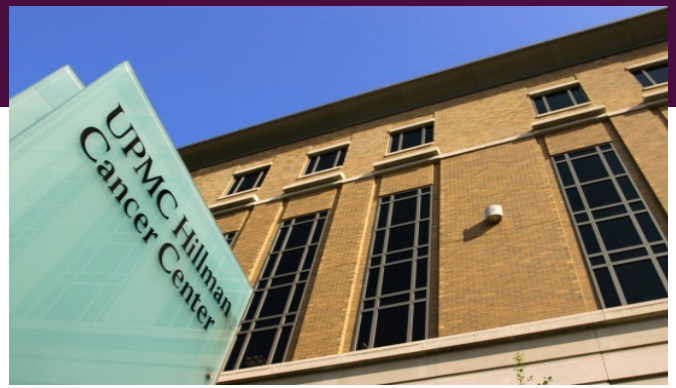


Project OPTIMUS

-

Optimizing Dose and Schedule in Early Phase Clinical Trials

Jan H. Beumer, PharmD, PhD, DABT
Professor - Pharmaceutical Sciences and Medicine
Director - Cancer Pharmacokinetics and Pharmacodynamics Facility
Co-Director - Immunotherapy and Drug Development Center
mPI – ETCTN Pittsburgh Cancer Consortium

UPMC | HILLMAN CANCER CENTER

NCI Designated Comprehensive Cancer Center

Overview

- The test case
- The rationale behind FDA Project Optimus
- How the rubber met the road
- Guidance, theory and practicalities
- Looking ahead… are we done with the right approved dose?

Cancer Letter

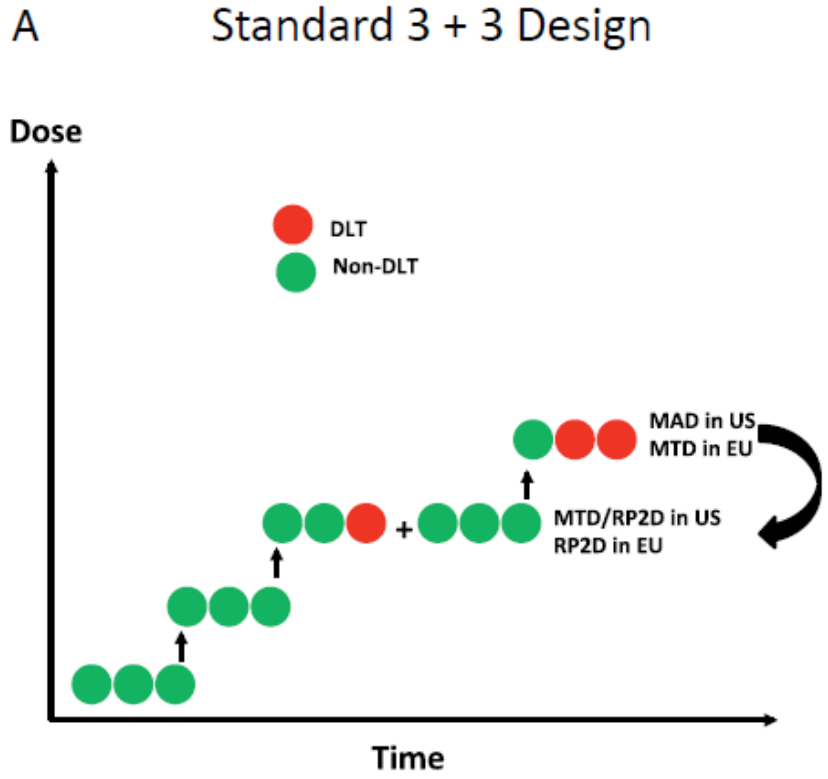
ISSUE 23 | VOL 47 | JUNE 11, 2021 | THE CANCER LETTER

RIP MTD: FDA to require sponsors to determine optimal dosage before initiating pivotal trials in cancer

By Paul Goldberg

FDA officials said drug sponsors will soon be required to conduct randomized studies to determine optimal dosages of cancer drugs before proceeding to testing safety and efficacy in pivotal trials.

June 11 2021



N=6 patients in 1st cycle determine MTD

Hansen. Cancer Control 2014: 200

Sotorasib first approved RAS inhibitor – but…

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 24, 2021 VOL. 384 NO. 25

Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation

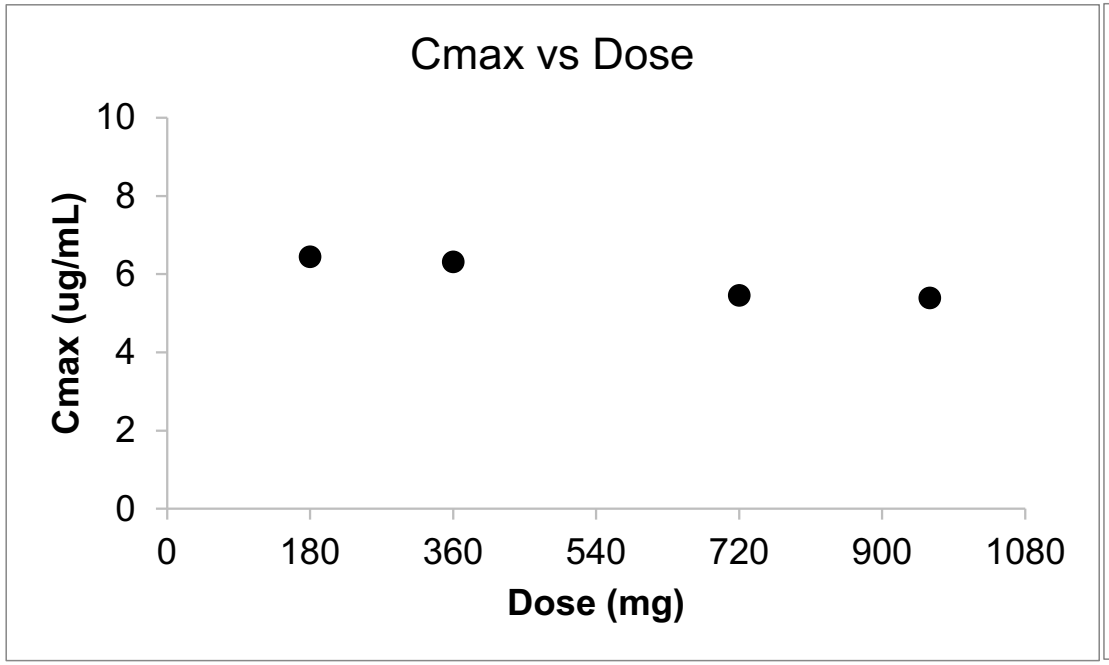
PMR 2

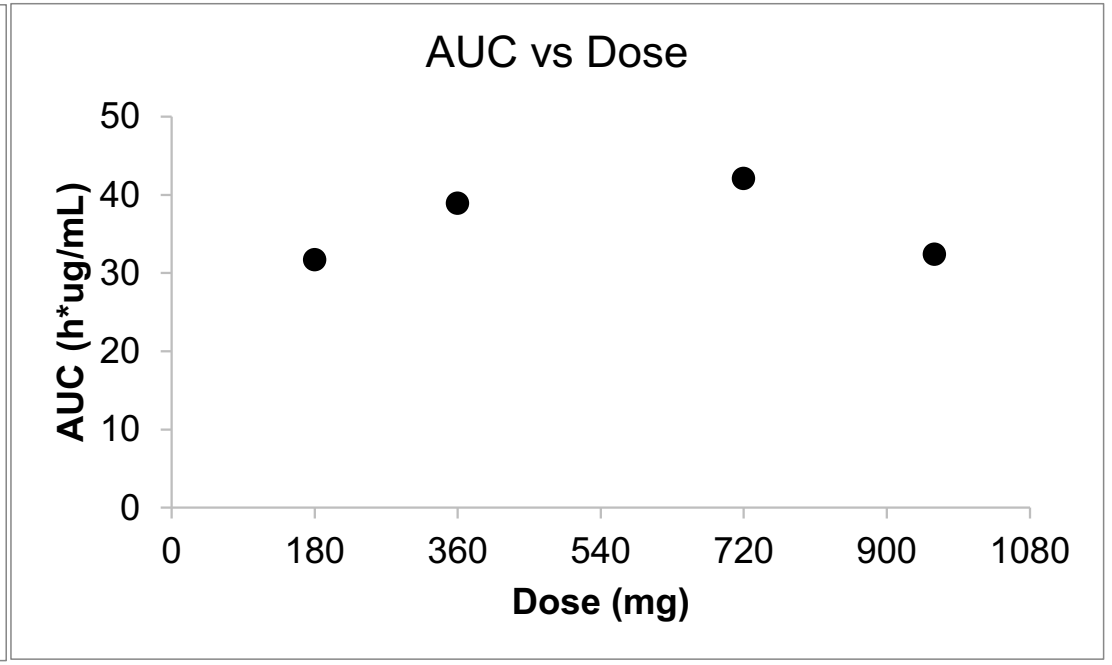
- …further characterize SAEs, including GI toxicity and **compare the safety and efficacy of sotorasib 960 mg daily versus a lower daily dose**

- *Rationale:* **Sotorasib demonstrated saturable absorption** with steady-state exposures (Cmax and AUC0-24h) **comparable among 180 mg to 960 mg** QD dose levels.

Shah. NEJM 2021: 1445
FDA review sotorasib

Sotorasib – FDA review





- What did the phase 1 study show?!
  - PK?
  - MTD?

FDA review sotorasib

Sotorasib – phase 1

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 24, 2020 VOL. 383 NO. 13

KRAS^{G12C} Inhibition with Sotorasib in Advanced Solid Tumors

Cohort 1	Cohort 2	Cohort 3	Cohort 4
180 mg	360 mg	720 mg	960 mg
(N=6)	(N=27)	(N=11)	(N=85)

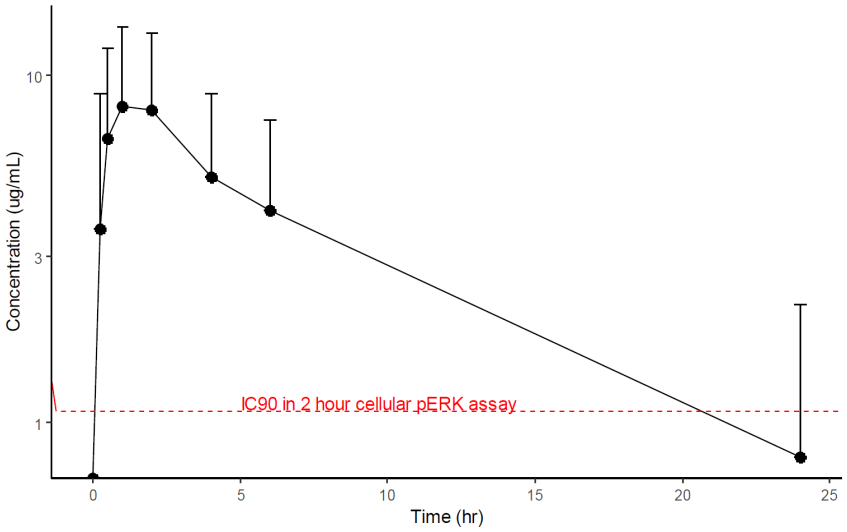
- A two-parameter Bayesian logistics-regression model was used to guide dose escalation. ? Target DLT rate
- No dose-limiting toxic effects were observed.
- ..the dose level review team reviewed all available safety, laboratory, pharmacokinetic, and efficacy data to make a recommendation to proceed to phase 2.

Hong. NEJM 2020: 1207

- Pharmacokinetics section
  - "The PK profile of sotorasib administered at a dose of 960 mg daily is shown in Figure S3. ..."
  - "The dose of 960 mg administered daily was identified as the dose for the expansion cohort."

Figure S3. Pharmacokinetics of Sotorasib

PK data cutoff was July 24, 2019. Data from 32 patients were used. Only the top error bars are shown for clarify on a semi-logarithmic scale (non-symmetric scale).



The rationale behind FDA Project Optimus

The Drug-Dosing Conundrum in Oncology — When Less Is More

Mirat Shah, M.D., Atiqur Rahman, Ph.D., Marc R. Theoret, M.D., and Richard Pazdur, M.D.

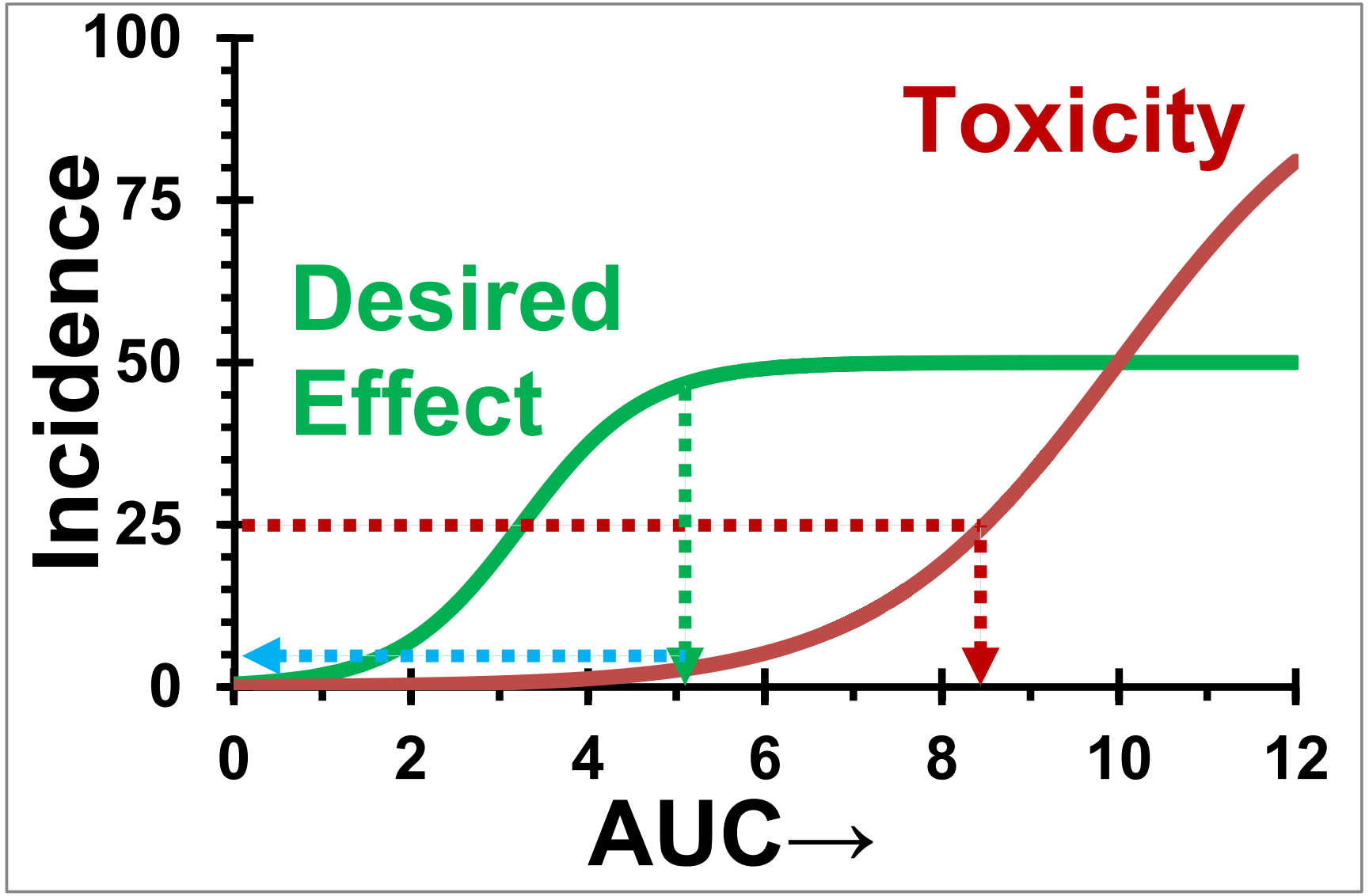
Examples of Drugs Whose Doses or Schedules Were Modified for Safety or Tolerability after Approval.*

Drug	Initial Dose and Trials	Modified or Added Dose and Trials	Reason for Modified or Added Dose
Small-molecule drugs			
Ceritinib	750 mg PO daily fasted (ASCEND-1)	450 mg PO daily with food (ASCEND-8)	Reduce gastrointestinal toxic effects
Dasatinib	70 mg PO twice daily (CA180013, CA180005, CA180006, and CA180015)	100 mg PO daily (CA180034)	Reduce hematologic toxic effects and fluid retention
Niraparib	300 mg PO daily (NOVA)	200 mg PO daily (PRIMA)	Reduce thrombocytopenia in patients with a lower platelet count or lower body weight
Ponatinib	45 mg PO daily (PACE)	45 mg PO daily, then 15 mg PO daily once ≤1% *BCR-ABL* is achieved (OPTIC)	Reduce vascular occlusive events
Chemotherapy			
Cabazitaxel	25 mg/m² IV every 3 wk (TROPIC)	20 mg/m² IV every 3 wk (PROSELICA)	Reduce hematologic toxic effects and infections
Antibody–drug conjugates			
Gemtuzumab ozogamicin	9 mg/m² IV on days 1 and 15 (Study 201, Study 202, and Study 203)	3 mg/m² IV on days 1, 4, and 7 (Mylofrance-1)	Reduce veno-occlusive disease and treatment-related mortality

* Adapted from the Food and Drug Administration.[2] IV denotes intravenous, and PO by mouth.

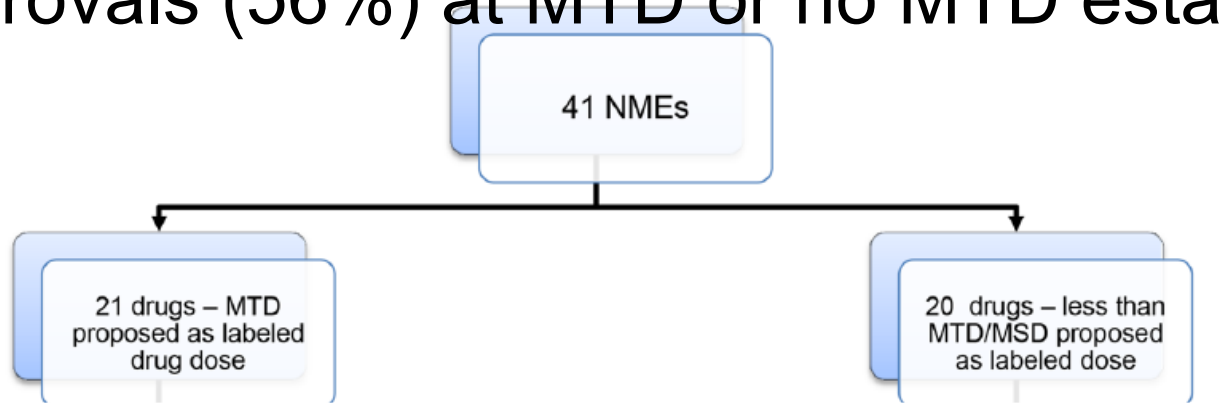
Shah NEJM 2021; 1445

Exposure-response (activity vs toxicity)



PMR's (Post Marketing Requirements)

- 11 of 41 NME approvals (27%) had dose optimization-related PMRs issued by the FDA
- 7 approvals (17%) included non-MTD dose strategy
- 23 approvals (56%) at MTD or no MTD established



Cancer Chemother Pharmacol (2016) 77:459–476
DOI 10.1007/s00280-015-2931-4

REVIEW ARTICLE

A survey of new oncology drug approvals in the USA from 2010 to 2015: a focus on optimal dose and related postmarketing activities

Lu CCAP 2016; 459

FDA Project Optimus

- Poorly characterized dose and schedule may lead to selection of a dose that provides:
  - more toxicity
  - dose reductions
  - premature discontinuation
  - persistent or irreversible toxicities

- Goals of project OPTIMUS
  - Communicate expectations through Guidance, workshops, etc.
  - Provide opportunities … to meet with FDA Oncology Review Divisions early in their development programs,.., to discuss dose-finding and dose optimization.
  - Develop strategies …that leverages nonclinical and clinical data

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

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KNOWLEDGE CONQUERS CANCER

Getting the Dose Right: Optimizing Dose Selection Strategies in Oncology
An FDA-ASCO Virtual Workshop

Dates: May 3 and 5, 2022

What Oncology Drug Developers Should Expect from FDA's Project Optimus

February 24, 2022

David Wicks
Vice President, Listing Services
Nasdaq

Julie M. Bullock, PharmD
VP, Global Head Clinica
Certara

U.S. FOOD & DRUG ADMINISTRATION | ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Second Annual Workshop on Getting the Dose Right:
Optimizing Dose Selection Strategies in Combination Anticancer Therapies

An FDA-ASCO Virtual Workshop

September 6-7, 2023

How the rubber hit the road

Remember to distinguish:

- FIM vs later trial
- Single agent vs combination
- Pharma vs IIT/CTEP trial

Example FDA comments

- Inadequately justified dosages may result in a clinical hold of an IND …
- To select the MTD as the RP2D for dose expansion is not an ideal approach…
- FDA recommends including preliminary study cohort(s) to determine the effect of gastric pH on the absorption/PK of {parent drug}.
- We strongly recommend including an evaluation of the food effect in the planned study.
- ..
- Qtc..
- Exposure response modeling..

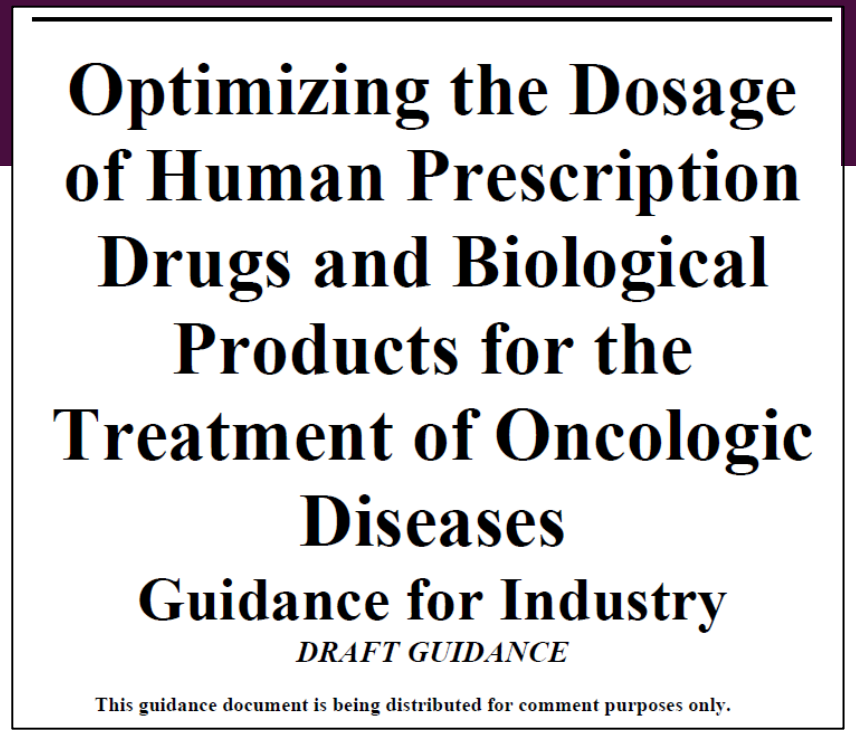
- Each trial gets the book thrown at them

ETCTN / CTEP experience

- Support the FDA goal of optimizing dosing
- Thoughtful implementation
- Templated responses to templated FDA comments
- Focus on how we better determine dose for further study
  - Distinguish MTD vs P2RD
  - Data review and protocol MOD at end of escalation
  - More emphasis on including limited PK and PD assays in early phase 2 studies

Draft Guidance (2023)

- Traditional MTD paradigm does not adequately evaluate data other than DLT:
  - low-grade toxicities (i.e., grade 1-2)
  - dosage modifications
  - drug activity
  - dose- and exposure response relationships
  - relevant specific populations (defined by age, organ impairment, concomitant medications or concurrent illnesses)
- Relevant nonclinical and clinical data, as well as the dose- and exposure-response relationships for safety and efficacy should be evaluated to select a dosage(s) for clinical trial(s).


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

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

https://www.fda.gov/media/164555/download 2023

Draft Guidance

- A. Collection and Interpretation of Clinical Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Data
  - Dose-linearity; after multiple doses; facilitate POP-PK
  - Specific populations (e.g., weight, age, sex, race and ethnicity, or organ impairment)
  - Food
  - PGx

https://www.fda.gov/media/164555/download 2023

Draft Guidance

- B. Trial Designs to Compare Multiple Dosages
  - Selected based on the relevant nonclinical and clinical data.
  - Prior to initiating a trial directly comparing multiple dosages, it may be reasonable to add more patients to dose-level cohorts in a dose-finding trial... This would allow for further assessment of activity and safety.
  - A recommended trial design to compare these dosages is a randomized, parallel dose-response trial.
    - ..should be sized to allow for sufficient assessment of activity, safety, and tolerability for each dosage.
    - ..does not need to be powered to demonstrate statistical superiority of a dosage or statistical non-inferiority among the dosages.

https://www.fda.gov/media/164555/download 2023

Draft Guidance

- C. Safety and Tolerability
  - Duration of exposure; % planned doses; % interruptions; % reductions; % drug discontinuations for AE; …across the multiple dosages.
  - Specific AEs, including “less severe” (e.g., Grade 1-2 diarrhea)

- D. Drug Formulation

- E. Subsequent Indications and Usages

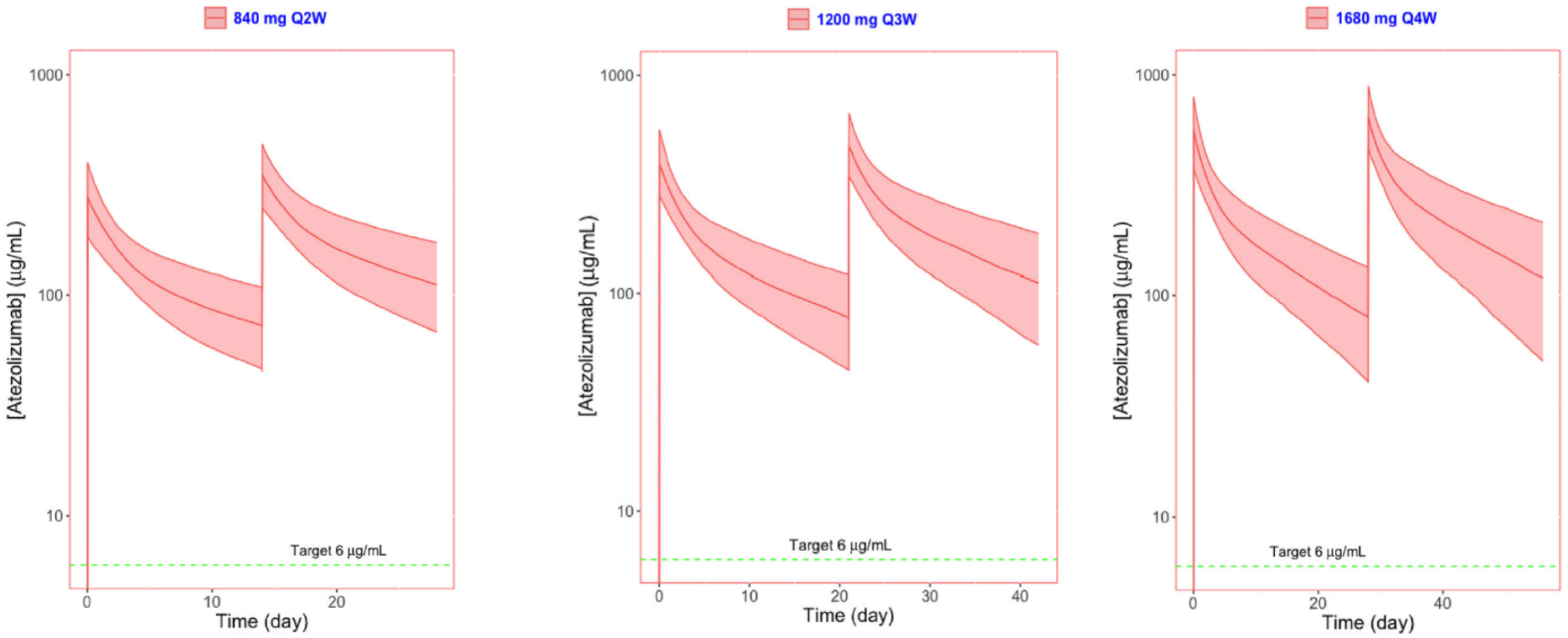
https://www.fda.gov/media/164555/download 2023

Theory

- Integrated analysis of
  - Preclinical data
  - PK
  - PD
  - Toxicity
  - Response
- No automatic MTD=P2RD

Practicalities – PK target

- Preclinical: Atezolizumab
  - Target C_{min} is 6 µg/ml
- Exposure-toxicity !

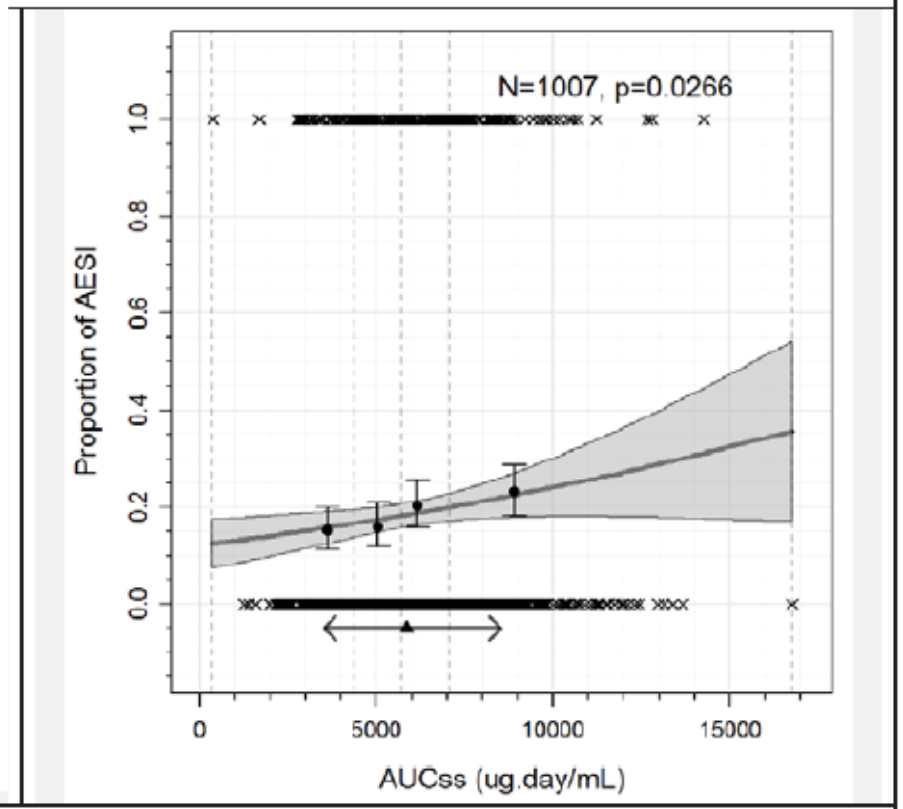


Peer. The Journal of Clinical Pharmacology 2023: 672

Practicalities – PK target

- Clinical
  - Exposure-toxicity !

Figure 6 : Incidence of AEs vs. Atezolizumab AUCss in Patients with NSCLC:



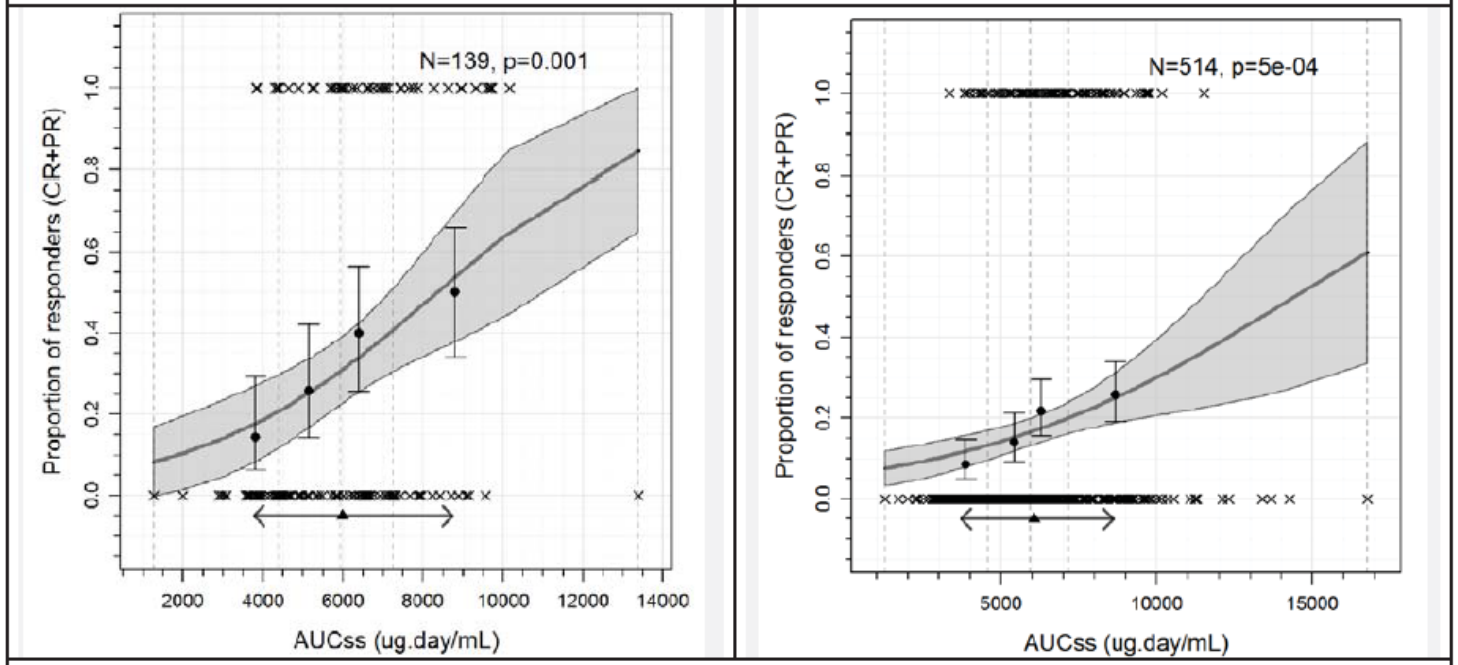
Source: Synopsis of applicant's ER Report 1067243, Figure C

FDA. Clinical Pharmacology and Biopharmaceutics Review, 761041Orig1s000 2016

Practicalities – PK target

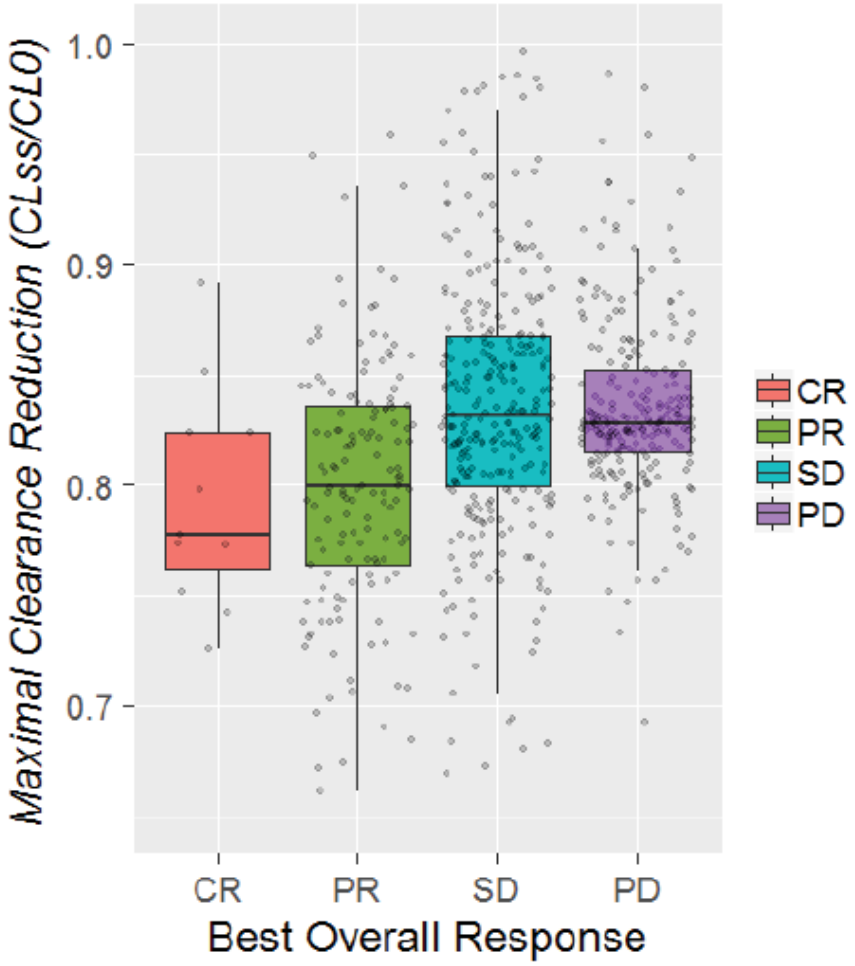
- Clinical
  - Exposure-response?

Figure 5 : Objective Response Rate vs. Atezolizumab AUCss (BIRCH)



Source: Synopsis of applicant's ER Report 1067243, Figure 4-1 and Appendix 8.1.5

Reviewer's comment: Applicant's exposure-ORR analysis is biased because the atezolizumab exposure could be affected by the disease progression post treatment. See reviewer's analysis in section 4 for more details.



FDA. Clinical Pharmacology and Biopharmaceutics Review, 761041Orig1s000 2016

Practicalities - Design

Phase 1 designs (also combinations)

- Backbone still the same; more bells and whistles
- Practical endpoint to make escalation decisions still toxicity
- More PK (multiple timepoints, multiple dose occasions)
- PD (biomarkers for target engagement)
- Expansion cohorts MTD, MTD-1
- Biopsies during escalation, backfilling dose levels

FIM followed by randomized dosage phase 2 (dose-ranging)

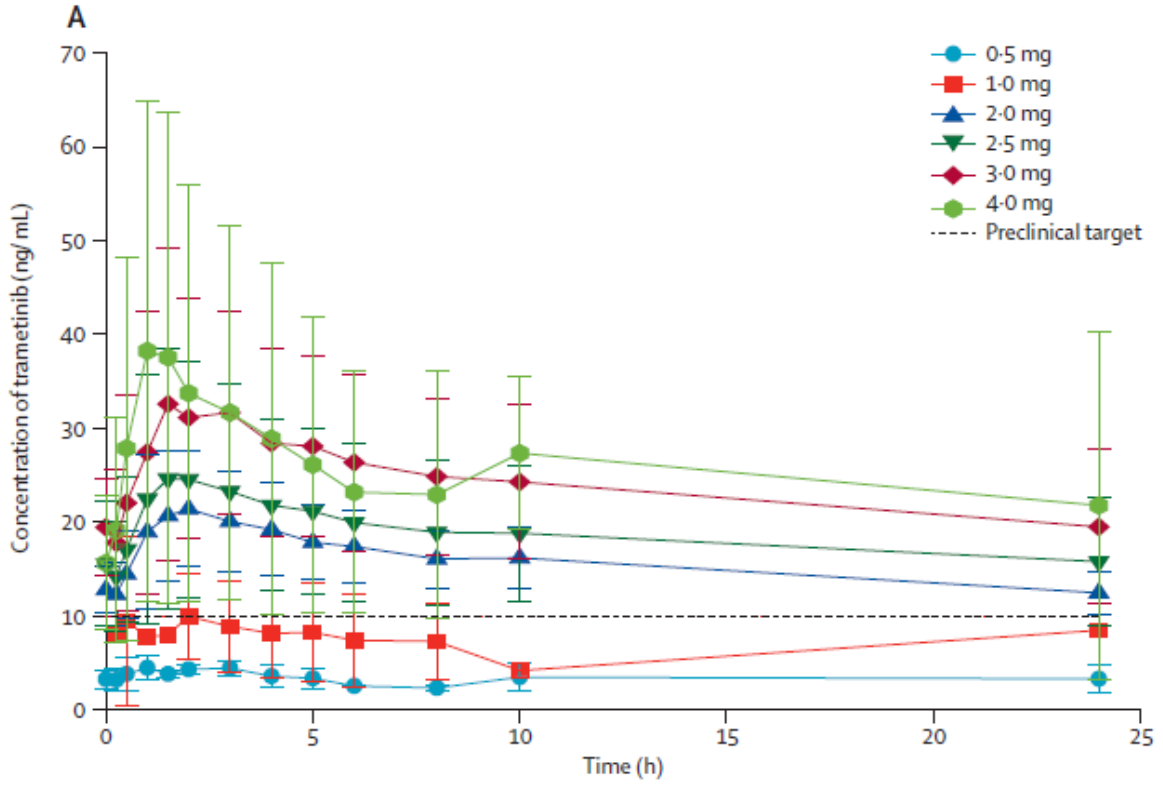
Practicalities - Biomarkers

- Cancer is not hypertension (BP), diabetes (Hb_{A1c}), hypercholesterolemia (cholesterol)
- …survey indicates that biomarker data may be supportive in select cases (5/41)
  - Trametinib (tumor)
  - Abiraterone (serum marker)
  - Carfilzomib (PBMC)
  - Enzalutamide (PSA response)
  - Ibrutinib (receptor occupancy)

Lu CCAP 2016; 459

Practicalities - Biomarkers

- Trametinib Phase 1
  - 0.5-4 mg
  - **2 mg** PK above target
  - **2 mg** minimum for tumor marker
  - Rash or dermatitis acneiform of grade 2 or higher
    - **2 mg** 36%
    - 2.5 mg 48%
    - 3 mg 58%

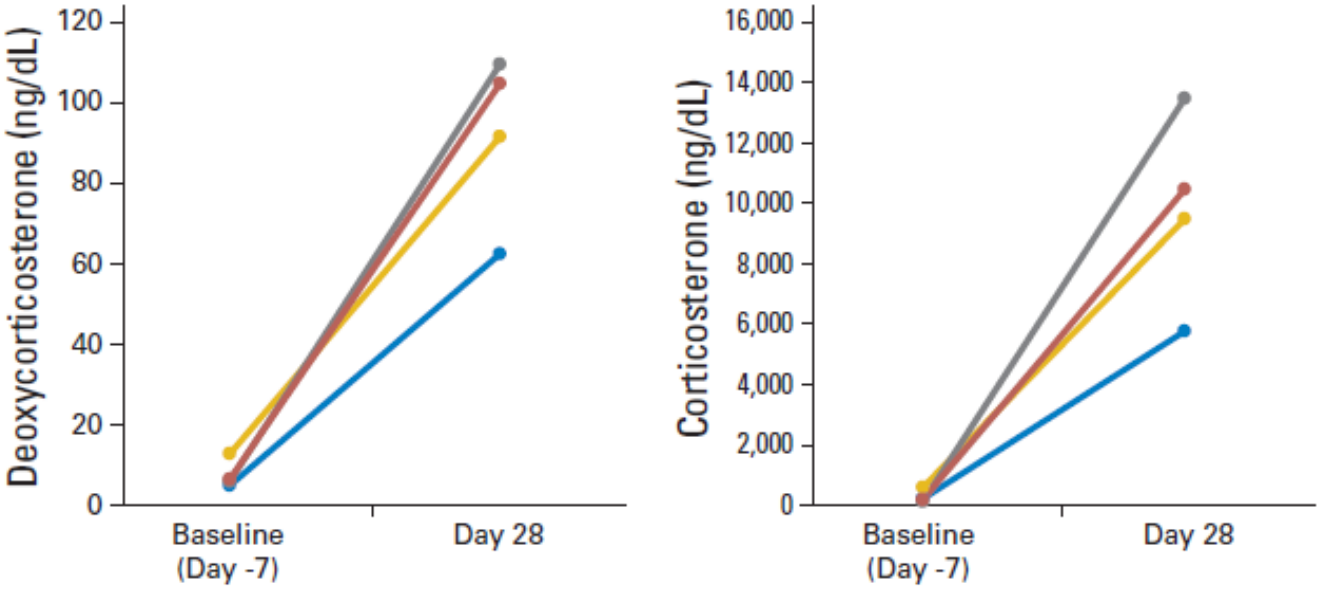


	All tumor types and mutation status[b]		
	pERK	Ki67	p27
0.5 (n=8)	2.6	-3.9	3.6
1.0 (n=4)	3.8	-2.1	35.2
2.0 (n=10)	-30.0[c]	-54.4	83.0

Infante LANCET ONC 2012; 773

Practicalities - Biomarkers

- Abiraterone (CYP17 inhibitor)
  - Deoxycorticosterone and corticosterone (upstream of CYP17)
  - Near maximal increase at the 750 mg dose
  - **1000 mg** and 2000 mg did not further raise the levels



FDA. Clinical Pharmacology and Biopharmaceutics Review, 202379Orig1s000 2010

Ryan JCO 2010: 1481

Practicalities - Biomarkers

- Carfilzomib
  - Chymotrypsin-like activity in blood and PBMC plateaus at 11 mg/m^2
  - 20/27 mg/m^2 primarily based on the safety and ORR

Figure 5. Proteasome Chymotrypsin-like Activity vs. Carfilomib dose in Whole Blood (A) and PBMCs (B).

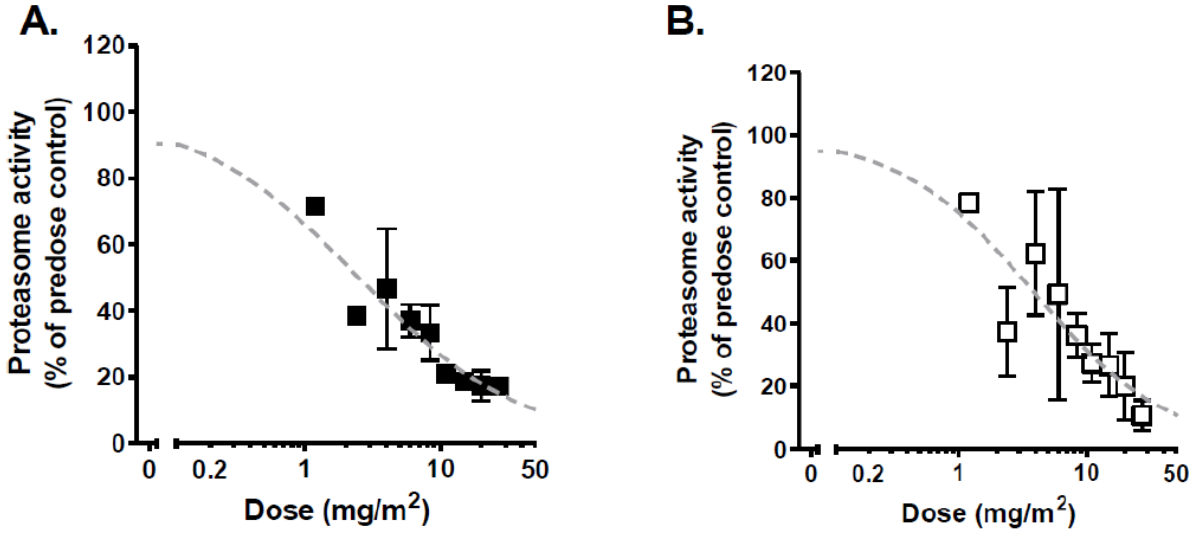
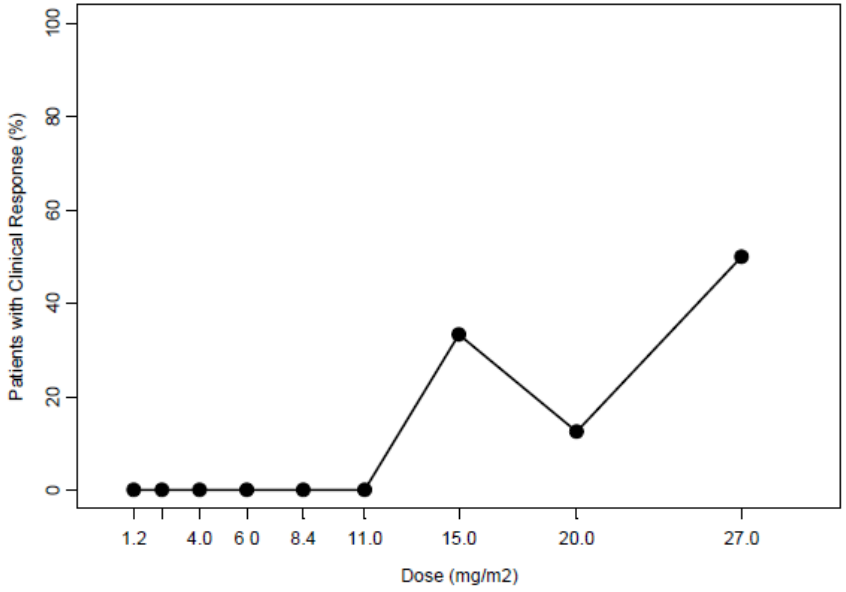


Figure 4. Clinical response rate vs. carfilzomib dose.



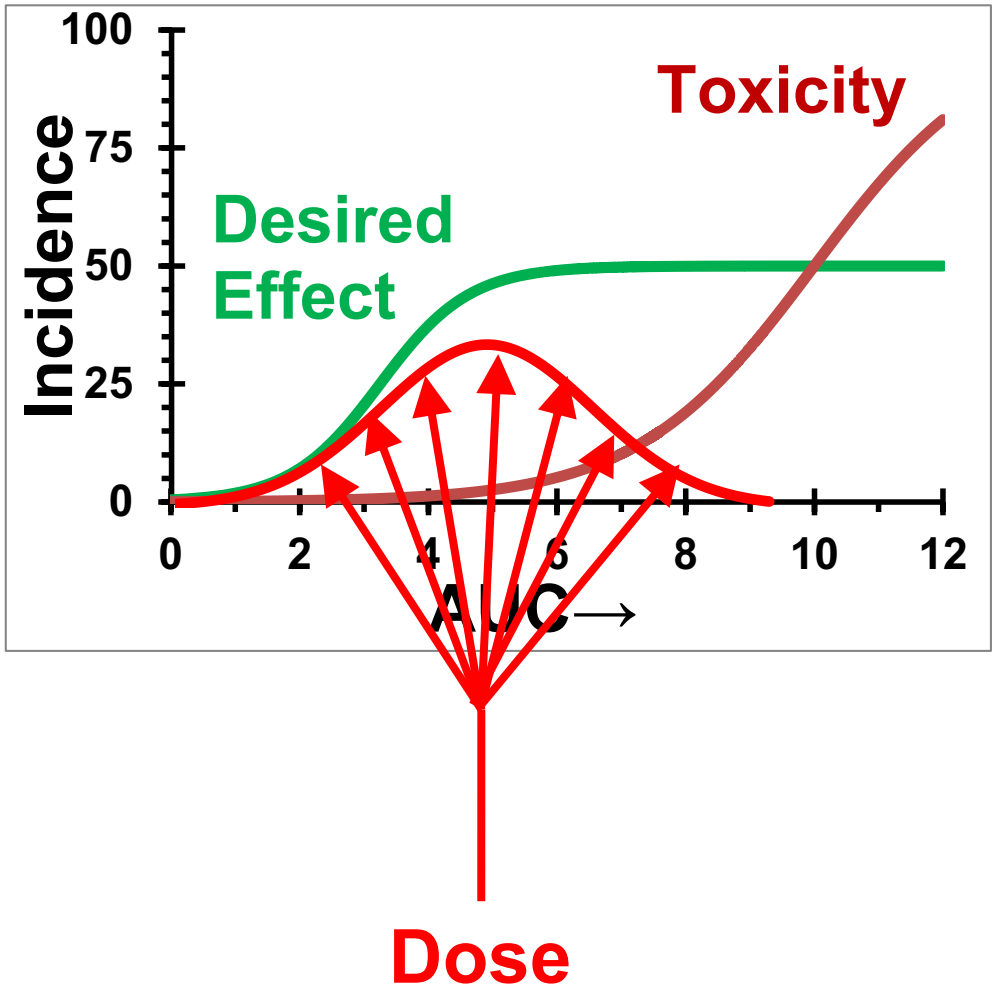
FDA. Clinical Pharmacology and Biopharmaceutics Review, 202714Orig1s000 2012

Looking ahead… are we done with the right approved dose?

- Poorly characterized dose and schedule may lead to selection of a dose that provides:
  - more toxicity
  - dose reductions
  - premature discontinuation
  - persistent or irreversible toxicities

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

Looking ahead… are we done with the right approved dose?



FDA Project Optimus – Friends of Cancer Research

- "Establishment of a therapeutic window based on activity and an acceptable level of toxicity, derived from a characterization of PK and PD metrics is integral"

- This would allow Therapeutic Drug Monitoring (TDM)

https://www.fda.gov/media/164555/download 2023

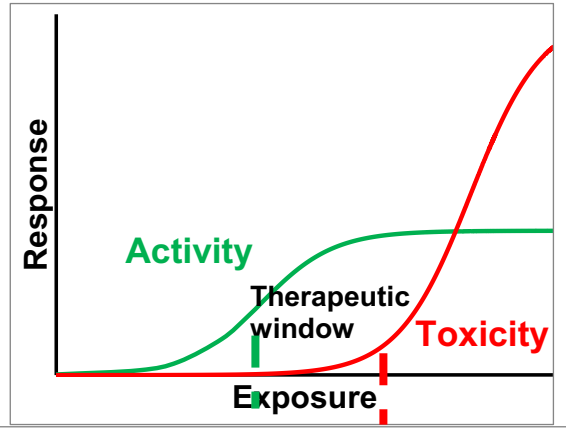
https://friendsofcancerresearch.org/sites/default/files/2021-11/Optimizing_Dosing_in_Oncology_Drug_Development.pdf

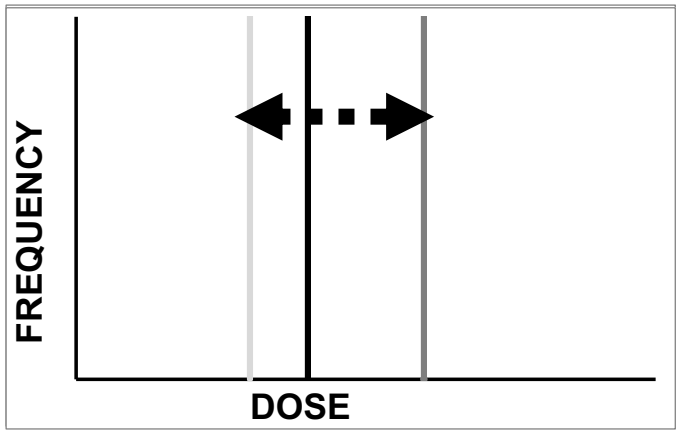
Is a Phase 3 Trial Needed for TDM?

- Its not a new drug (it's fine-tuning a drug with proven activity)
  - Just like dose ranging with project OPTIMUS (not powered for stats)
- We correct for factors based on PK all the time:
  - Renal/hepatic impairment
  - Enzyme inducer/inhibitor
  - Inhibitors of transporters
  - Enzyme polymorphism
- Target exposure-matching generally accepted (Package Insert)
  - E.g. % change in AUC in presence of liver hepatic impairment

Groenland CCR 2021; 6644

Dreams of TDM



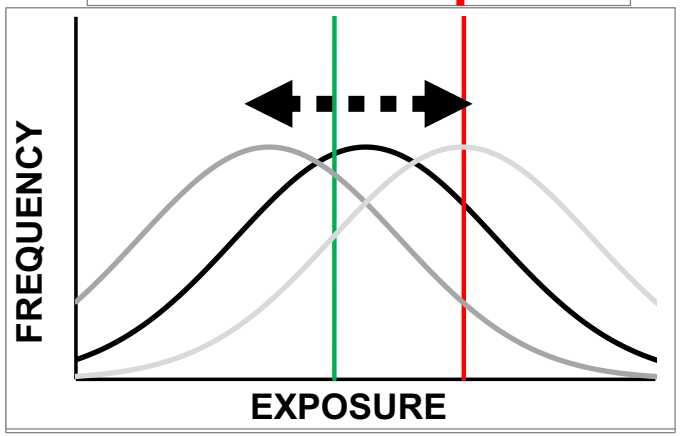


PROJECT

SINGLE

-fine tuning

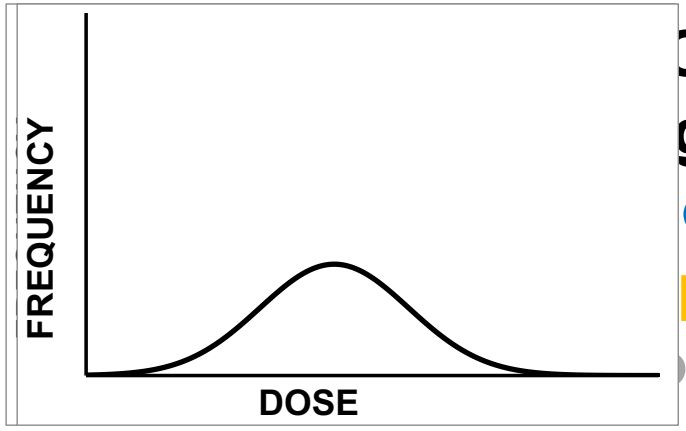
single MTD



PAST

FUTURE?

PRESENT



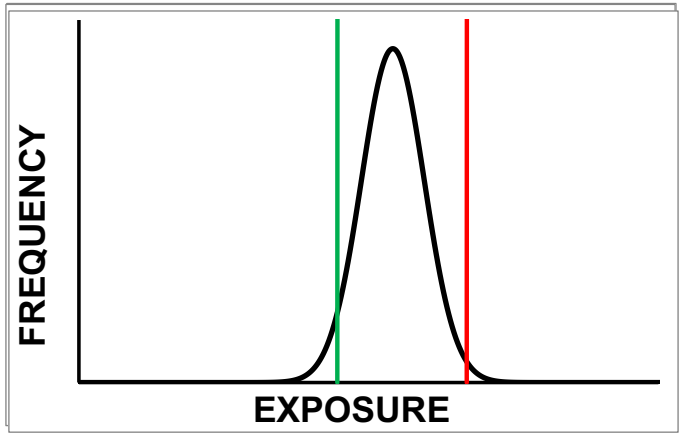
THERAPEUTIC

DRUG

MONITORING

“EXPOSURE-

MATCH”



Only the regulator can make things happen

- Drug exposure is often the best biomarker for toxicity / effect
  - Not practical for all drugs

- Logical extension of Project Optimus:
  - Labeling should not merely list dosing, but an exposure range

Overview

- The test case — Odd stick
- The rationale behind FDA Project Optimus — Solid
- How the rubber met the road — Some skid marks
- Guidance, theory and practicalities — Drug development aint easy
- Looking ahead… are we done with the right approved dose? — No, TDM!
- Schedule?

Acknowledgements

- ETCTN
  - Pittsburgh Cancer Consortium
  - PITT-CAL U24 Consortium (Tim Synold)
  - Percy Ivy
  - Jeff Moscow
  - Michelle Rudek
  - Joga Gobburu
  - Friends at the California Cancer Consortium

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  - U24 CA247643
  - P30 CA047904

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