PLÉNIÈRE

Méthodologie des essais cliniques : vers une optimisation de la recherche de dose, comment les phases précoces s'adaptent aux nouvelles réglementations ?

Débat animé par : Fabrice Barlesi et David Pérol

Avec la participation de : Olivier Mir, Xavier Paoletti, Sophie Postel-Vinay

Project Optimus

Olivier Mir, MD, PhD

Early Clinical Development, Oncology - Amgen

omir@amgen.com

COI statement

Dr. Mir is an employee and shareholder of Amgen, Inc.

The opinions and ideas exposed in the present presentation are mine, not those of the company

Background

Dose selection for registration trials should be guided by pharmacokinetic and pharmacodynamic data collected early in clinical development. After the initial dose-escalation trial, two or more doses should be selected on the basis of exposure, target saturation, and other pharmacodynamic markers and subsequently evaluated in a randomized trial.

Using randomized trials to guide dose selection may also be an option when sponsors are considering submitting a drug for approval on the basis of a single-group efficacy trial. In these cases, an early, randomized trial examining response rates for several doses can be performed with a prespecified dose–response analysis for dose selection. The trial

With targeted drugs, chronic, low-grade toxic effects may interfere with prolonged administration, require dose reductions and delays, and hinder adherence to a treatment schedule, which may result in disease progression. It's important to consider the frequency of lower-grade toxic effects and of dose modifications, including those that may occur after the first treatment cycle, when selecting a dose.

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.

N ENGL J MED 385;16 NEJM.ORG OCTOBER 14, 2021

⇒ ***Early dose optimization***
⇒ ***Randomized design***
⇒ ***Useful for single arm trials aiming for an AA***
⇒ ***AEs beyond the DLT window***

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 (Zykadia)	750 mg PO daily fasted (ASCEND-1)	450 mg PO daily with food (ASCEND-8)	Reduce gastrointestinal toxic effects
Dasatinib (Sprycel)	70 mg PO twice daily (CA180013, CA180005, CA180006, and CA180015)	100 mg PO daily (CA180034)	Reduce hematologic toxic effects and fluid retention
Niraparib (Zejula)	300 mg PO daily (NOVA)	200 mg PO daily (PRIMA)	Reduce thrombocytopenia in patients with a lower platelet count or lower body weight
Ponatinib (Iclusig)	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 (Jevtana)	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 (Mylotarg)	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

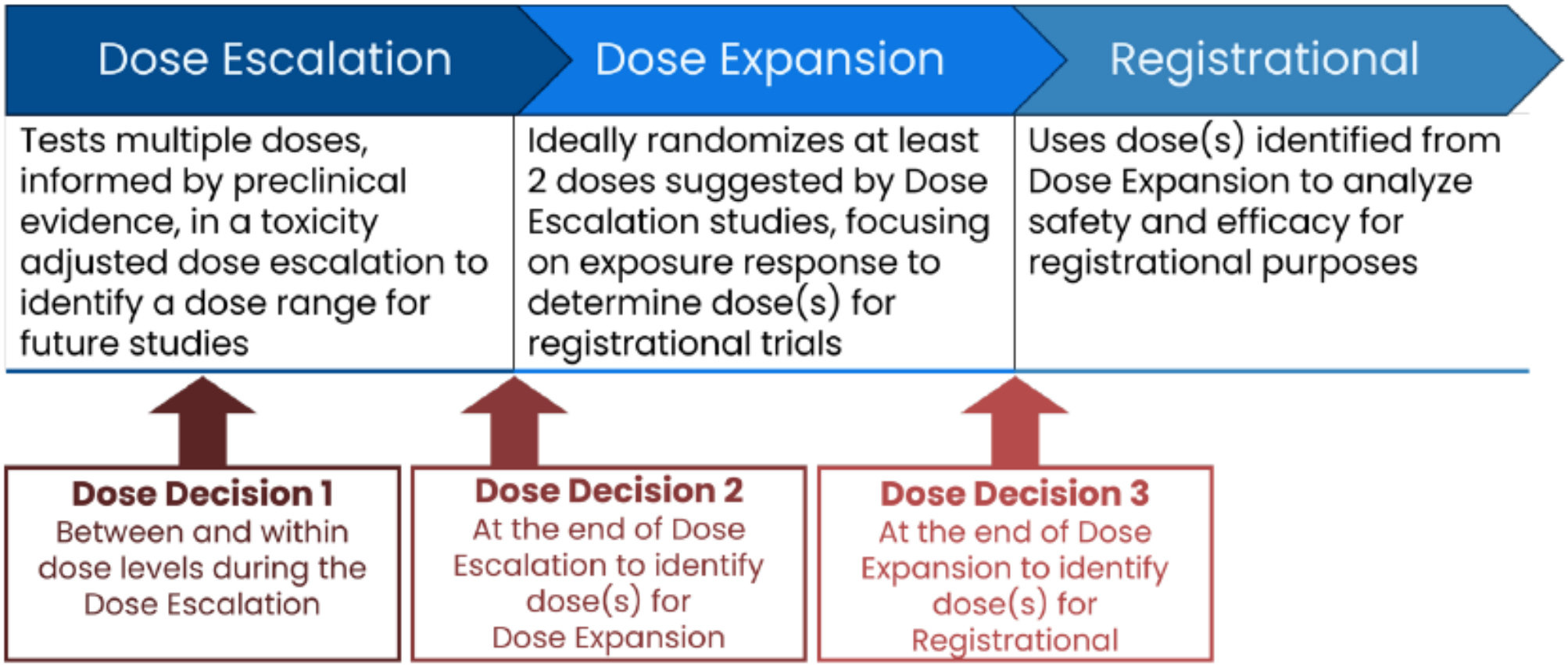
* Adapted from the Food and Drug Administration.[2] IV denotes intravenous, and PO by mouth.

FRIENDS of CANCER RESEARCH

A FRIENDS OF CANCER RESEARCH WHITE PAPER

Interpreting Data from Dose-Finding Studies in Early Phase Oncology Trials to Determine the Optimal Dose

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



Recent data from AMG 757 (tarlatamab)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer

M.-J. Ahn, B.C. Cho, E. Felip, I. Korantzis, K. Ohashi, M. Majem, O. Juan-Vidal, S. Handzhiev, H. Izumi, J.-S. Lee, R. Dziadziuszko, J. Wolf, F. Blackhall, M. Reck, J. Bustamante Alvarez, H.-D. Hummel, A.-M.C. Dingemans, J. Sands, H. Akamatsu, T.K. Owonikoko, S.S. Ramalingam, H. Borghaei, M.L. Johnson, S. Huang, S. Mukherjee, M. Minocha, T. Jiang, P. Martinez, E.S. Anderson, and L. Paz-Ares, for the DeLLphi-301 Investigators*

DOI: 10.1056/NEJMoa2307980

In the ongoing phase 3 DeLLphi-304 trial (ClinicalTrials.gov number, NCT05740566), investigators are comparing tarlatamab (10 mg every 2 weeks) with standard care in patients with previously treated extensive-stage small-cell lung cancer.

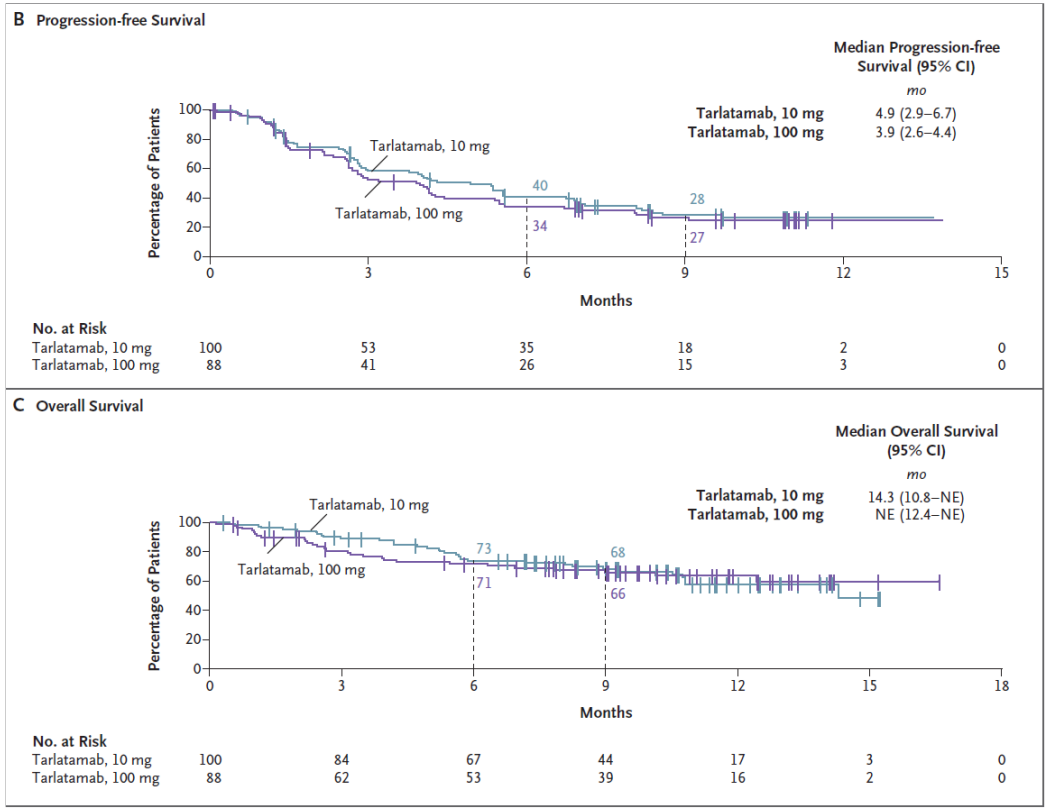


Table 2. Treatment Response According to Blinded Independent Central Review (Analysis Population for Antitumor Activity).*

Variable	Tarlatamab, 10 mg (N=100)	Tarlatamab, 100 mg (N=88)
Best overall response — no. (%)		
Objective response		
Confirmed complete response	1 (1)	7 (8)
Confirmed partial response	39 (39)	21 (24)
Stable disease	30 (30)	27 (31)
Progressive disease	20 (20)	13 (15)
Not evaluable†	2 (2)	4 (5)
Death before postbaseline scan†	6 (6)	13 (15)
No postbaseline scan†	2 (2)	3 (3)
Percentage of patients with objective response (97.5% CI)	40 (29–52)	32 (21–44)

Adverse Events	Tarlatamab, 10 mg		Tarlatamab, 100 mg
	Parts 1 and 2 (N=99)	Part 3, Reduced Monitoring (N=34)	Part 1 (N=87)
	number of patients (percent)		
Events during treatment period			
According to severity			
Any grade	96 (97)	34 (100)	87 (100)
Grade ≥2	86 (87)	33 (97)	83 (95)
Grade ≥3	57 (58)	22 (65)	56 (64)
Grade ≥4	16 (16)	7 (21)	13 (15)
Fatal	3 (3)	4 (12)	5 (6)
Serious adverse event	58 (59)	14 (41)	62 (71)
Event leading to dose interruption, dose reduction, or both	31 (31)	5 (15)	39 (45)

=> « Less is more »

Open questions…

- Small molecules vs. biologics ?
  - Less PK variability with biologics
  - More delayed AEs with IO agents
  - Therapeutic window, dose-effect curves ?

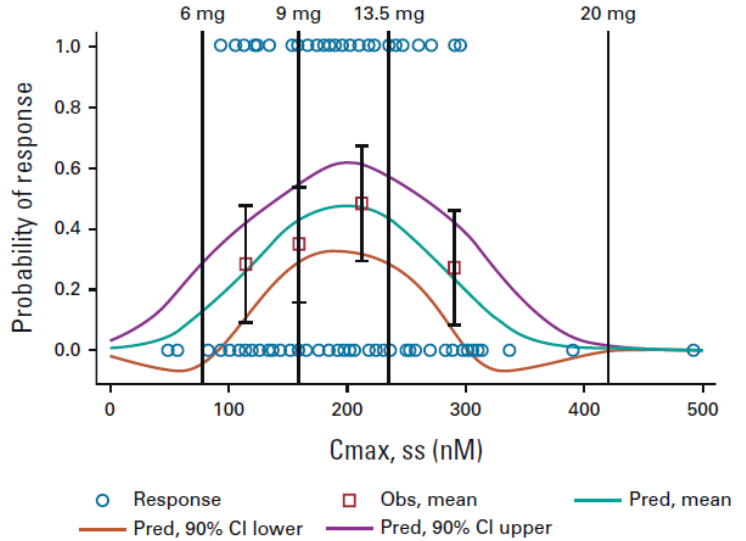
- Combinations ?

SPECIAL SERIES: STATISTICS IN ONCOLOGY

Improving Dose-Optimization Processes Used in Oncology Drug Development to Minimize Toxicity and Maximize Benefit to Patients

Jeanne Fourie Zirkelbach, PhD[1]; Mirat Shah, MD[2]; Jonathon Vallejo, PhD[3]; Joyce Cheng, PhD[3]; Amal Ayyoub, PhD[1]; Jiang Liu, PhD[1]; Rachel Hudson, PhD[1]; Rajeshwari Sridhara, PhD[3]; Gwynn Ison, MD[2]; Laleh Amiri-Kordestani, MD[2]; Shenghui Tang, PhD[3]; Thomas Gwise, PhD[3]; Atiqur Rahman, PhD[1]; Richard Pazdur, MD[4]; and Marc R. Theoret, MD[4]

J Clin Oncol 40:3489-3500. Published by American Society of Clinical Oncology



Phase of Development	Recommendation
Early clinical development	Aim to identify several candidate dosages or a dosage range to further evaluate after dose escalation and initial dose expansion
	Determine whether there are PD biomarkers that may help inform dose optimization
	Consider integrating modeling and simulation with emerging clinical data to support dose optimization
Later clinical development	Pursue randomized dose trials to further evaluate multiple dosages
	Incorporate safety information beyond DLTs, such as dose modifications and low-grade but persistent toxicities which may affect ability to take a drug
Throughout development	Plan dose-optimization strategy early
	Collect exposure data from multiple dosages to gain better understanding of exposure-efficacy and exposure-safety relationships
	Use emerging information throughout clinical development to update decisions regarding which dosages to further evaluate
	Dose optimization can occur within a seamless development program with sufficient planning

Abbreviations: DLT, dose-limiting toxicity; PD, pharmacodynamic.

Drug Name	Dose-Optimization Strategies				
	Trial Design Features That Allow for Dose Optimization	Biologic Optimum Dose Selection Strategy Used	Optimization Considered More Than One Dose or Dosage	Dosage Informed and Confirmed by Preclinical Data, Modeling, and Simulation	ER Analysis for Safety and Efficacy Conducted?
Selpercatinib	Single seamless trial supports approval Large expansion cohorts at biologic optimum dosage in targeted populations	Yes	Once daily *v* twice daily on the basis of safety signals	Continuously updated tumor growth modeling on the basis of emerging clinical data	Yes, and supports dosage for approval
Pemigatinib	Dose-finding trial, with expansion of cohorts to evaluate a targeted dose range where efficacy and safety may be optimized Subsequent pivotal trial in targeted populations to support approval	Yes	QD continuous *v* intermittent regimen tested and selected on the basis of tolerability	Narrow range of dose levels where efficacy may be optimized were compared for target inhibition (ex vivo phosphorylated FGFR2α)	Yes, and supports dosage for approval
Erdafitinib	Pivotal trial with randomized dose finding	Yes	Randomized multiple-dose design in a pivotal trial	Yes; interim analysis with PK/PD modeling to optimize dosage	Yes, conducted over a wide dose range and supports dosage for approval
Belantamab mafodotin	Pivotal trial with randomized dose finding	Not applicable; antibody-drug conjugate with antitumor activity through MMAF-induced apoptosis	Yes, 2.5 mg/kg IV every 3 weeks and 3.4 mg/kg IV every 3 weeks	Not applicable	Yes, and supports dose for approval and need for a postmarketing requirement

Abbreviations: ER, exposure-response; FGFR, fibroblast growth factor receptor; IV, intravenously; MMAF, monomethyl auristatin F; PD, pharmacodynamic; PK, pharmacokinetics;.

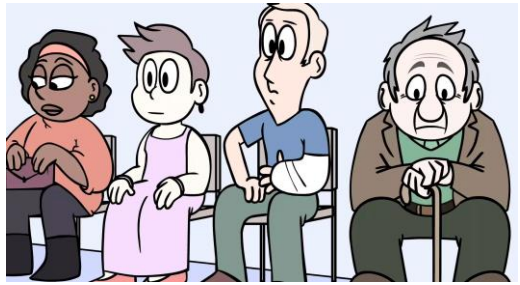
2nd annual workshop on *Getting the dosage right* : Optimizing Dosage Selection in Combination Anticancer Therapies

- Clearly defined and documented MoA to support the combination
- Support IND for combo with nonclinical studies
- Lean heavily on findings from monotherapy
- Investigating mono and combo in parallel
  - *Short combo cycle within mono, or sequential*
- Additive vs. synergistic combinations
  - *If additive, dose selection is safety-driven only*
- Get as much as possible out of the dose escalation phase
  - *Explore dose and schedule*
  - *Utilize back-fill and flexible protocol*
  - *Exposure-response analysis*
  - *Overlapping toxicities ?*
- Personalized combination strategies
- Emphasis on learnings from HIV drug development

Anticipated consequences ?

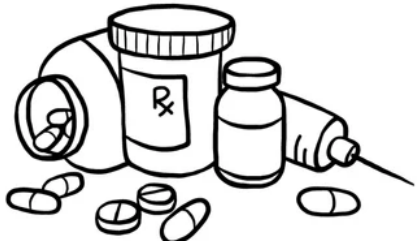
Dose optimized before P2/3

More slots in the FIH
Data entry (safety) will be critical



Patients

Investigators



DRUG CANDIDATE

Sponsor / Industry

HA / Regulatory

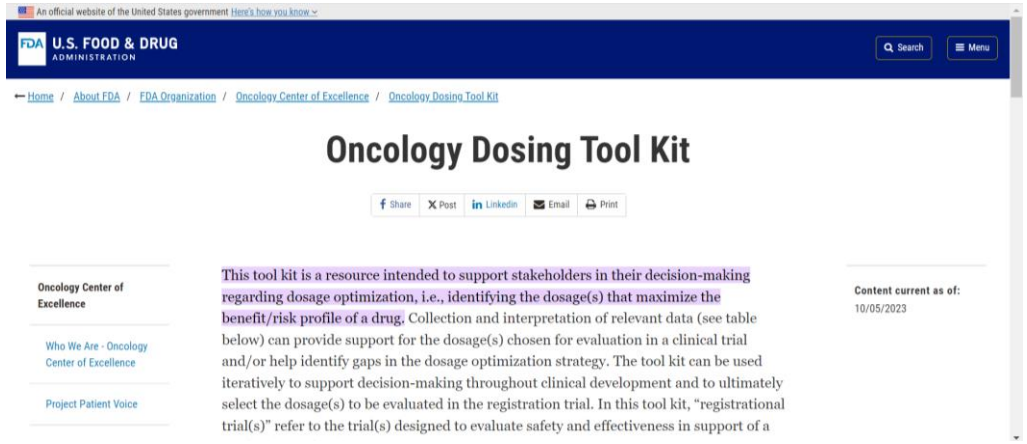
FDA

Higher cost for early dev
Longer timelines for late dev

Decision making if dose was not optimized ?

Additional info needed ?

https://www.fda.gov/about-fda/oncology-center-excellence/oncology-dosing-tool-kit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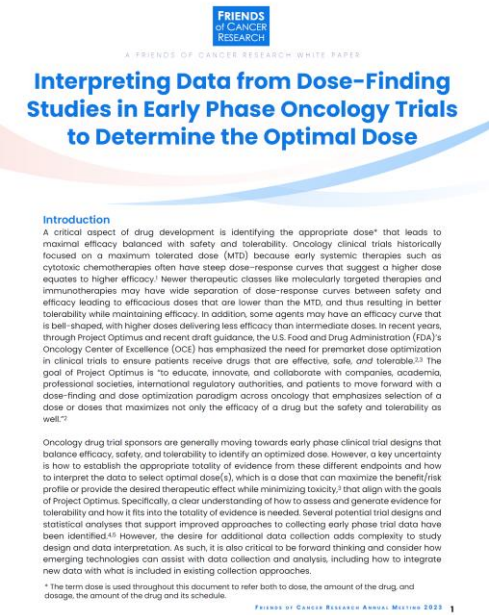
Who We Are - Oncology Center of Excellence

Project Patient Voice

This tool kit is a resource intended to support stakeholders in their decision-making regarding dosage optimization, i.e., identifying the dosage(s) that maximize the benefit/risk profile of a drug. Collection and interpretation of relevant data (see table below) can provide support for the dosage(s) chosen for evaluation in a clinical trial and/or help identify gaps in the dosage optimization strategy. The tool kit can be used iteratively to support decision-making throughout clinical development and to ultimately select the dosage(s) to be evaluated in the registration trial. In this tool kit, "registrational trial(s)" refer to the trial(s) designed to evaluate safety and effectiveness in support of a

Content current as of: 10/05/2023


FRIENDS of CANCER RESEARCH

A FRIENDS OF CANCER RESEARCH WHITE PAPER

Interpreting Data from Dose-Finding Studies in Early Phase Oncology Trials to Determine the Optimal Dose

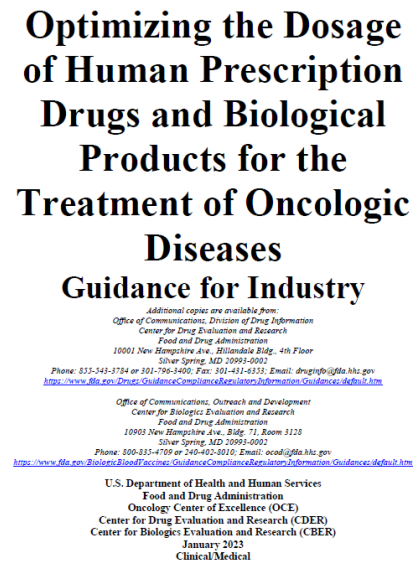
Introduction

A critical aspect of drug development is identifying the appropriate dose* that leads to maximal efficacy balanced with safety and tolerability. Oncology clinical trials historically focused on a maximum tolerated dose (MTD) because early systemic therapies such as cytotoxic chemotherapies often have steep dose–response curves that suggest a higher dose equates to higher efficacy.[1] Newer therapeutic classes like molecularly targeted therapies and immunotherapies may have wide separation of dose–response curves between safety and efficacy leading to efficacious doses that are lower than the MTD, and thus resulting in better tolerability while maintaining efficacy. In addition, some agents may have an efficacy curve that is bell-shaped, with higher doses delivering less efficacy than intermediate doses. In recent years, through Project Optimus and recent draft guidance, the U.S. Food and Drug Administration (FDA)'s Oncology Center of Excellence (OCE) has emphasized the need for premarket dose optimization in clinical trials to ensure patients receive drugs that are effective, safe, *and* tolerable.[2,3] The goal of Project Optimus is "to educate, innovate, and collaborate with companies, academia, professional societies, international regulatory authorities, and patients to move forward with a dose-finding and dose optimization paradigm across oncology that emphasizes selection of a dose or doses that maximizes not only the efficacy of a drug but the safety and tolerability as well."[2]

Oncology drug trial sponsors are generally moving towards early phase clinical trial designs that balance efficacy, safety, and tolerability to identify an optimized dose. However, a key uncertainty is how to establish the appropriate totality of evidence from these different endpoints and how to interpret the data to select optimal dose(s), which is a dose that can maximize the benefit/risk profile or provide the desired therapeutic effect while minimizing toxicity,[3] that align with the goals of Project Optimus. Specifically, a clear understanding of how to assess and generate evidence for tolerability and how it fits into the totality of evidence is needed. Several potential trial designs and statistical analyses that support improved approaches to collecting early phase trial data have been identified.[4,5] However, the desire for additional data collection adds complexity to study design and data interpretation. As such, it is also critical to be forward thinking and consider how emerging technologies can assist with data collection and analysis, including how to integrate new data with what is included in existing collection approaches.

* The term dose is used throughout this document to refer both to dose, the amount of the drug, and dosage, the amount of the drug and its schedule.

FRIENDS OF CANCER RESEARCH ANNUAL MEETING 2023 1


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

Guidance for Industry

Additional copies are available from:
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Center for Drug Evaluation and Research
Food and Drug Administration
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Silver Spring, MD 20993-0002
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https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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