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

FDA Final Guidance

Mirat Shah, MD
Medical Oncologist, Breast and Gynecologic Malignancies
Clinical Lead, Project Optimus
U.S. Food and Drug Administration

Outline

- Project Optimus
- Guidance Overview
- Questions and Discussion

Oncology Center of Excellence

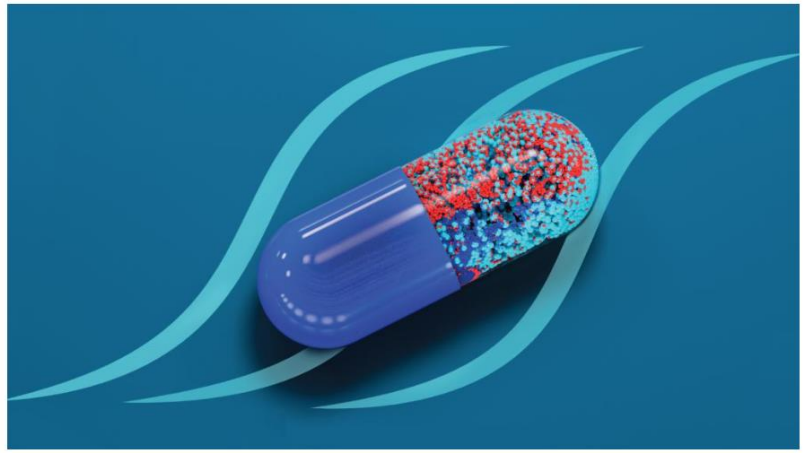
Project Optimus

Mission: To reform the dosing paradigm in oncology drug development

Main Message: Dosage optimization is essential to safe and effective cancer therapies

Who We Are: A multidisciplinary team of medical oncologists, clinical pharmacologists, biostatisticians, toxicologists, and other scientists with expertise in key facets of dosage optimization

More Info: Project Optimus website



Consequences of Not Optimizing the Dosage Premarket

- Drug may be poorly-tolerated at the approved dosage
  - Patients exposed to avoidable toxicities
  - Patients stop taking a potentially efficacious therapy
  - Patients choose a different therapy
- It takes a long time to revise the dosage postmarket
- The drug does not make it to market or must be withdrawn from the market

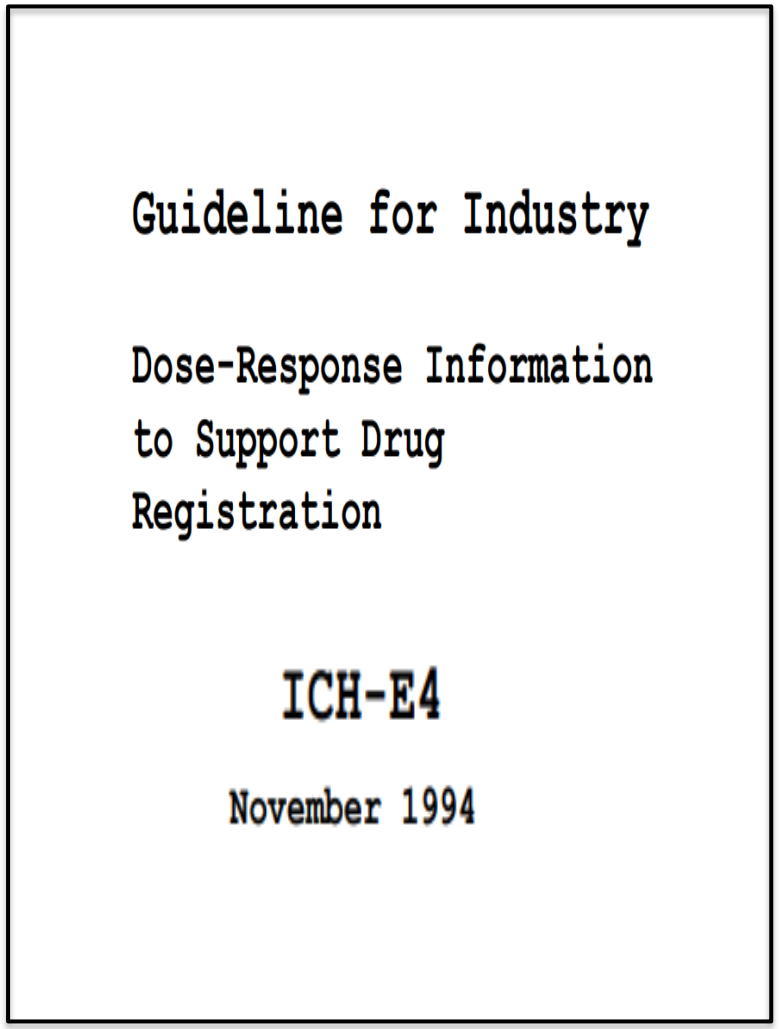
Right Time for Dosage Optimization = Prior to Approval

- Improves decision-making for the drug development program
- Prevents avoidable toxicity → increases uptake and improves adherence
- More efficient, more feasible
- Allows for more rapid development of new indications and combination therapies

"Dose is the foundation of drug development. Having the wrong dose is like building a house on quicksand."

- Rick Pazdur

Guidance Documents



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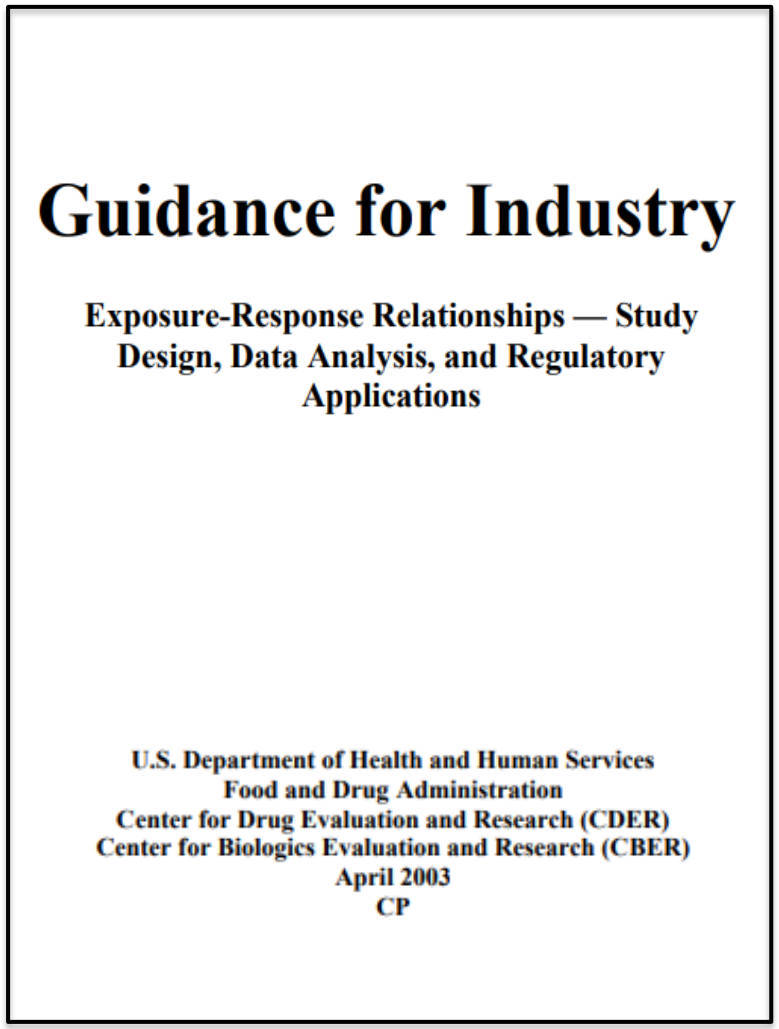

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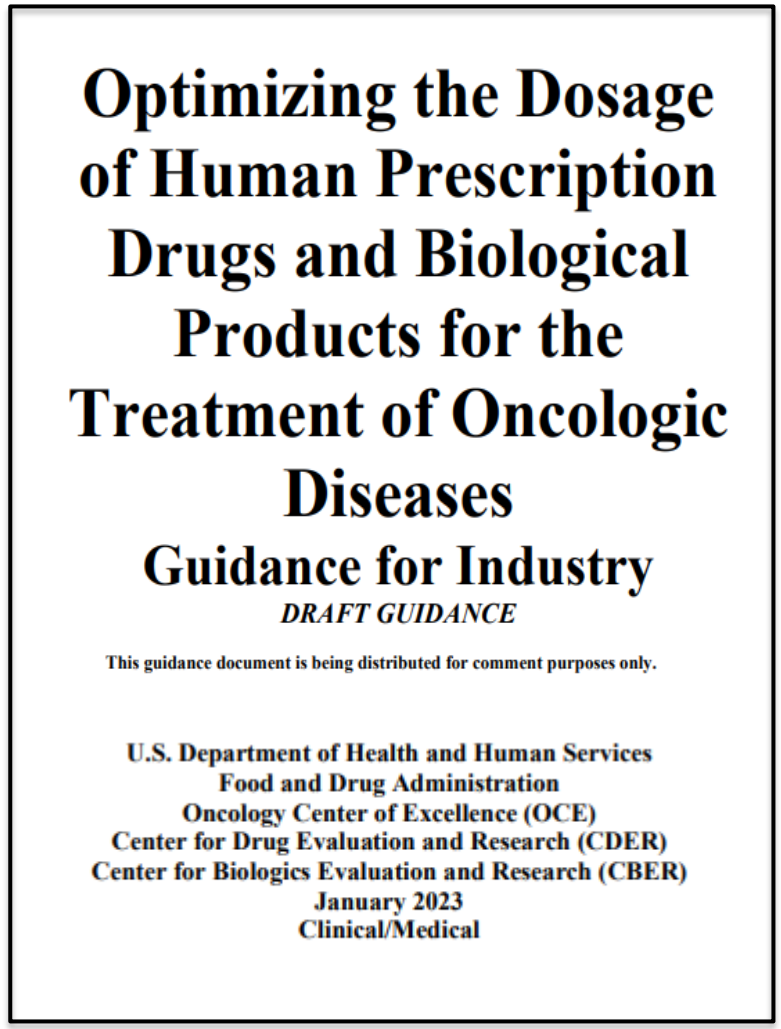
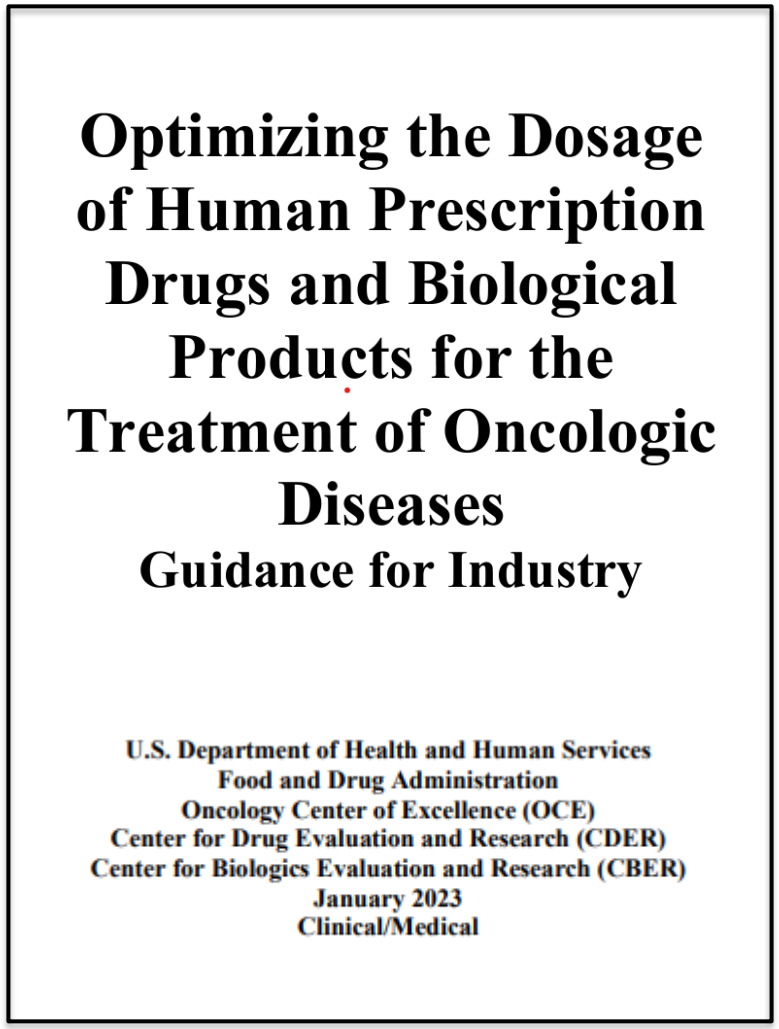


2023

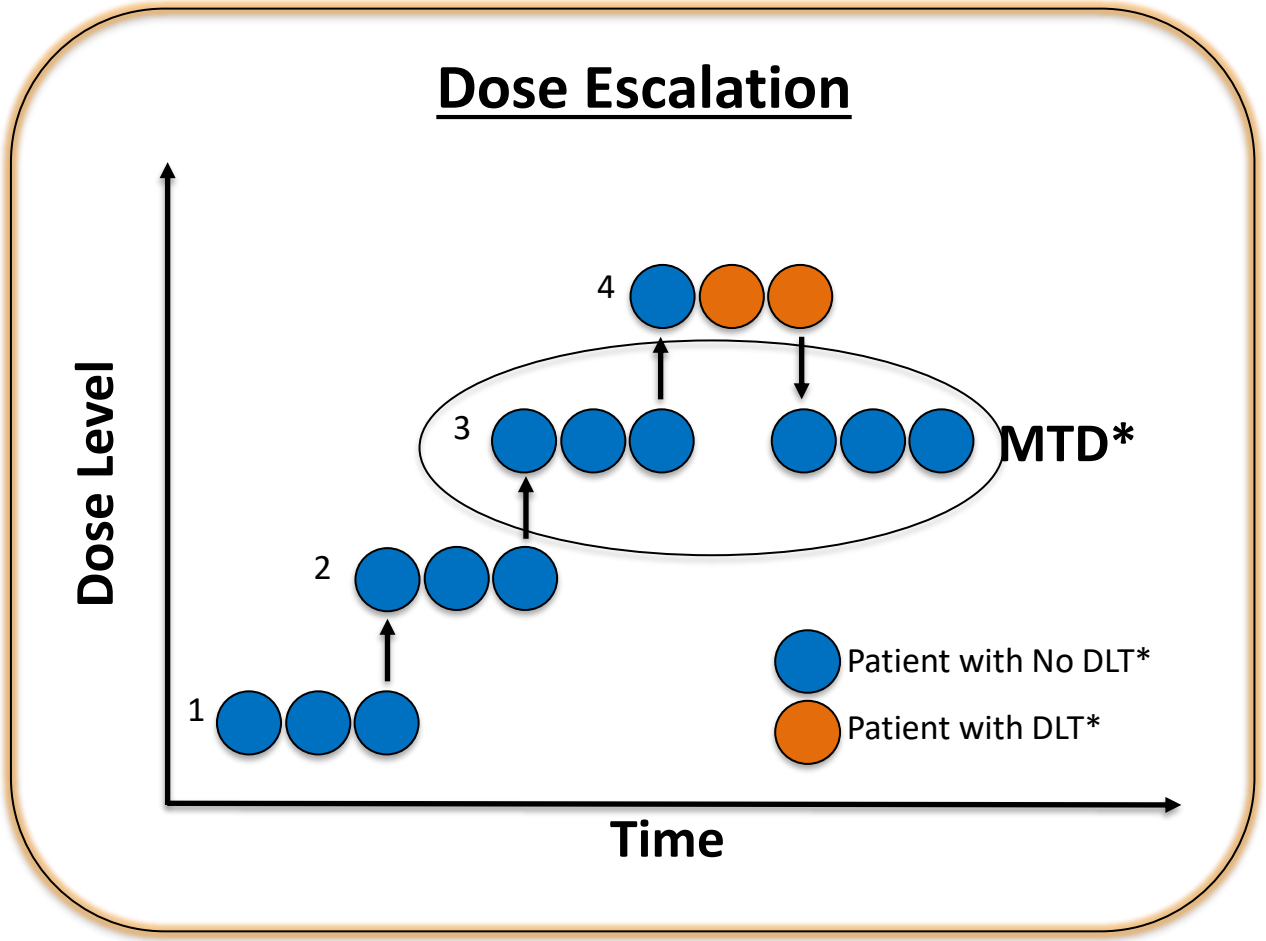
Oncology Dosage Optimization Guidance

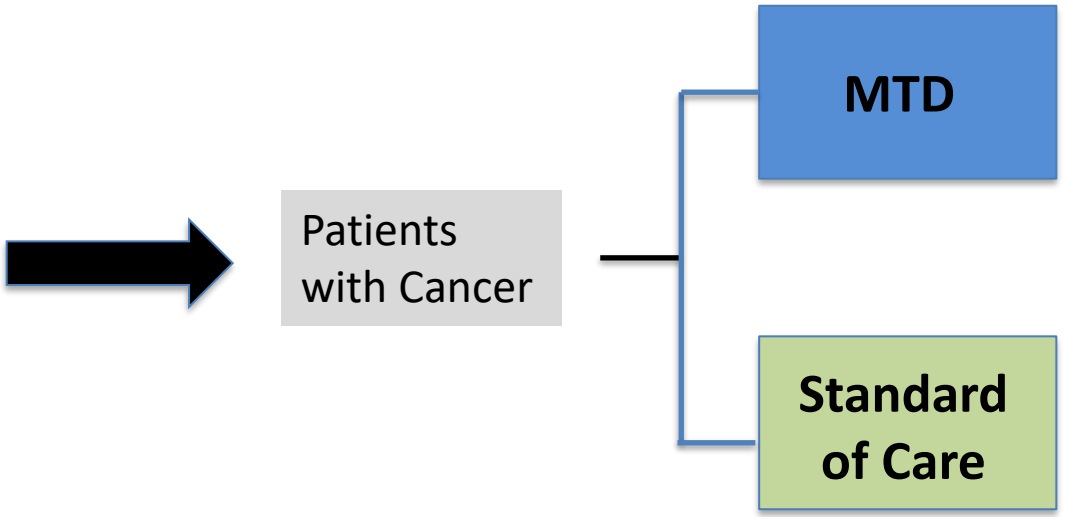


2024

- Use the totality of data for dosage selection
  - Including dose- and exposure- response relationships for efficacy and safety
- Randomized comparisons support identification of optimized dosage(s)
- Safety assessments should include low-grade symptomatic toxicities which affect tolerability
- Dosage optimization important for all products, including those with rapid development timelines
- No one size fits all → Meet with FDA early to discuss plans

Traditional Dosage Selection





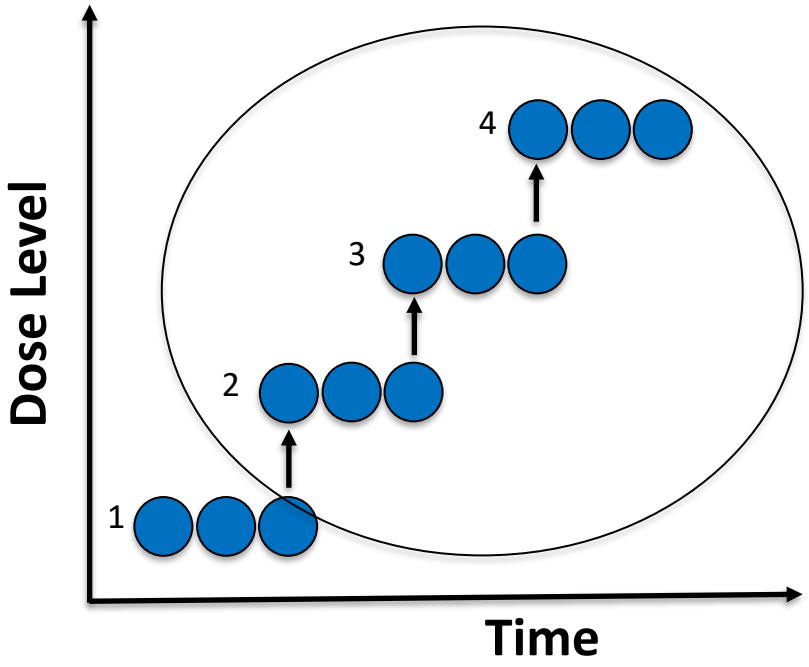
*DLT Dose-limiting toxicity,
*MTD Maximum tolerated dose

Hallmarks:

- Few patients at each dose level
- Short observation period for DLTs
- Emphasis on DLTs, but not other safety

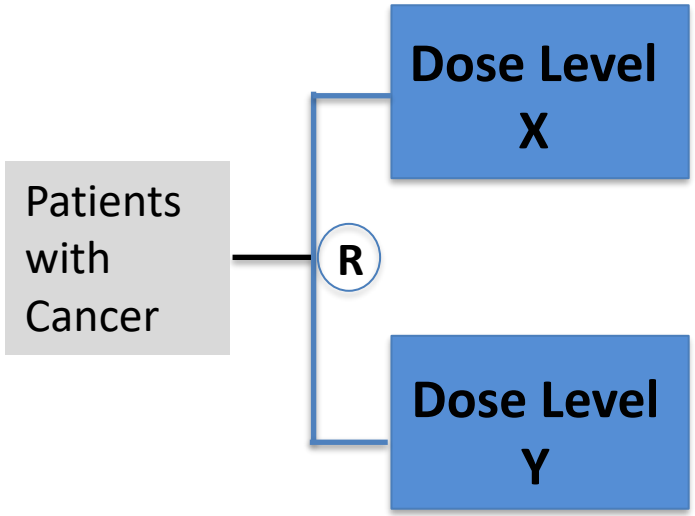
Updated Dosage Selection Strategy

Dose Escalation



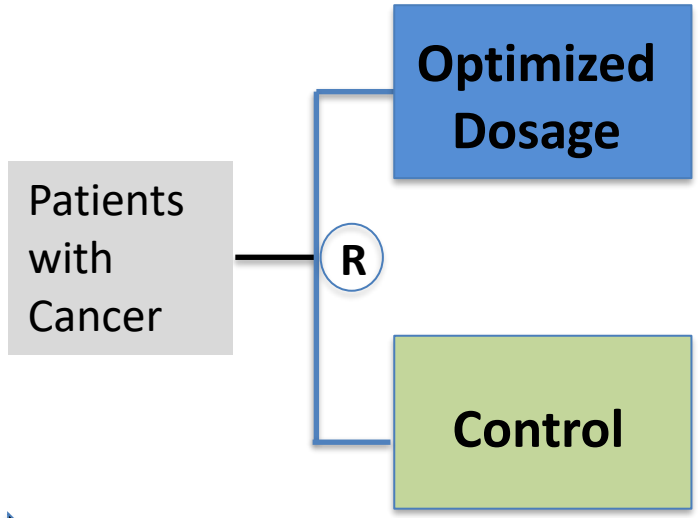
Identify Target Dosage Range

Dosage Optimization



Further Evaluate Dosages

Registration



Compare to Standard of Care

Updated Dosage Selection Strategy

Early Development

- Characterize PK
- Identify PD endpoints for safety and activity
- Consider backfilling cohorts in dose escalation
- Evaluate preliminary dose- and exposure- relationships

Dosage Optimization

- Evaluate multiple dosages in a randomized trial
- Target a specific disease(s)
- Randomization preferred to reduce bias/improve interpretability of dose and exposure- relationships
- Further characterize dose- and exposure- relationships

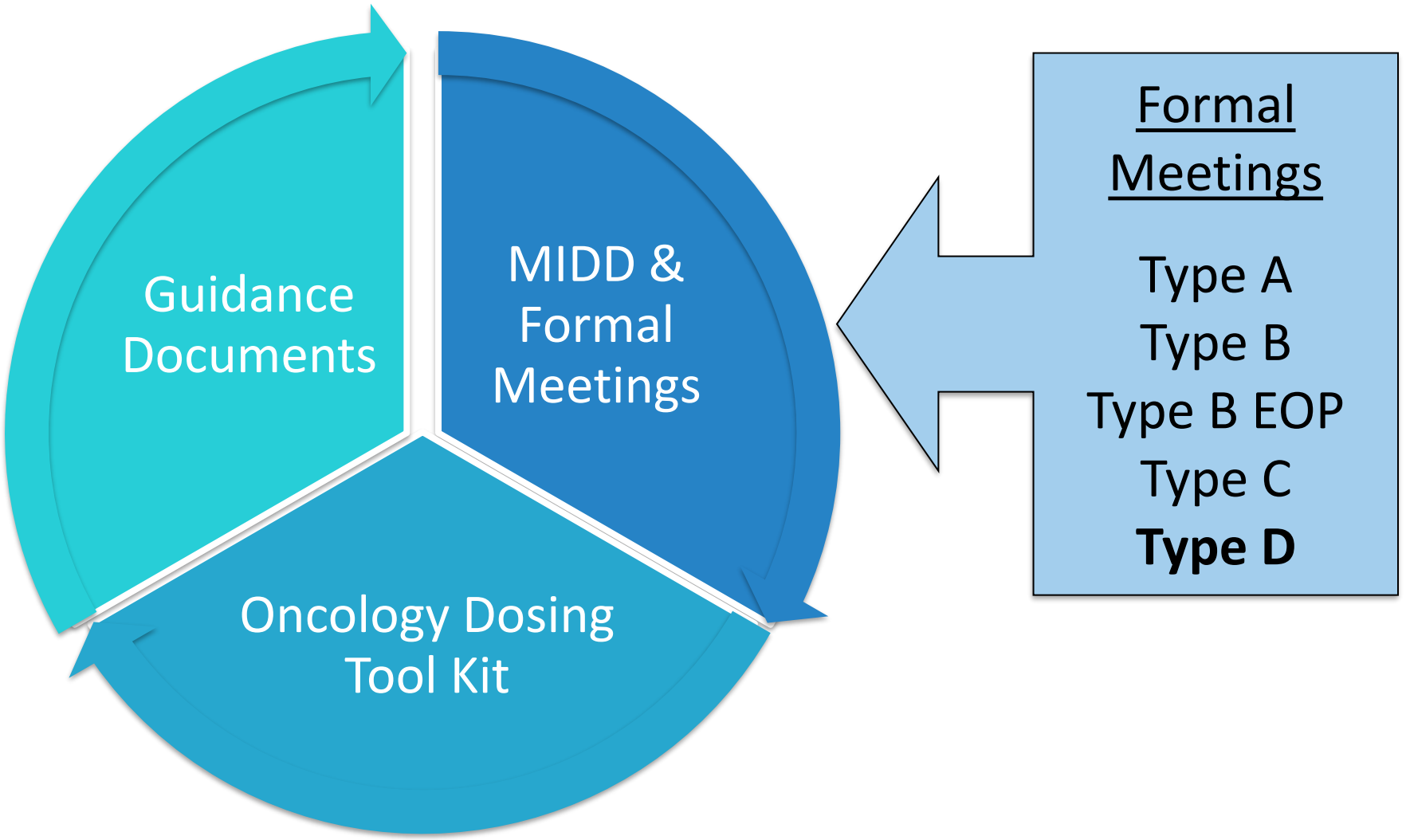
Registrational Trial

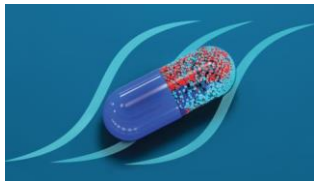
- Develop more comprehensive assessment of efficacy and safety/tolerability

Use the Totality of Data:

- Nonclinical
- PK
- PD
- Safety
- Tolerability
- Activity
- Dose- and exposure-response relationships
- Data in other populations or settings

FDA Tools to Support Dosage Optimization





Oncology Dosing Tool Kit

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 marketing application.

Overarching Questions

- Which dosages will be evaluated during dose escalation?
- Which dosages will be chosen for further investigation; e.g., in a randomized dosage evaluation*?
- What dosages will be selected for the registration trial(s)?

Tool Kit Key Areas

- Translational Evidence
- PK Characteristics
- Safety
- Efficacy
- Dose- and Exposure-Response
- Other Information

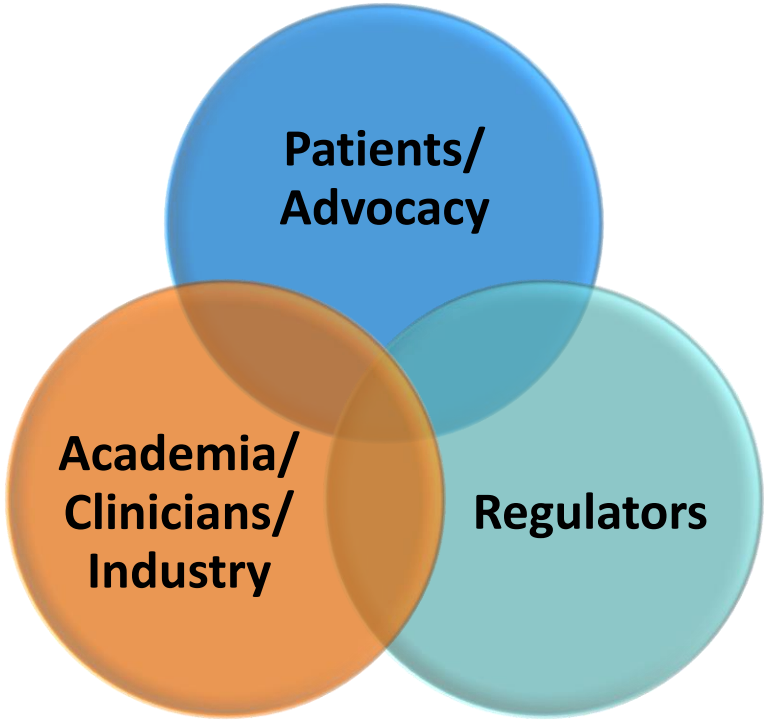
More Info: Oncology Dosing Tool Kit website

Recent Discussions

- Dosage optimization for combination therapies
  - **FDA- ASCO Combination Therapies Workshop**
  - September 2023
  - Materials
- Modeling and simulation to support dosage optimization
  - **FDA-ISOP Workshop Series**
  - October 16 and November 9, 2023
  - Materials
- Quantitative methods for dosage optimization
  - **FDA- AACR Workshop**
  - February 15, 2024
  - Materials

Since Initiation of Project Optimus…

- Growing consensus among stakeholders on need for dosage optimization
- The focus has shifted from “why?” to “how?”
- Ensuring that the approach is tailored to the specific drug development program is an ongoing challenge



Conclusions

- Premarket dosage optimization offers benefits to patients, drugmakers, and oncology overall
- It is important to consider the totality of data at each step of dosage selection
- Randomized trials support selection of a dosage optimized for benefit-risk
- One size doesn’t fit all oncology product development programs
- FDA is committed to engaging with stakeholders to realize the promise of this new dosing paradigm in oncology

Dosage Optimization Resources

Multi-Stakeholder Meetings

- Friends of Cancer Research Annual Meeting 2021
- Friends of Cancer Research White Paper 2021
- FDA- ASCO Workshop: Getting the Dose Right
- Pediatric ODAC 2023: Dosage Optimization in Pediatric Oncology Clinical Trials
- FDA-ASCO Second Annual Workshop: Getting the Dosage Right for Combination Therapies
- FDA-AACR Workshop: Quantitative Approaches To Select Dosages for Clinical Trials
- Friends of Cancer Research Annual Meeting 2023
- FDA- AACR Workshop: Optimizing Dosages for Oncology Products

Publications

- The Drug-Dosing Conundrum in Oncology- When Less is More
- How to Get the Dose Right
- Improving Dose-Optimization Processes Used in Oncology Drug Development to Minimize Toxicity and Maximize Benefit to Patients

Guidance Documents

- ICH E4: Dose-Response Information to Support Drug Registration
- Exposure- Response Relationships
- Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

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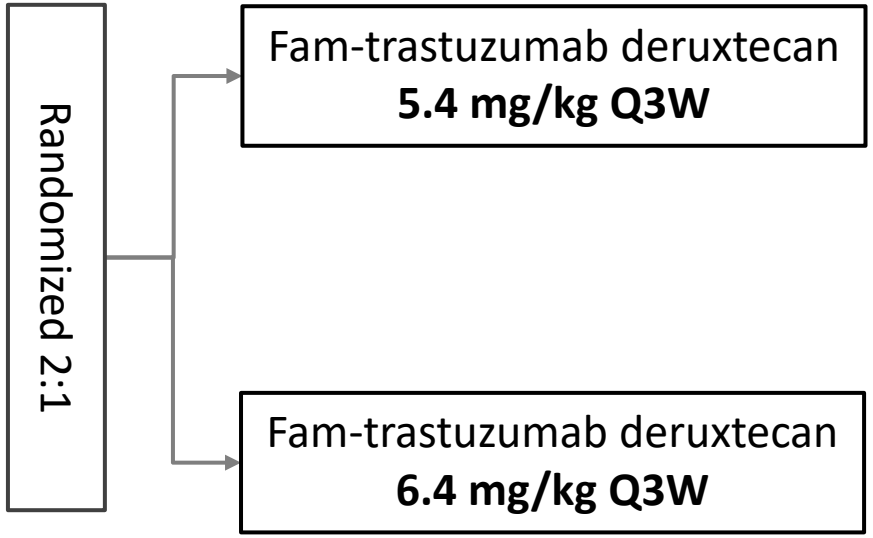
Backup

Example: Fam-Trastuzumab Deruxtecan

DESTINY-Lung02

Key Eligibility Criteria

- Metastatic Non-Small Cell Lung Cancer (NSCLC)
- Activating *HER2* mutation
- No history of interstitial lung disease



Key Endpoints

- Overall response rate (ORR)
- Duration of response (DOR)

DESTINY-Lung02: Efficacy and Safety

Efficacy	5.4 mg/kg* (N=52)	6.4 mg/kg** (N=28)
Overall Response Rate (ORR) % (95% CI)	**58** (43, 71)	**43** (25, 63)
Duration of Response (DOR) (months), median (95% CI)	8.7 (7.1, NE)	5.9 (2.8, NE)

Toxicity	5.4 mg/kg* (N=101) %	6.4 mg/kg** (N=50) %
Interstitial Lung Disease (ILD)/Pneumonitis	6	14
Drug Discontinuation	8	16

- Lack of clinically significant exposure-efficacy relationship for ORR
- Positive exposure-safety relationships for ILD/pneumonitis, grade 3+ TEAEs

*From USPI drugs@FDA
**From ESMO 2022