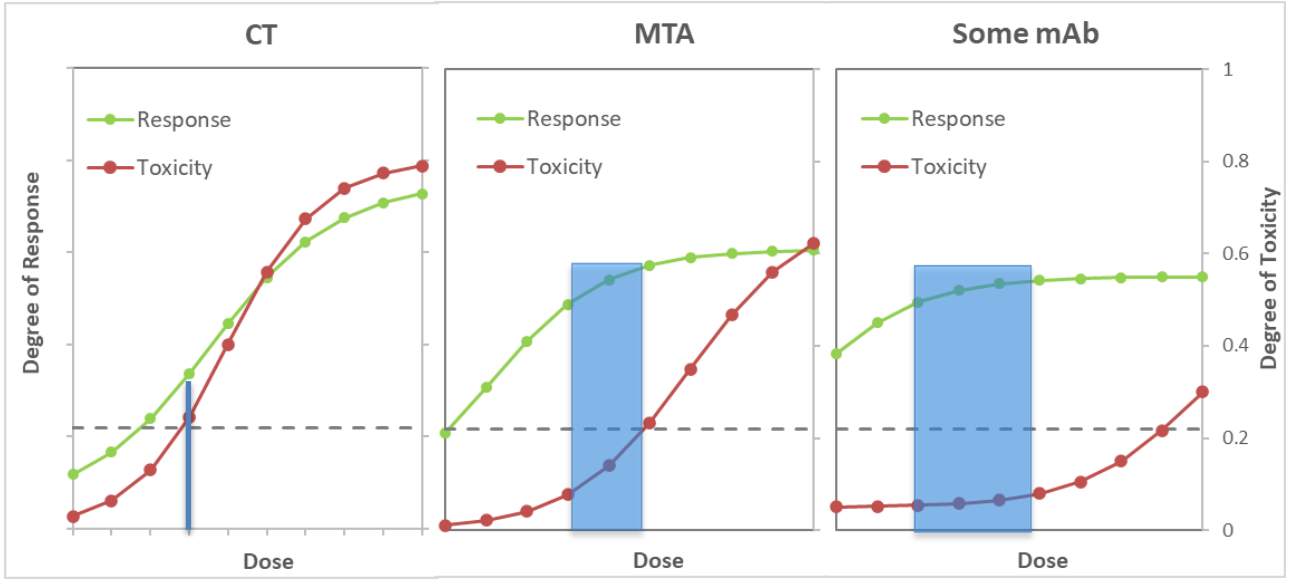


# Factors Affect Dose Finding & Optimization



# Drug Factors for Dose Selection - Modality

## Modality: CT, MTA, mAb, IO, ADC, BsAbs, RNAi



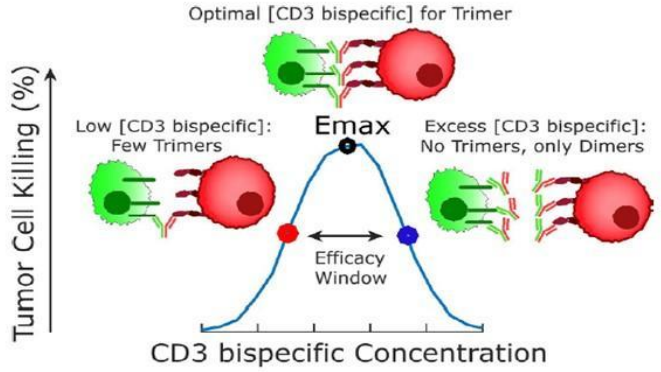
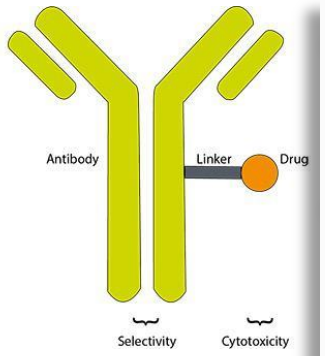



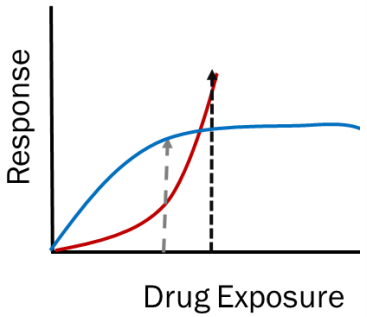

**Figure 2** Bell-shaped concentration response relationship observed for CD3 bispecific antibodies. $E_{max}$, maximum effect.

*Alison Betts, Clin Pharm & Ther, 2020*

## ADC:

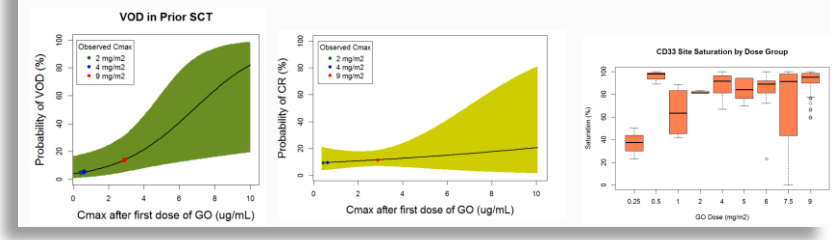



- Multiple moieties contributing to safety and efficacy
- Therapeutic range – *Narrow!*




Gemtuzumab ozogamicin (Mylotarg) *accessdata.fda.gov*

9 mg/m$^2$ -> withdrawal -> fractionated dose (3 mg/m$^2$ on Day 1, 4, 7)

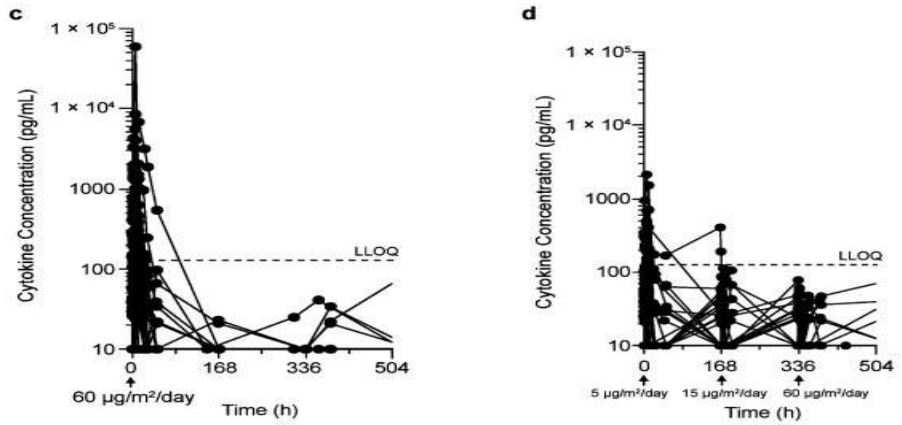


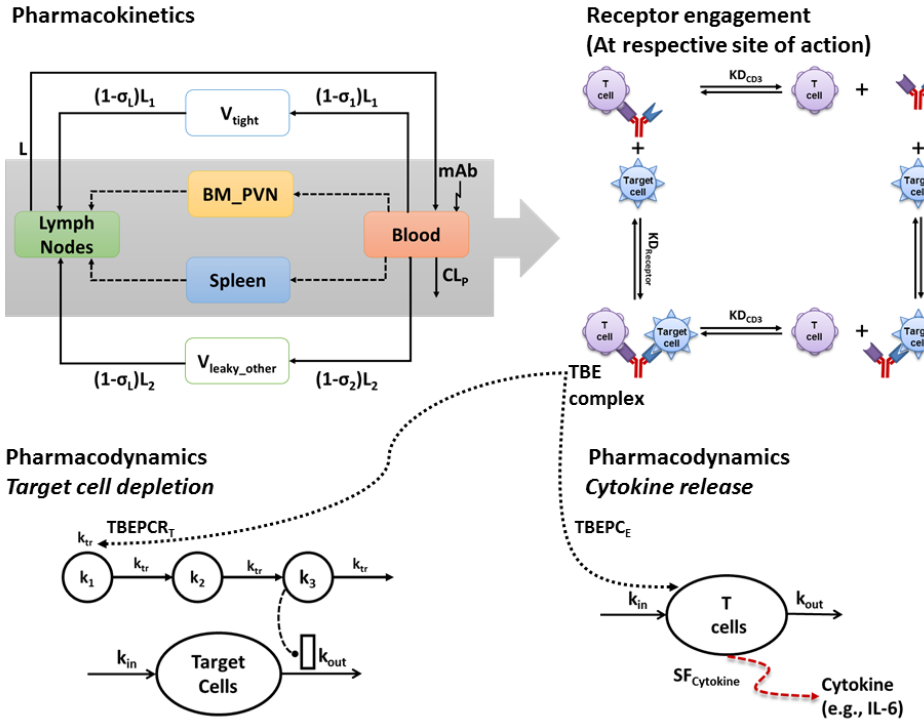
# Drug Factors for Dose Selection - MOA

MOA: class specific effect (activity/toxicity), FIC? Metabolite?

- Target-related 'class' effects (e.g. KIs)
  - Dermal toxicity (Acneiform rash) for EGFR
  - Hypertension and ocular toxicity for VEGFR
- Immune agonists:
  - MABEL
  - CRS/IRR – stepwise priming dosing for BiTE

**Blinatumomab**



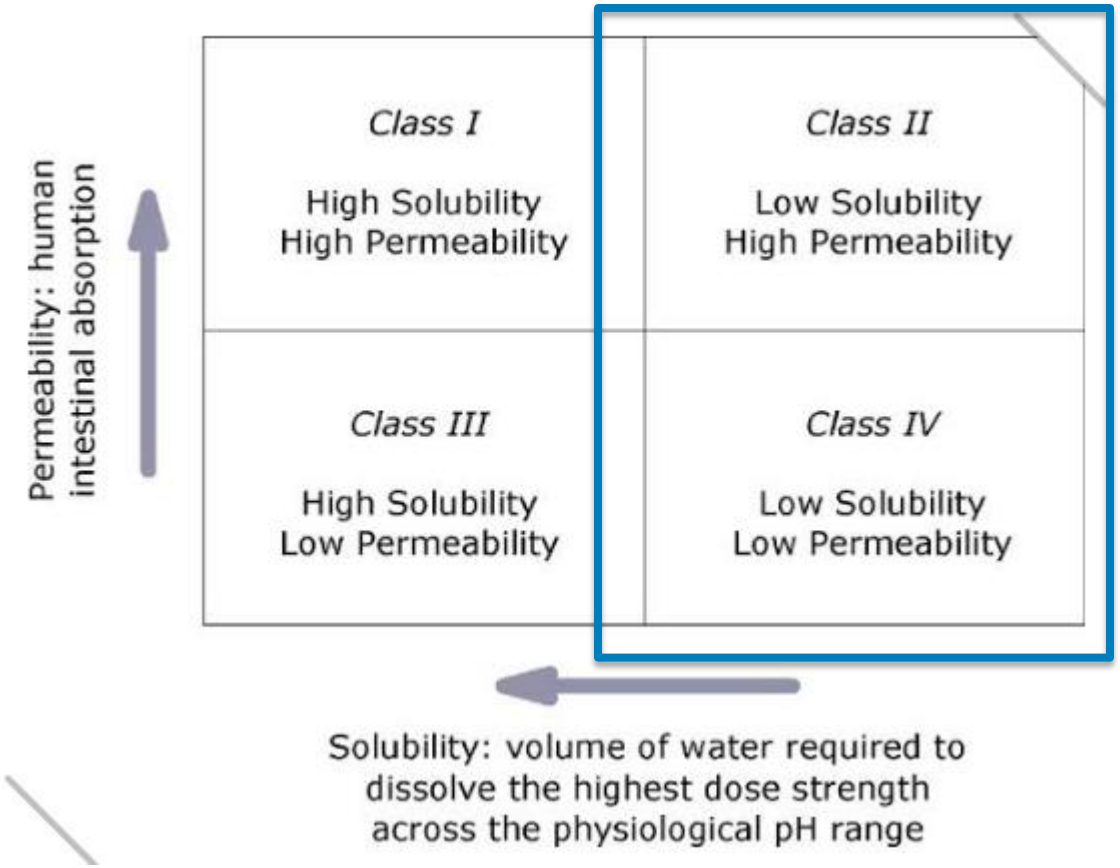




*Hijazi Y. Curr Clin Pharmacol. 2018*

*Jiang X, et al. MAbs. 2018*

# Drug Factors for Dose Selection - Biopharmaceutics

- Biopharmaceutics Classification System (BCS) and formulation




Drug Absorption affected by:

- Formulation
- Dose
- Food
- Gastric PH dependent drugs

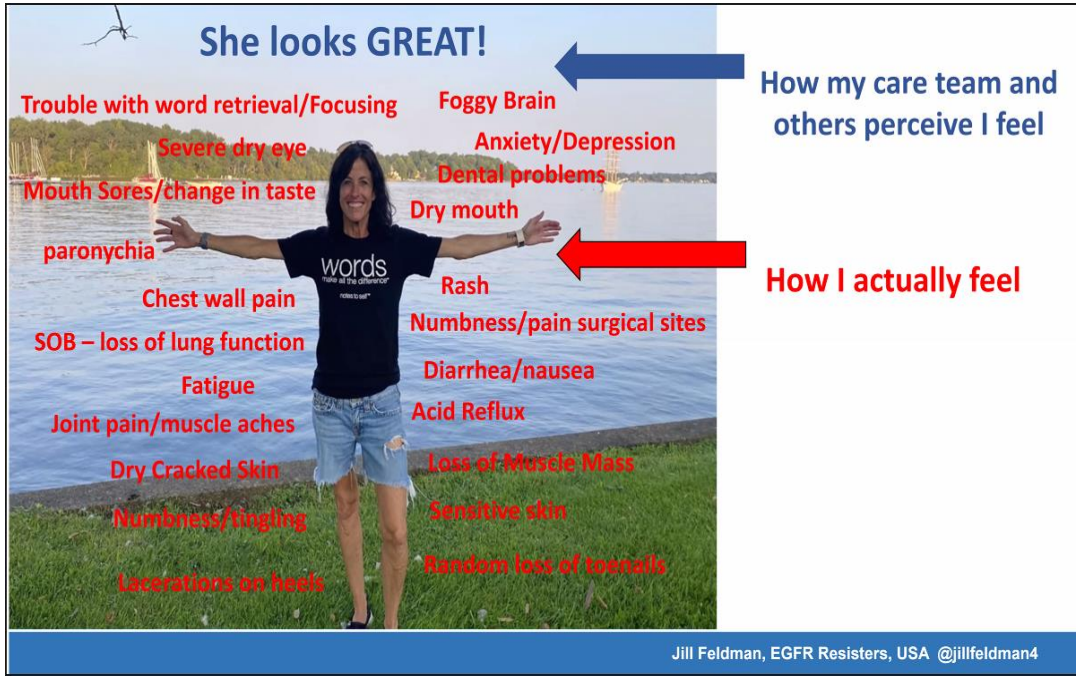
# Drug Factors for Dose Selection - Combination

## Complex Journey

- Data to support the biological activity and safety of the combination (based on nonclinical or clinical)
  - Assess potential PK and PD interaction
  - Additivity, synergy, or detrimental?
- Combination scenarios:
  - Both agents are approved: combinations anchored around the approved doses
  - One approved agent with a novel agent: 1) anchored at the approved dose first and evaluate different dose levels of the novel agent; 2) additional dose optimization of the approved agent around the several dose levels of the novel agent
  - Two novel agents: 1) dose finding for each agent alone; 2) full factorial combination
- Use totality of data with modeling and simulation to explore various scenarios

# Subject Factors for Dose Selection

- Intrinsic
  - **Age**
  - **Body size**
  - Gender
  - Race
  - **Organ impairment**
  - Disease
  - **Genetic polymorphism**
  - Pregnancy
  - …




*FDA-ASCO Workshop: Getting the Dose Right.*

- Extrinsic
  - **Food/Diet**
  - **Concomitant Drug**
  - Herbal products
  - Smoking
  - Alcohol
  - …

# Subject Factors for Dose Selection – Ceritinib Food Effect

- Ceritinib **(BCS IV) 750 mg** original approved for the treatment of ALK positive metastatic NSCLC
- Dose selection: escalation - expansion phase (fasting)

| Dose Level (mg) | 50 | 100 | 200 | 300 | 400 | 500 | 600 | 700 | 750 |
|---|---|---|---|---|---|---|---|---|---|
| Number of subjs (n) | 2 | 2 | 3 | 3 | 14 | 10 | 10 | 5 | 10 (MTD) |

- >60% dose reduction/interruption mainly due to AR (GI toxicity: N/V/abdominal pain/diarrhea)
- Food effect (↑ 58% (low-fat meal) and 73% (high-fat meal)) study was completed almost after the Phase 1 study

| **Gastrointestinal** | **750 mg without Food (N=255)** | | **400 mg without Food (N=108)** | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3-4 (%) | All Grades (%) | Grade 3-4 (%) |
| Diarrhea | 86 | 6 | 59 | 1 |
| Nausea | 80 | 4 | 43 | 1 |
| Vomiting | 60 | 4 | 38 | |

Dose was decreased to **450 mg** with food based on the PMR

*https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211225s004lbl.pdf*

# Disease Factors for Dose Selection

- Rare disease – feasibility of a specific dose finding trial?
- Indications/disease stage (tumor type, adjuvant-neoadjuvant-metastatic setting, treatment setting, genomic)
  - PI3K Inhibitors (idelalisib, copanlisib, duvelisib, umbralisib)
    - Different benefit/risk ratio among diseases -> Different dosing strategies
- Biomarker-selection

# Disease Factors for Dose Selection - Trastuzumab Deruxtecan (T-DXd)

HER2-directed antibody-drug conjugate for the treatment of HER2-positive breast cancer or gastric cancer (**5.4 or 6.4** mg/kg Q3W, respectively)

DS8201-A-J101 (Solid Tumors)

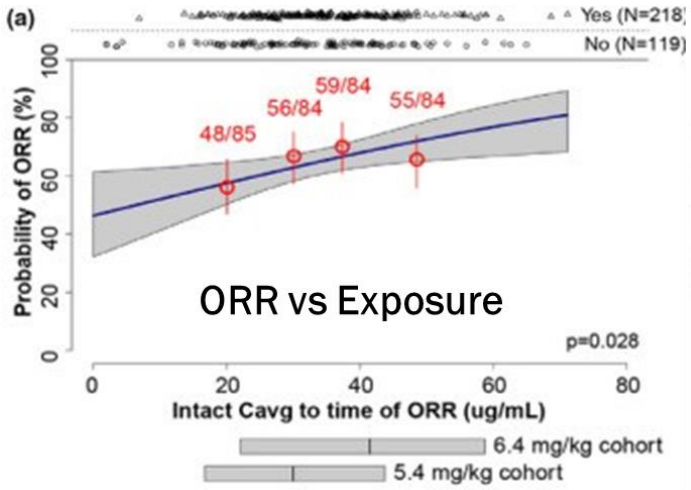
- 0.8 - 8 mg/kg Q3W, 7.4 mg/kg Q3W (n=20, PK only)
- 6.4 mg/kg Q3W (n=66)
- 5.4 /kg Q3W (n=49)

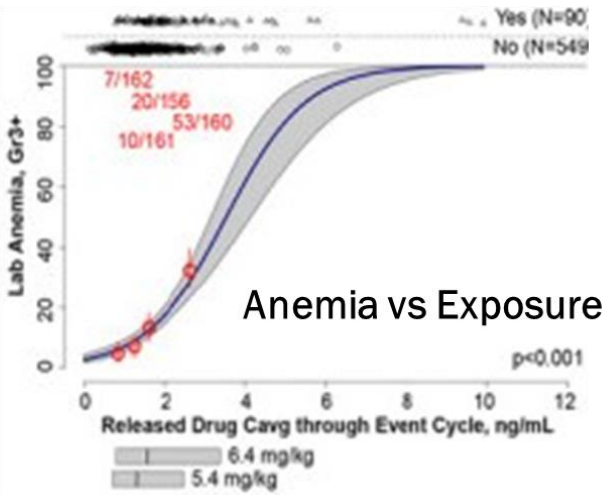
DS8201-A-U201 (BC)

- 6.4 mg/kg Q3W (n=20+30)
- 5.4 mg/kg Q3W (n=100)

DS8201-A-J202 (GC)

- 6.4 mg/kg Q3W (n=126)




| | T-DXd (ADC) | | |
|---|---|---|---|
| | $C_{max}$ (µg/mL) | $AUC_{last}$ (µg/mL*d) | $C_{trough}$ (µg/mL) |
| **Breast cancer (BC)** 5.4 mg/kg (n=232) | 124 (33) | 545 (163) | 5.5 (5.1) |
| **Gastric cancer (GC)** 6.4 mg/kg (n=149) | 126 (28) | 597 (152) | 5.6 (3.1) |

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s017s020lbl.pdf

# Trial Factors for Dose Selection

| Preclinical | FIH - Escalation | Expansion - POC | Confirmation | Lifecycle |
|---|---|---|---|---|
| Safe dose for first in human evaluation<br>• Pharmacology – MOA<br>• General (or special) Toxicology<br>• PK/TK/PD<br>• Allometric<br>• NOAEL/STD/ HNSTD/MABEL | Clinical Safety, PK, biological doses<br>• Escalation, highest dose, duration and schedule<br>• Trial design (population, sample size, duration …), data collection, information process | Two main goals:<br>▪ POC in targeted patients<br>▪ Selection of dose(s) for confirmatory trials<br>• Understand efficacy<br>• Understand key safety<br>• D-E-(PD)-R | Confirm clinical benefit/risk<br>• A&WC trial(s)<br>• Confirm safe and effective dose in general and specific population | Safety monitoring and continual dose optimization/ individualization<br>• PMR/PMC<br>• RWD/RWE |

# Case Example 1: Sotorasib

## DOSE FINDING/OPTIMIZATION: FROM LAB TO LIFECYCLE

*accessdata.fda.gov*

# Approval Information

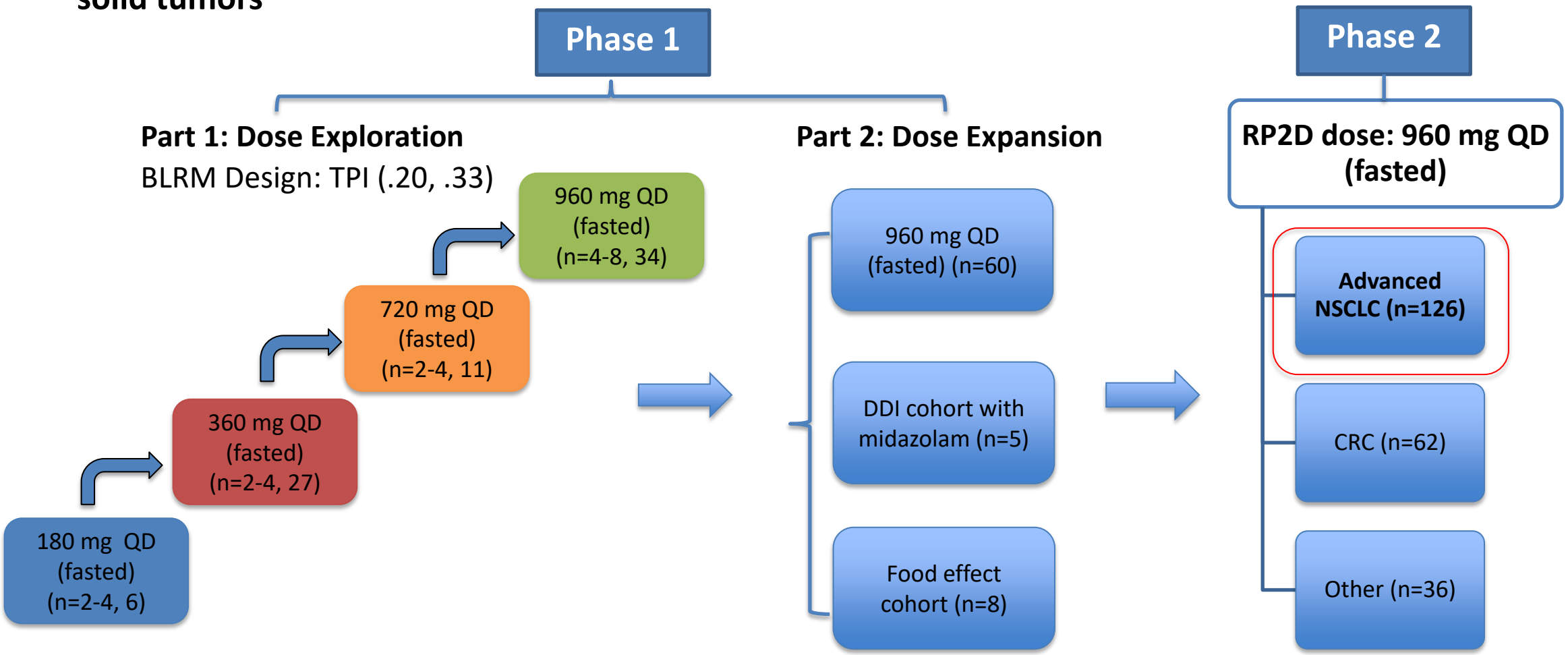
- First approved (AA, OR) KRAS inhibitor for NSCLC with KRAS G12C mutation
  - Efficacy: ORR: 36% (28%, 45%), mDOR: 10 m
  - Safety: SAE (50%), Dose interruption/reduction due to AE (22%), Grade 3+ TEAE (59%), Diarrhea (43%), Nausea (27%)

- Approved Dosage
  - **960 mg** orally once daily (QD) with or without food

- A dose-finding PMR study to investigate a lower dosage (**240 mg** QD) is required

# Study CodeBreak 100

**A single-arm, open label, multicenter study of sotorasib in patients with *KRAS p.G12C*-mutated solid tumors**




1st: Safety & tolerability, MTD
2nd: PK, PD, food, QT

# Pharmacology for Dose Selection

- Pharmacology studies support the mechanism of action
  - Sotorasib binds irreversibly to the P2 pocket of KRAS and inhibits the SOS1-catalyzed nucleotide exchange of $KRAS^{G12C}$ ($IC_{50}$ = 92.6 nM; ~51.9 ng/mL) thereby locking $KRAS^{G12C}$ in the inactive GDP-bound conformation
  - Sotorasib does not inhibit WT KRAS
  - Sotorasib reduced ERK1/2 phosphorylation and exhibited in vivo anti-tumor activity at 10 mg/kg against xenografts expressing $KRAS^{G12C}$, but not $KRAS^{G12V}$ or $KRAS^{G12D}$
- TGI models predicted 30 to 240 mg QD as clinical biological doses

# Dose-Exposure of Sotorasib

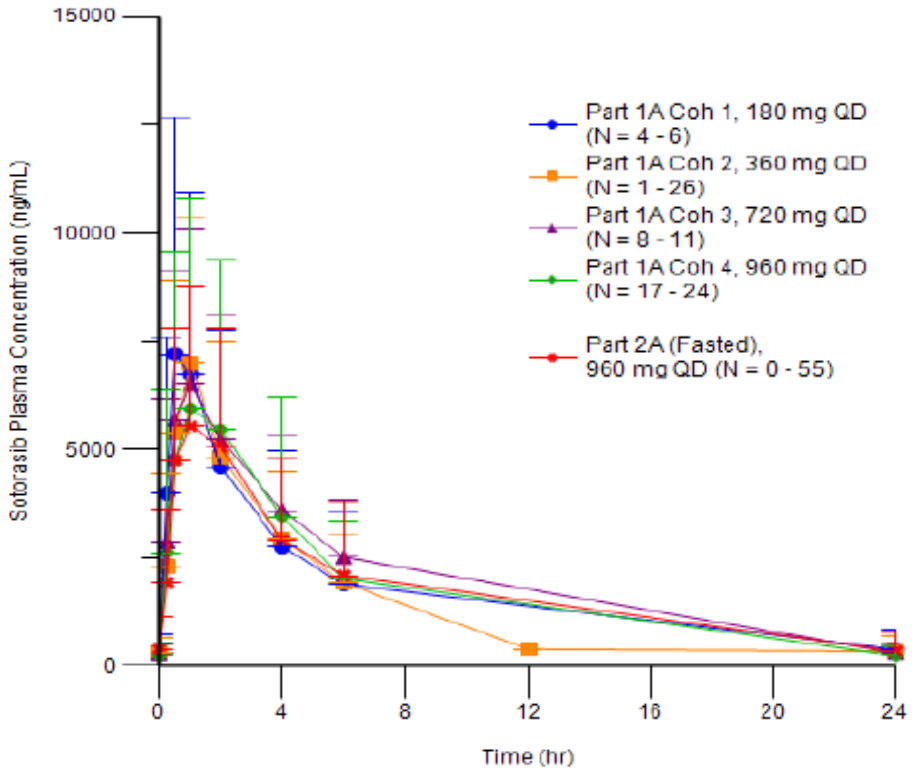
- **Similar steady-state exposure among doses 180 mg to 960 mg**

**Steady-State PK Parameters**

| Dose (mg) | N | $t_{max}$ (hr) | $C_{max}$ (µg/mL) | $AUC_{0\text{-}24h}$ (hr*µg/mL) | $t_{1/2,z}$ (hr) |
|---|---|---|---|---|---|
| 180 | 6 | 0.75 (0.50 – 1.0) | 6.44 (7.63, 67%) | 33.5 (41.7, 85%) | 5.38 (5.96, 46%) |
| 360 | 25 | 1.0 (0.25 – 4.0) | 5.97 (7.01, 46%) | 37.4 (42.4, 50%) | 5.52 (5.71, 28%)[a] |
| 720 | 11 | 1.0 (0.50 – 4.0) | 5.45 (6.76, 50%) | 43.9 (50.8, 49%) | 4.92 (5.06, 24%)[b] |
| 960 | 25 | 1.0 (0.50 – 24) | 4.91 (6.57, 69%) | 32.4 (42.2, 71%)[d] | 4.79 (5.03, 28%)[c] |

*Data presented as geometric mean (arithmetic mean, CV%) for all PK parameters except for Tmax, which is presented as median (range).*

**Steady-State PK Profiles**



# No Clear Dose-Response Trend for Efficacy Observed Among Doses

Proposed dose

| Sotorasib Monotherapy in NSCLC | | | | | |
|---|---|---|---|---|---|
| | 180 mg QD Fasted (N=3) **Phase 1** | 360 mg QD Fasted (N=16) **Phase 1** | 720 mg QD Fasted (N=6) **Phase 1** | 960 mg QD Fasted (N=34) **Phase 1** | 960 mg QD Fasted (N=123) **Phase 2** |
| **ORR n (%)** | 1 (**33**) | 4 (**25**) | 3 (**50**) | 16 (**47**) | 46 (**37**) |
| 95% CI | (0.8, 90.6) | (7.3, 52.4) | (11.8, 88.2) | (29.8, 64.9) | (28.8, 46.6) |

Although limited in sample size, ORR data suggested that lower dose could provide acceptable effectiveness for the proposed indication.

# Opinions during Drug Development - from Regulatory and Community

**FDA recommended dose optimization during IND:**

*"We notes that .., which does not support your proposed rationale of ... FDA recommends that Amgen includes additional dose finding cohort … to optimize the dose."*

Applicant did not follow FDA's recommendation during IND stage on exploring additional dose cohorts for dose optimization.


The ASCO Post

COVID-19 ABOUT NEWS MEETINGS TOPICS

Empowering the FDA to Require Dose Optimization of All New Oncology Drugs

By Mark J. Ratain, MD, FASCO, and Allen S. Lichter, MD, FASCO

January 25, 2021

- *"There is no evidence that the dosing regimen used in the Amgen pivotal trial (960 mg daily fasting) is optimal. In fact, it is likely that a much lower dose of the drug administered with food may have a superior therapeutic index."*
- *" We urge the FDA to require Amgen to optimize the dose as a condition of the likely accelerated approval ."*

# Proposed 960 mg Dose is not Optimized

- Failed to translate the nonclinical, biopharmaceutics, Dose-Exposure-Response information into dose selection decision:
  - In vitro target saturation occurs at exposure levels with lower doses
  - Similar steady-state exposure among doses 180 mg to 960 mg
  - No clear dose-response trend for efficacy observed among doses
- Safety concerns (i.e., local GI toxicities) associated with high dose
- High pill burdens (8 tablets)

PMR for dose optimization: Investigate a lower dosage that may provide comparable efficacy with improved safety as compared to 960 mg

# Case Example 2: Osimertinib

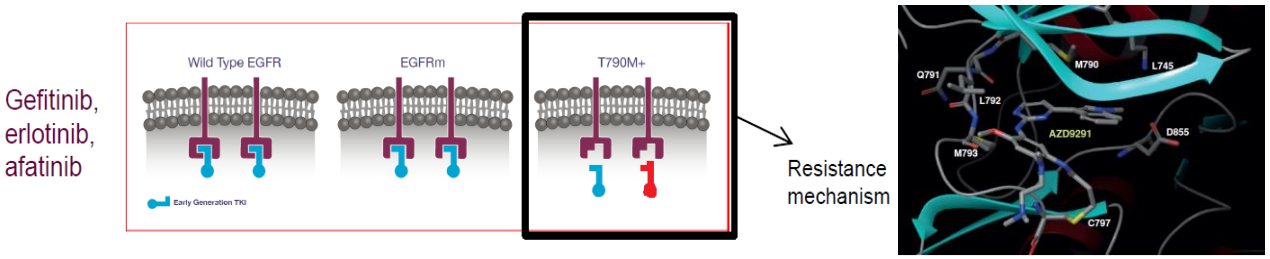
## DOSE FINDING/OPTIMIZATION: FROM LAB TO LIFECYCLE

# Approval 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

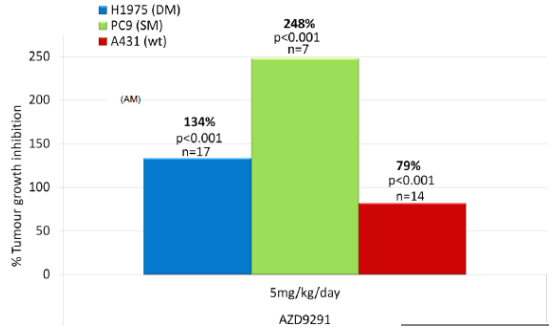
- Specific chemistry design (target & mechanism)



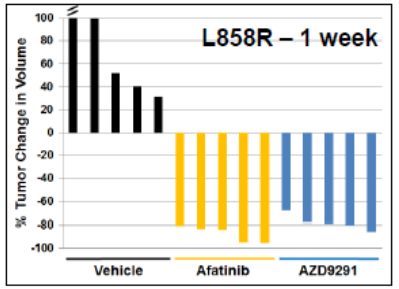

- Specific cell line models

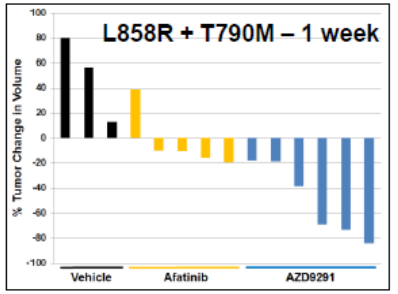
| Clinical EGFR mutation | Cell line model |
|---|---|
| Exon 19 del | PC-9, H1650, HCC827, (HCC4006)* |
| L858R | H3255, (11-18)* |
| Ex19del/ T790M | PC-9VanR |
| L858R/ T790M | H1975 |
| Wild-type EGFR | A431, H2073, LoVo |

- Xenograft disease models

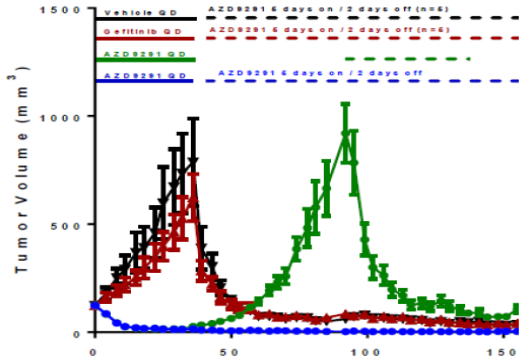



- Transgenic mouse models



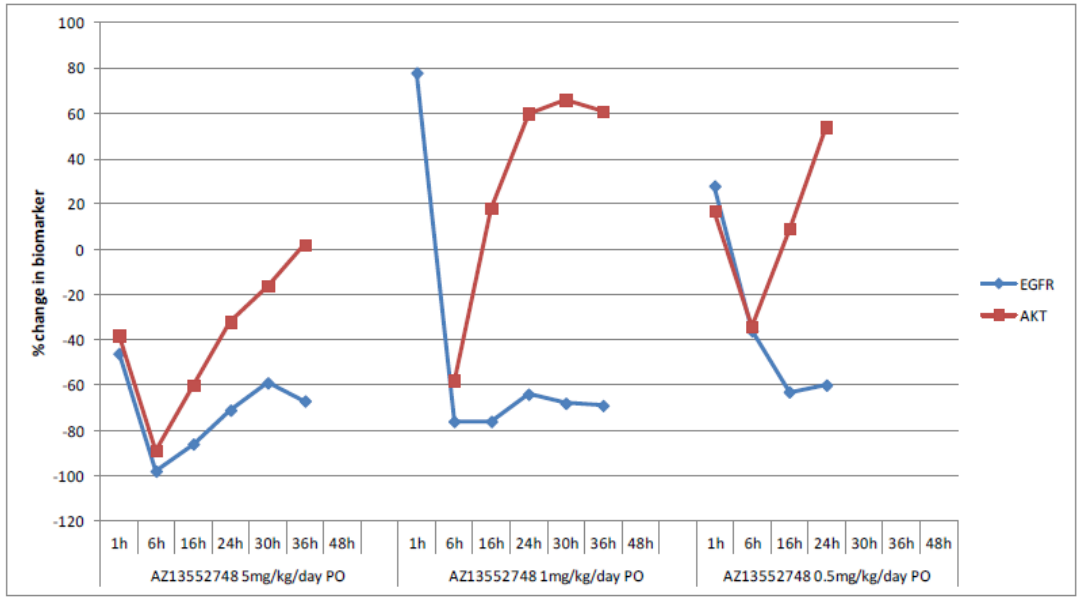

- Patient derived explant models




*Darren Cross, 2016 FDA-AACR Workshop*

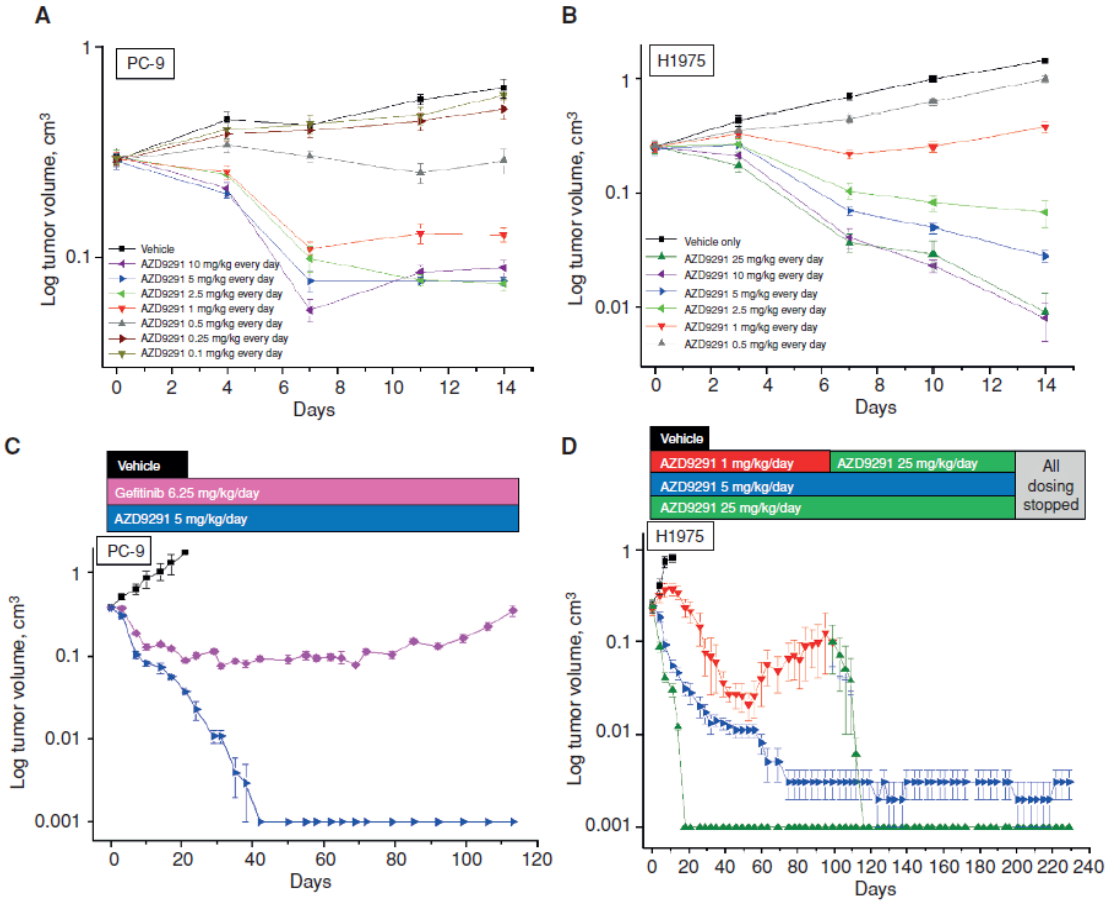
# Solid NonClinical Dose-Activity Evaluation

- Pharmacodynamic data




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

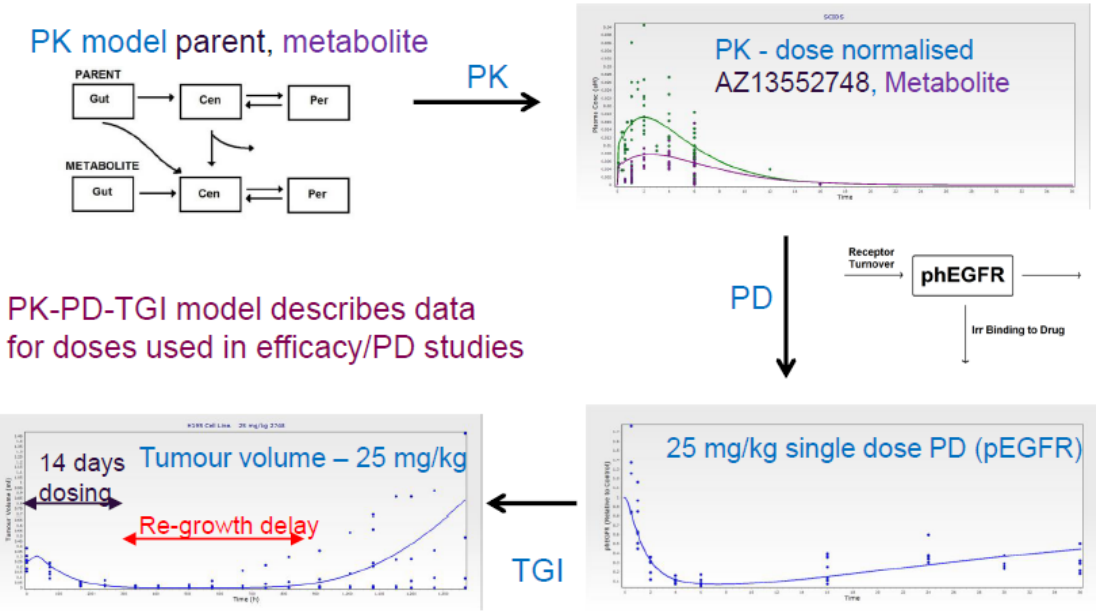
- Antitumor activity

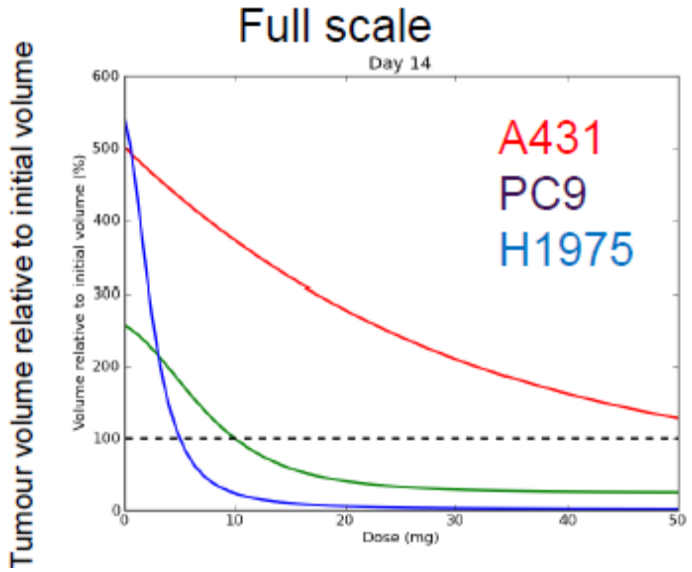



*Darren Cross, 2016 FDA-AACR Workshop*

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

# Strong Predictive Modeling for Forward Translation and Dose Finding

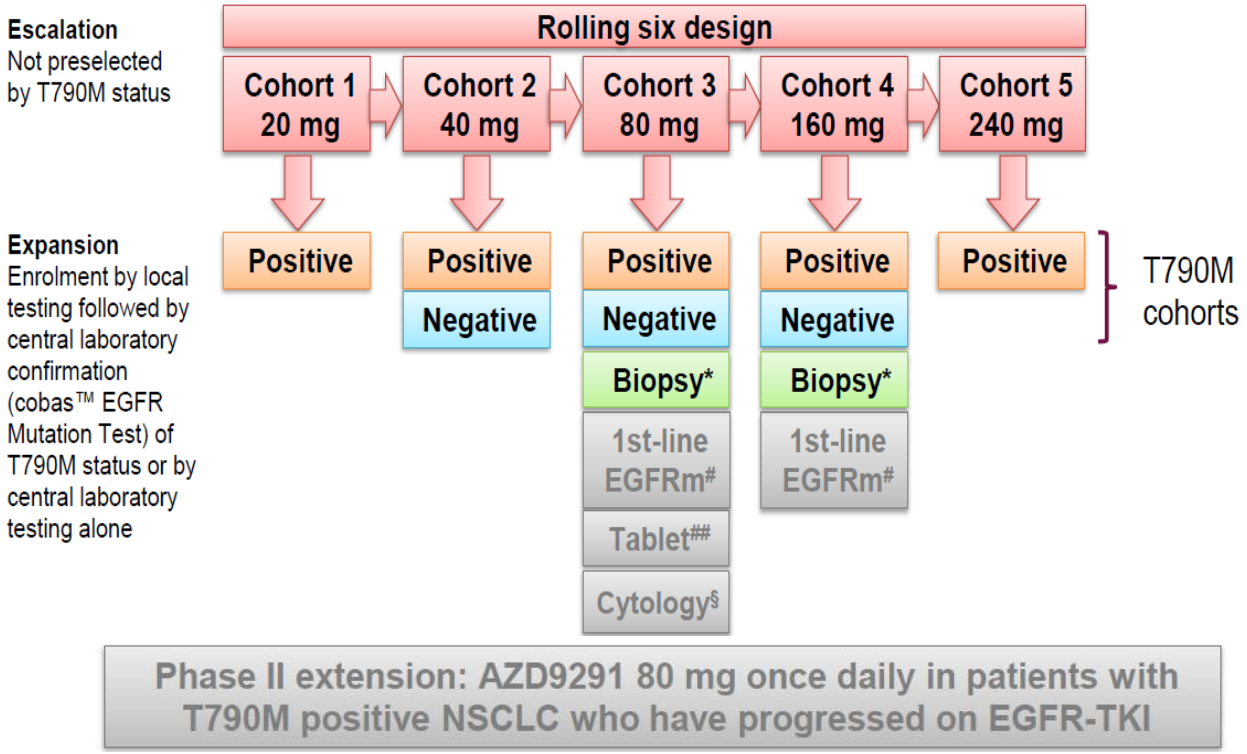



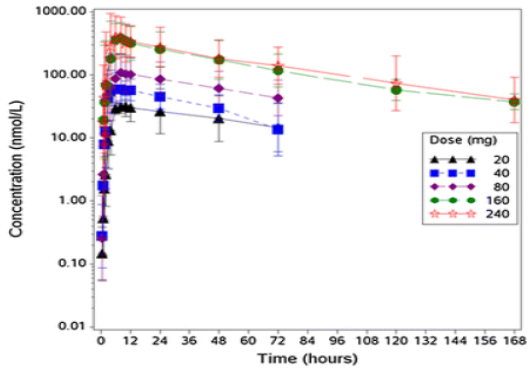



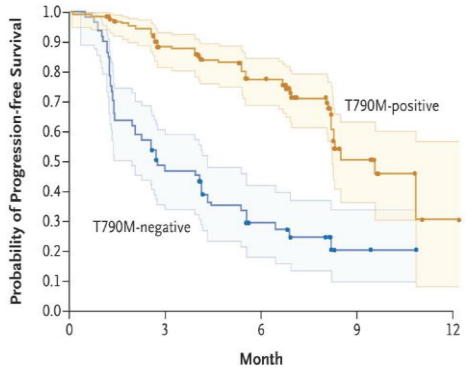

Modeling support taking drug into clinic and predict the first dose of 20 mg in human should provide antitumor activity

*Darren Cross, 2016 FDA-AACR Workshop*

# AURA Phase I Trial

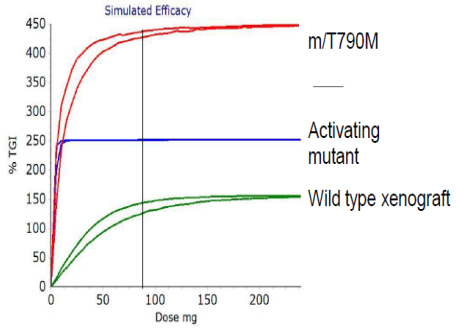



## Response rate in T790M positive cohorts

| | 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

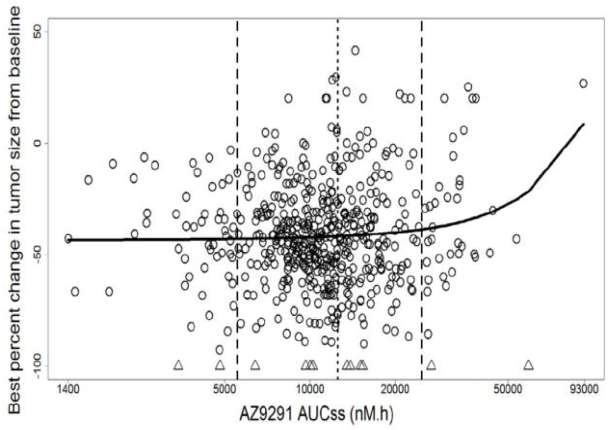
*Pasi Janne, 2016 FDA-AACR Workshop*

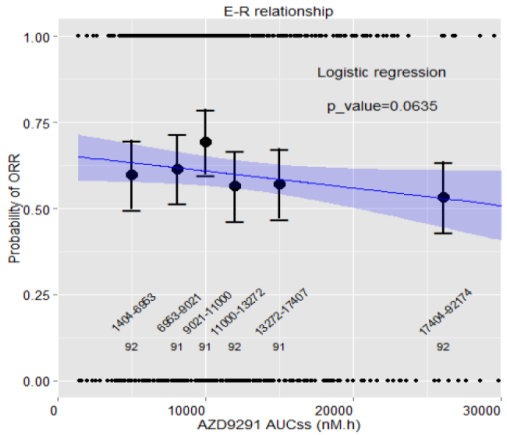
*Darren Cross, 2016 FDA-AACR Workshop*

# AURA and AURA 2 Phase II Trial (T790M+)

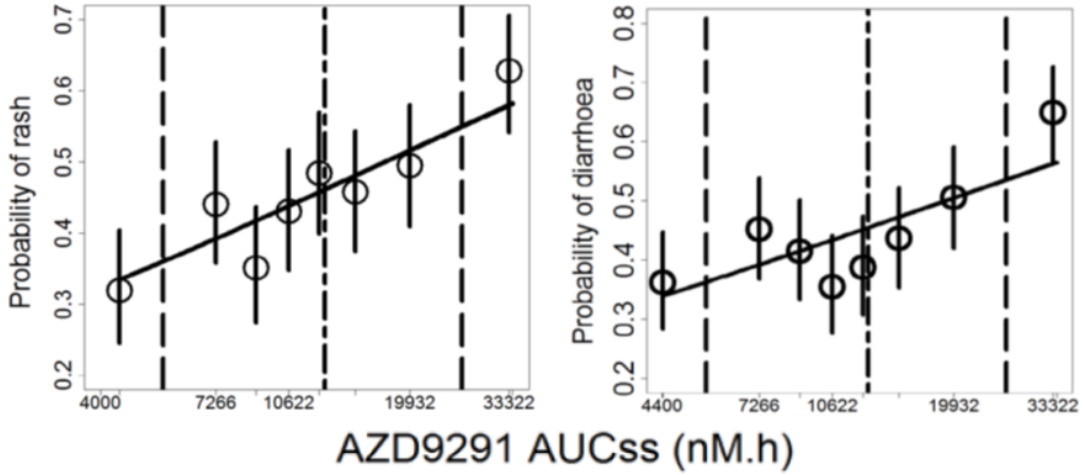
| Efficacy Measure (BICR) | Aura Extension (n=201) | AURA2 (n=210) | Pooled (n=411) |
|---|---|---|---|
| Confirmed Objective Response Rate | 57% | 61% | 59% |
| (95% CI) | (50, 64) | (54, 68) | (54, 64) |
| Complete Response | 0 | 1% | 0.5% |
| Partial Response | 57% | 60% | 59% |

ER for Efficacy



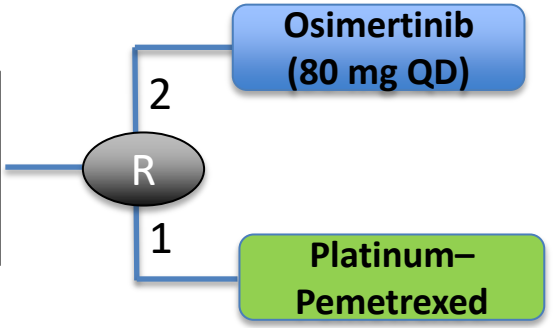

ER for Safety




*accessdata.fda.gov*

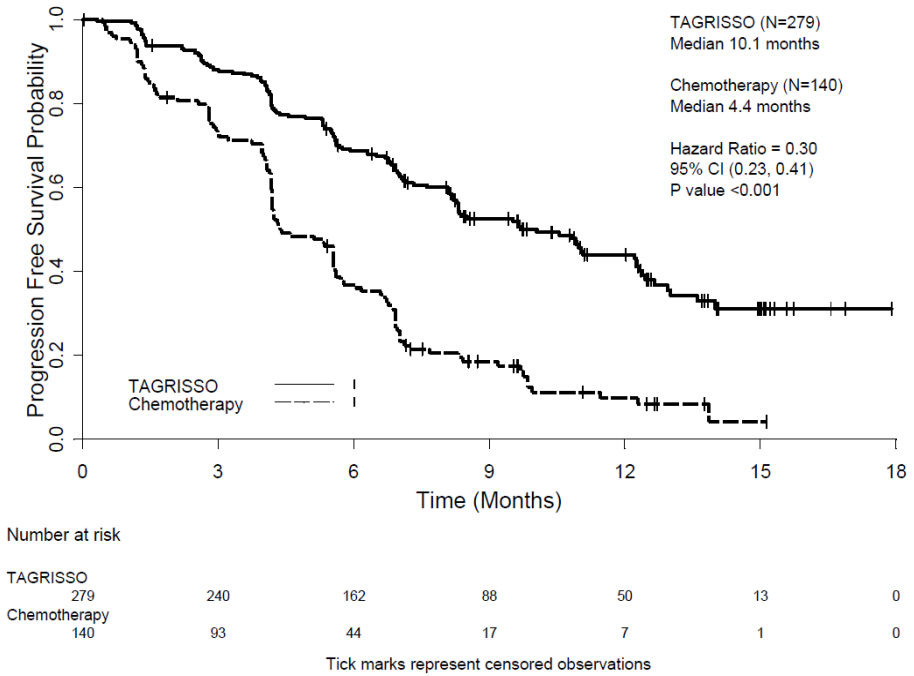
# AURA3 Phase III Trial vs. Chemo (T790M+) Initiated before AA

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




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) |

*accessdata.fda.gov*

# 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 |

# A Holistic Dose Finding/Optimization Approach

Iterative process as new nonclinical and clinical data become available

- Nonclinical evaluation
  - Activities - MOA
    - Cell based assay and animal models (xenograft, transgenic, patient derived explant)
    - Target engagement (IC50 , IC90)
    - PD markers for patient/dose selection
  - Toxicities
    - Attribution of toxicities to study drug
    - Management strategy
    - MRSD
  - PK/PD assessment for forward translation
    - Predictive modeling integrating Dose-Exposure-PD-Outcome for biologic dose

# A Holistic Dose Finding/Optimization Approach <2>

Iterative process as nonclinical and clinical data become available

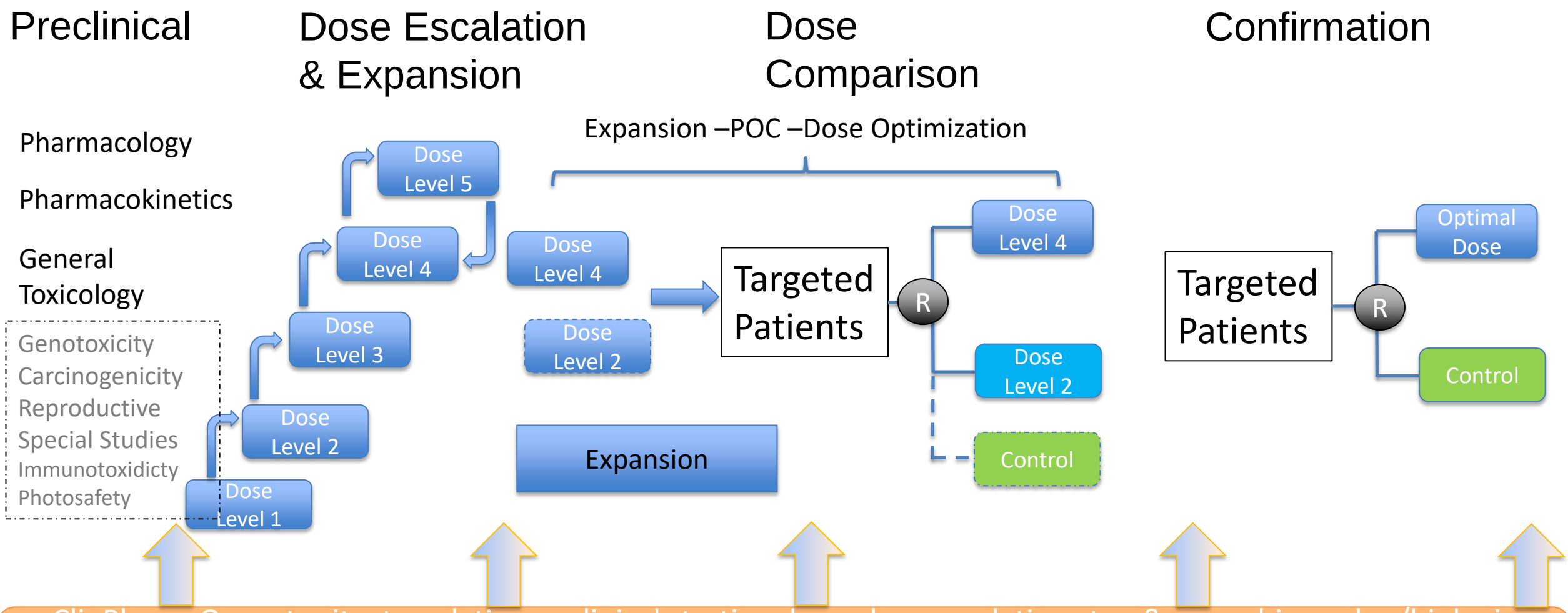
- Early clinical development
  - Dose finding trial
    - Evaluate both safety, PK, and activity
    - Evaluate toxicity/tolerability information beyond DLTs or DLT evaluation window if possible
    - Flexible to include additional patients, tumor types, dose levels, schedules, formulations, food condition
    - Model-based approach for repeated measures
    - Use of priors from non-clinical and other clinical information in the Bayesian model
  - **Dose comparison trial** (may not need to be a standalone trial)
    - Include sufficient number of targeted patients at biologic dose**s**
    - Randomization
    - Consider adaptive design to allow impact of 'Real-time' data on within-trial decisions
  - **MIDD** for Dose-Exposure-PD-Outcome with up-to-date nonclinical and clinical data to inform patients and dose(s) selection for subsequent trials

# A Holistic Dose Finding/Optimization Approach <3>

Iterative process as nonclinical and clinical data become available

- Late clinical development
  - Conduct population PK and exposure-response assessment for registration trial(s) using relevant efficacy and safety/tolerability endpoints including dose modifications and PROs
  - Consider 'dose individualization' if needed
- Lifecycle: Continual dose optimization/individualization post marketing
  - Postmarketing trials, potentially with RWD/RWE

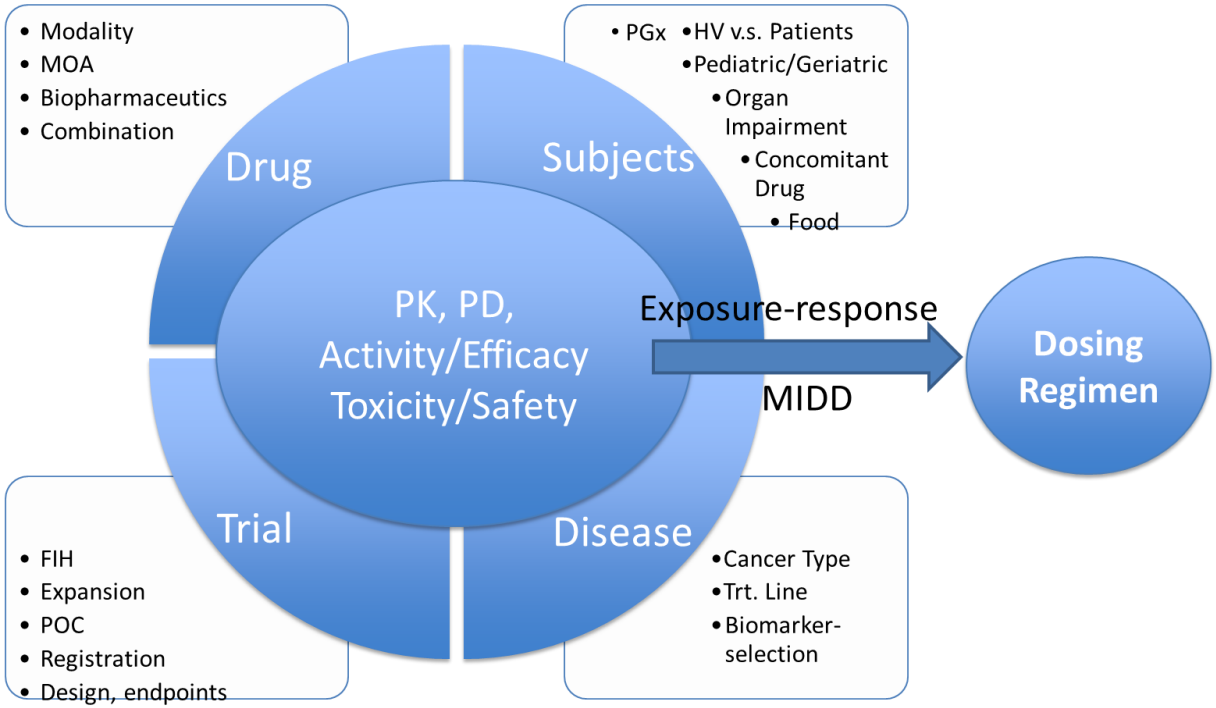
# Clin Pharm to Inform Dose Finding and Optimization




ClinPharm Opportunity: translating -> clinical starting dose, dose escalation step ⦥ biomarker/biologic dose/schedule/targeted patient identification; POC dose(s)- *RP2D*; dose approval- benefit/risk, individualized dosing; lifecycle optimization. MIDD: dose-exposure-PD-response

# Summary

- Dose optimization is an essential component of developing safe and effective cancer therapies and should be conducted prior to drug approval
- Pragmatic and holistic approach for dose finding and optimization will require multidisciplinary collaboration to establish a solid understanding of dose-exposure-PD-response relationships for activity/efficacy, and safety/tolerability
- Multiple dosages should be evaluated with a sufficient number of targeted patients in a clinical trial(s) to decrease uncertainty with identifying an optimal dosage(s)




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

# Acknowledgements


- Dr. Youwei Bi
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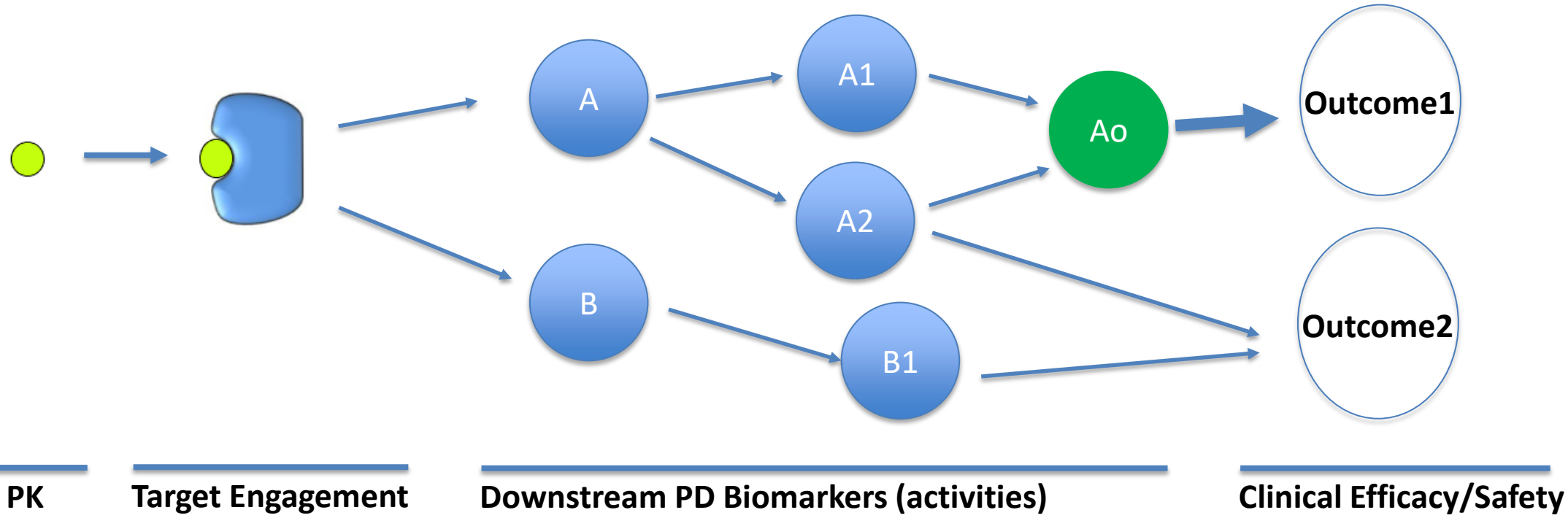
- Dr. Mirat Shah
- Dr. Marc Theoret
- All members of the Project Optimus team
- Colleagues in Division of Pharmacometrics
- Colleagues in Office of Clinical Pharmacology

# THANK YOU!

# Use of Biomarker for Dose Selection




- PD biomarkers generally are more sensitive to drug effects (e.g., ctDNA, TGI):
  - ➢ smaller sample size and shorter duration.
- Selection of biomarker:
  - MoA, physiological response pathway, and disease pathophysiology and process;
  - Ideally with strong correlation, but may not need to be a validated surrogate for clinical outcomes.

# PMR Dose Comparison Trial

- ~170 patients randomized 1:1
  - 240 mg QD (2 x 120 mg tablets) vs. 960 mg QD (8 x 120 mg tablets)
- Rationale for 240 mg dose selection:
  - Dose expected to be above concentration associated with 90% inhibition in vitro
  - Dose expected to approximate exposure at doses 180 mg and 360 mg daily
  - 120 mg tablet readily available
- Endpoints:
  - ORR, TEAEs, SAEs, and event of interest (EOIs), PK

A dosing regimen will be established based on the totality of data with respect to the efficacy, safety and clinical pharmacology endpoints.

*https://clinicaltrials.gov/ct2/show/NCT04933695*

# Examples

- BLC2001: phase 2, included a multicenter, randomized, adaptive cohort of 2 dosages of **erdafitinib** that informed selection of a 3rd dosage for evaluation in the single-arm registration cohort (supported accelerated approval for locally advanced or metastatic urothelial carcinoma)

- KEYNOTE-001: phase 1, included a randomized, dose-comparative, activity estimating cohort of **pembrolizumab** at 2 dose levels (supported accelerated approval for relapsed metastatic melanoma)

- KEYNOTE-010: phase 2/3, multicenter, randomized adaptive study of IV **pembrolizumab** at two dosing schedules vs. docetaxel (supported regular approval for metastatic non-small cell lung cancer)

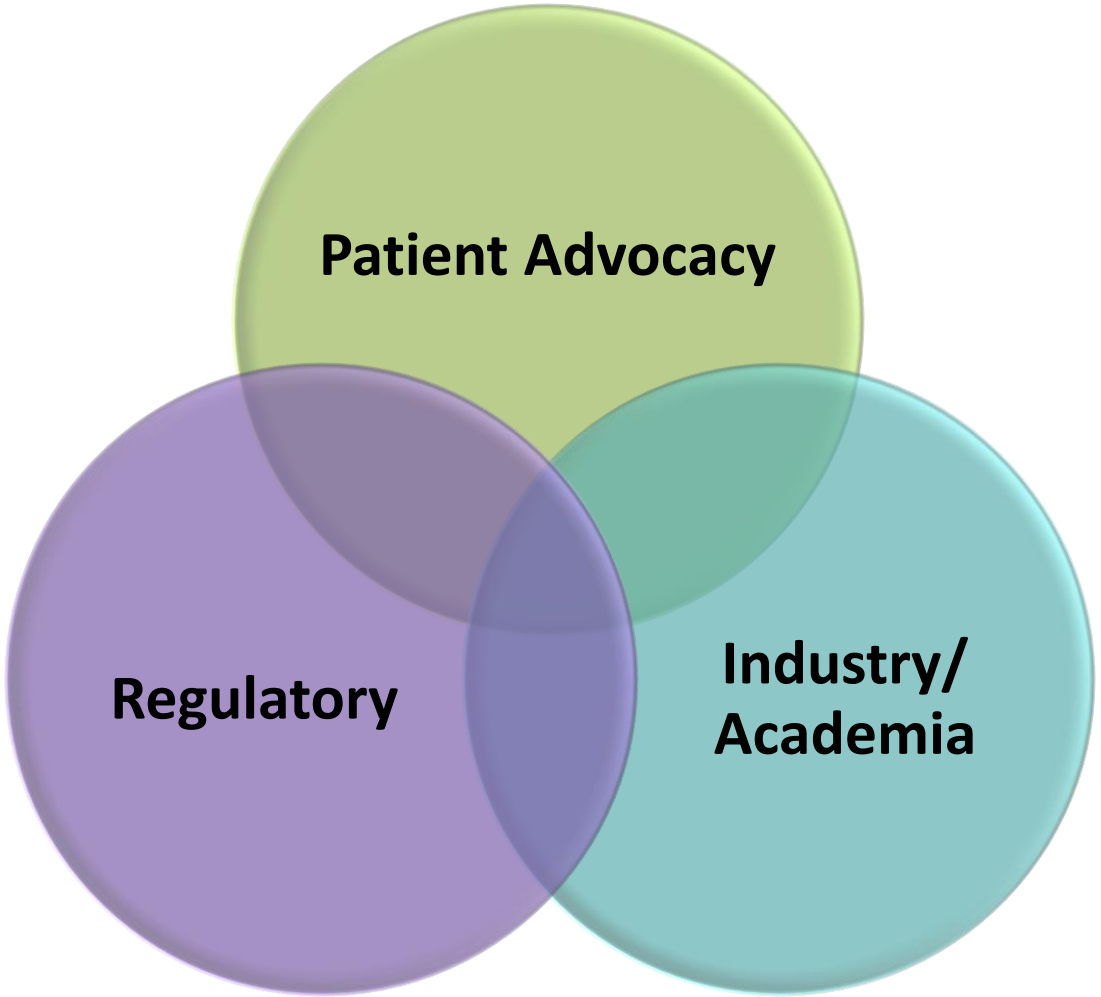
Erdafitinib, FDA review; Pembrolizumab, FDA review

# Recipe FOR Success of Project Optimus

**Patient Advocacy**
- Communicate expectations
- Provide input for rational drug development
- Participate in dose optimization trials

**Industry and Academics**
- Conduct adequate dose optimization trials
- Continue dose optimization throughout drug development
- Invest in innovative approaches
- Interact with FDA

**Regulatory**
- Provide Guidance
- Facilitate regulatory pathways
- Support innovation in trial design




*Mirat Shah, MDICT 2022*