Project Optimus

Changing the Dosing Paradigm for Cancer Drugs

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CDDF
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Disclaimer

- I have no conflicts of interest to disclose
- I will not be discussing off-label and/or investigational use of named products in this presentation
- These slides represent current thinking in a rapidly evolving field of regulatory science
- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Overview

- Introduce FDA Oncology Center of Excellence's Project Optimus
- Review the historical reliance on the "maximum tolerated dose" or "MTD" in oncology
- Outline the consequences of failing to optimize the dosage in the premarket setting
- Identify key principles and resources for achieving dosage optimization in the premarket setting

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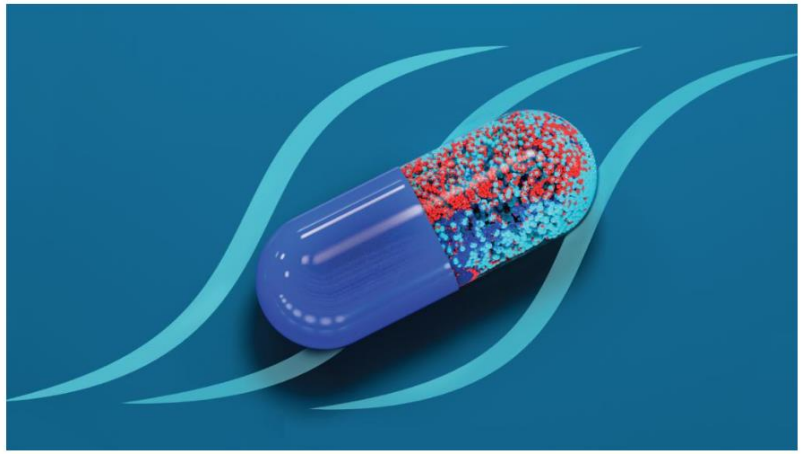
Oncology Center of Excellence

Project Optimus

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

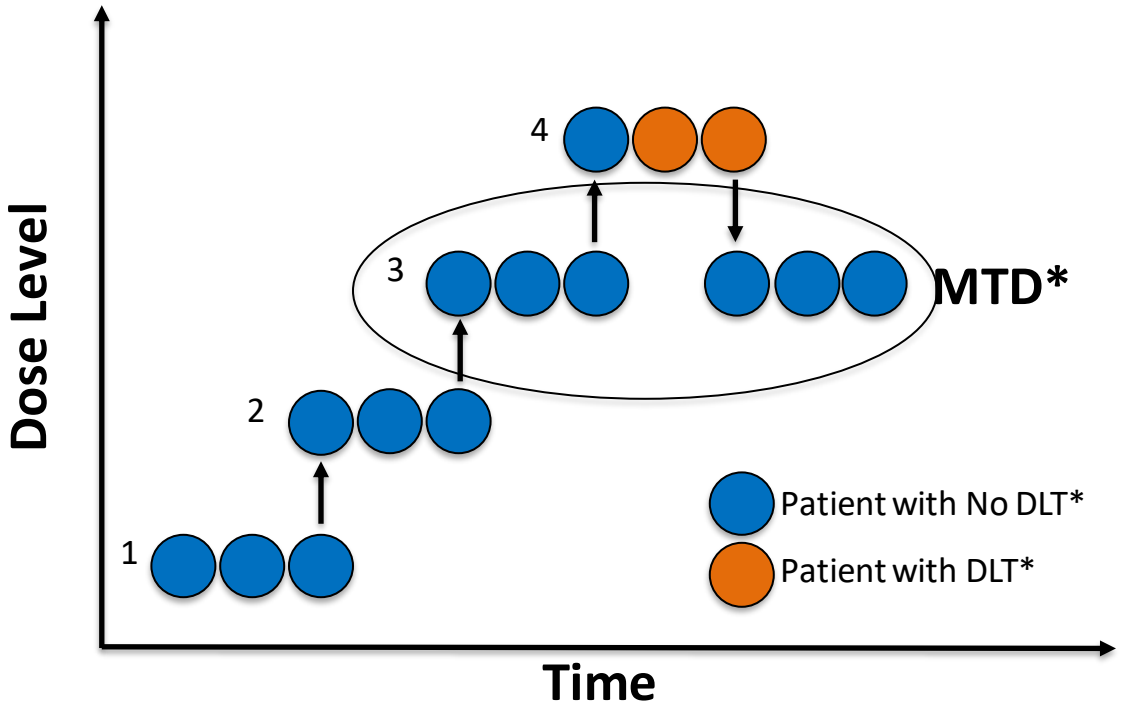
Who We Are: A multidisciplinary team of medical oncologists, clinical pharmacologists, biostatisticians, toxicologists, and other scientists with expertise in key facets of dosage optimization

More Info: Project Optimus website

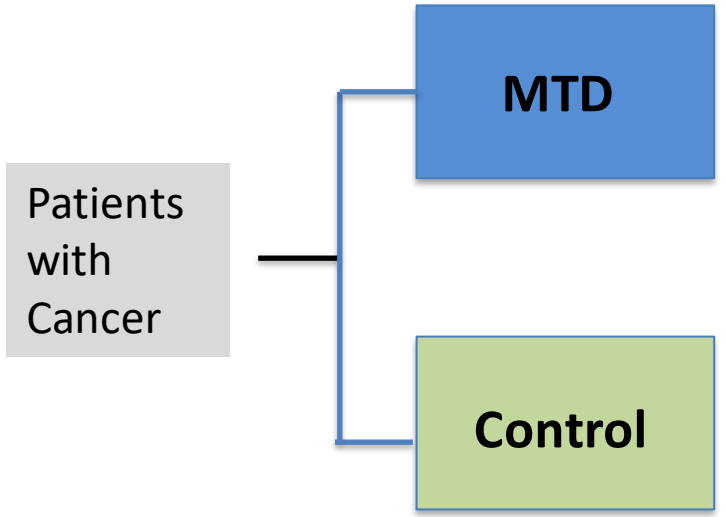


Traditional Dosage Selection Strategy

Dose Escalation



Registration



*DLT= Dose-limiting toxicity,
*MTD= Maximum tolerated dosage

Hallmarks:

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

Key Differences

Cytotoxic Chemotherapies

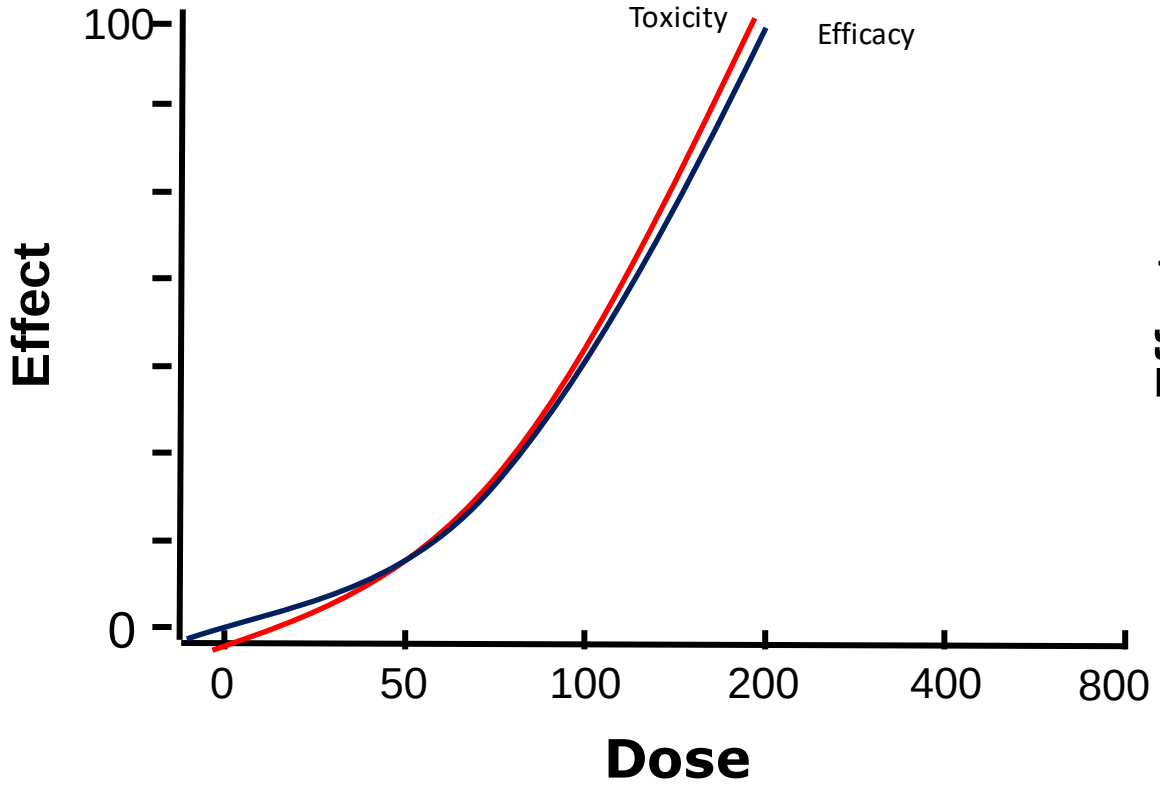
- Steep dose-response, narrow therapeutic index
- MTD reached
- Fixed number of cycles or short duration of treatment
- Serious toxicities predictable, occur early
- Patients recover with time off of treatment

Molecularly Targeted Agents

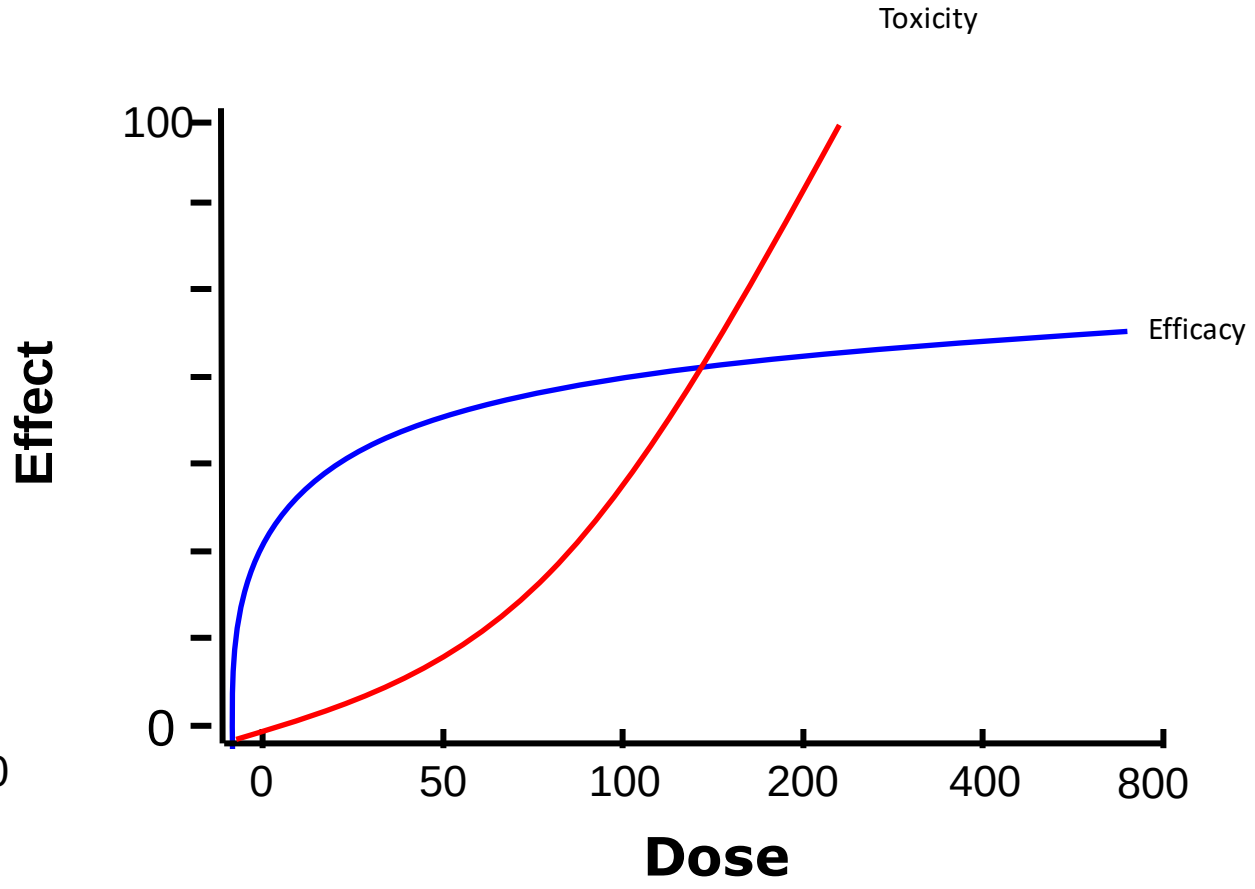
- Different dose-response, potentially wide therapeutic index
- MTD may not be reached (or needed)
- Treatment for many months to years
- Serious toxicities may occur later
- Long-term tolerability, including chronic symptomatic Grade 1-2 toxicities, very important
- No time off of treatment

Dose-Response for Oncology Products

Cytotoxic Chemotherapy



Targeted Therapy



National Cancer Institute (NCI)

Common Terminology Criteria for Adverse Events (CTCAE)

Diarrhea

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Increase of <4 stools per day over baseline	Increase of 4-6 stools per day over baseline	Increase of ≥7 stools per day over baseline; hospitalization indicated	Life-threatening consequences (e.g., hemodynamic collapse)	Death

DLT

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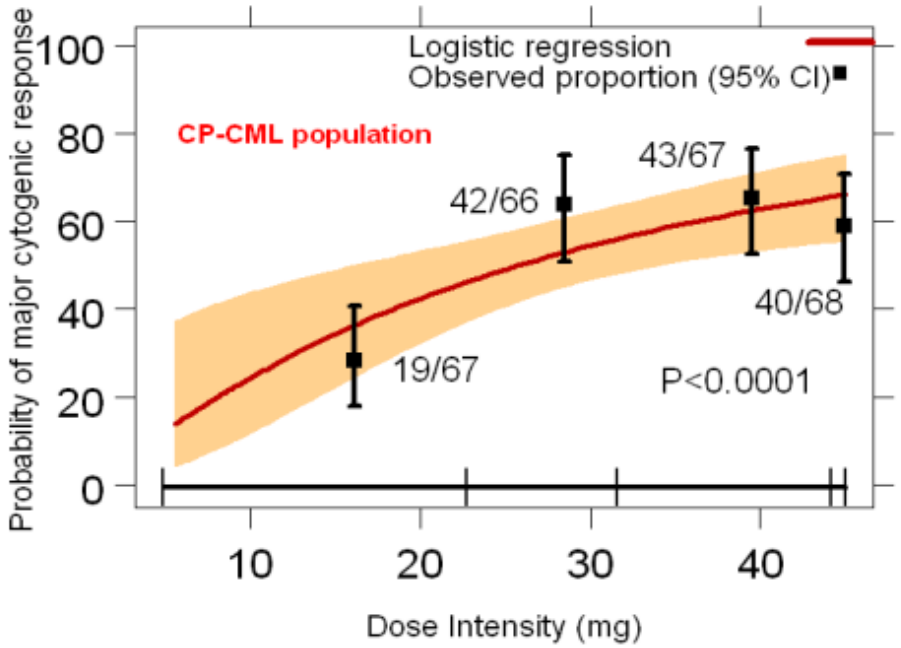
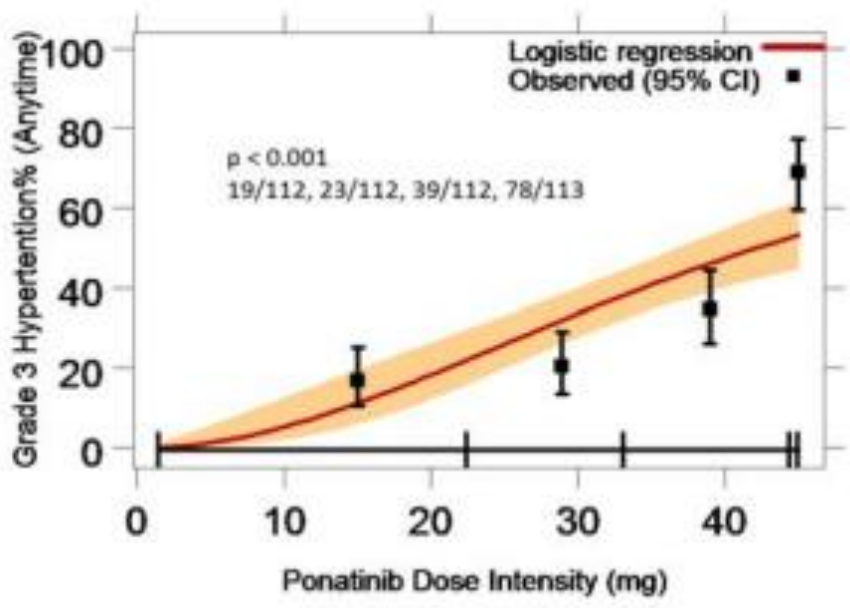
Example: Ponatinib

- **Disease:** Chronic myeloid leukemia- chronic phase
- **Initial approved dosage:** 45 mg orally once daily (2012)

Dose-Efficacy

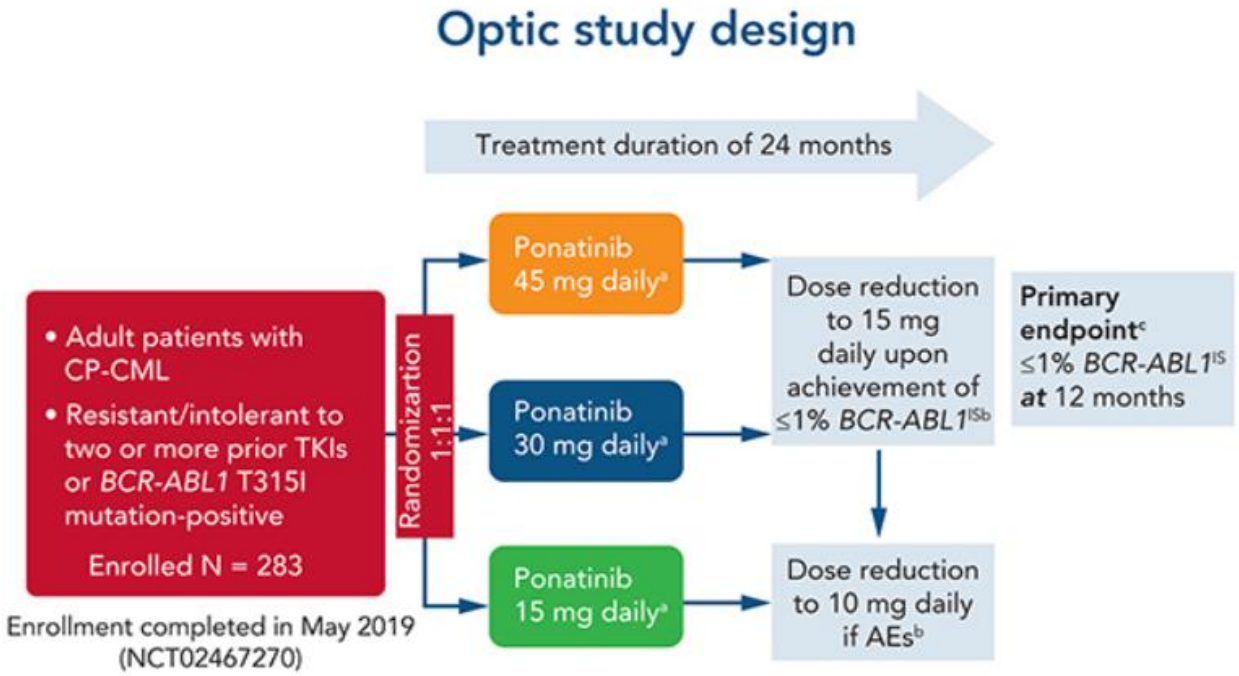


Dose- Safety



Ponatinib FDA Review, drugs@FDA

OPTIC: Ponatinib Dosage Optimization



J Cortes, et al., Blood, 2021

Results

Dose, mg, daily	45 → 15	30 → 15	15
Patients	88	86	87
MR2 at 12 months, % 95% CI	42 (32, 53)	28 (19, 39)	24 (16, 35)
Arterial occlusive events, %	13	15	12

ED Pulte, et al., The Oncologist, 2022

Consequences of Not Optimizing the Dosage Premarket

- Drug is poorly-tolerated at the approved dosage
  - Patients may stop taking a potentially efficacious therapy
  - Patients choose to try a different therapy

- It takes a long time to revise the dosage postmarket
  - Disease area moves on to other treatments

- The drug does not make it to market or must be withdrawn from the market

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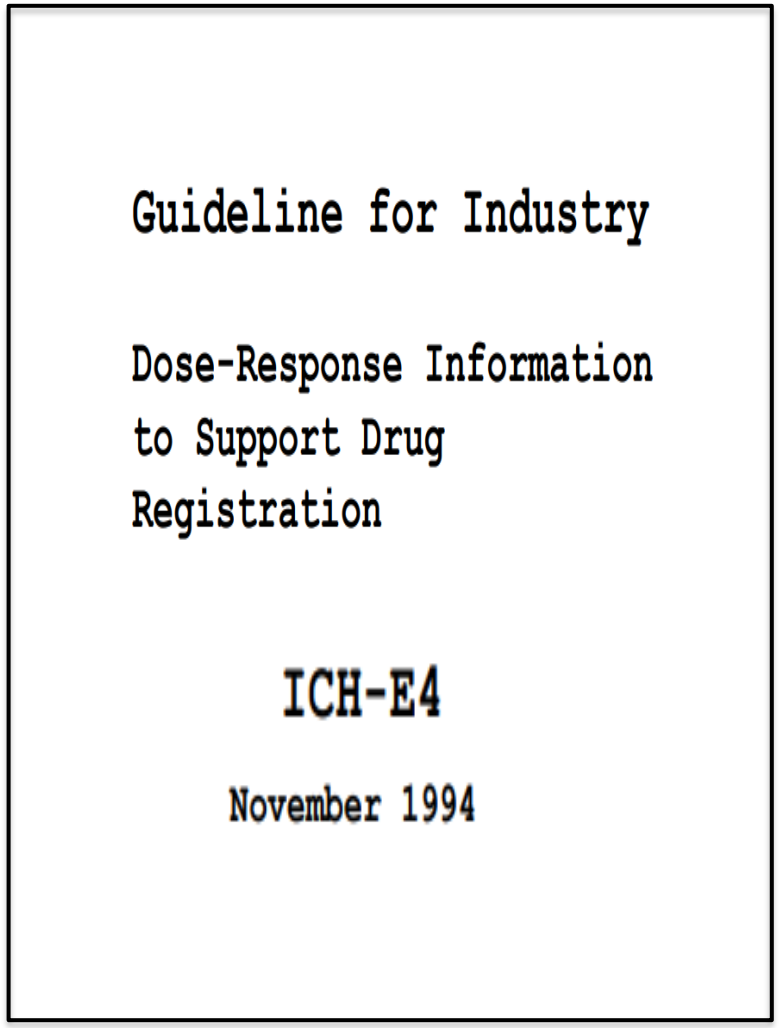
Right Time for Dosage Optimization = Prior to Approval

- 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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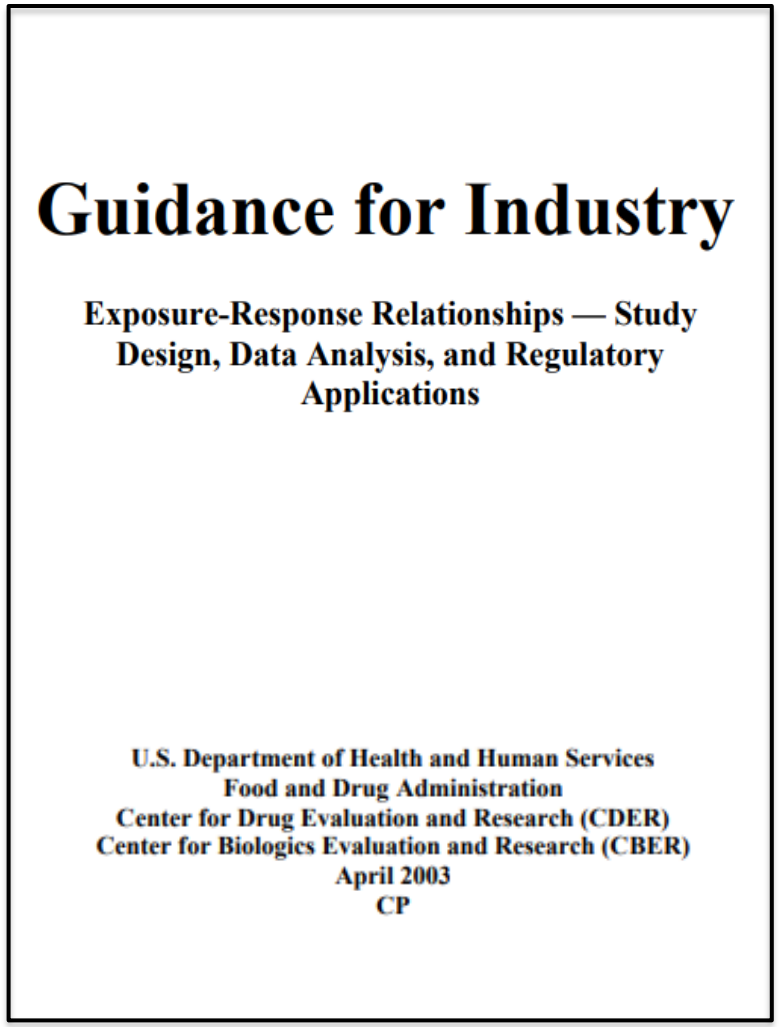
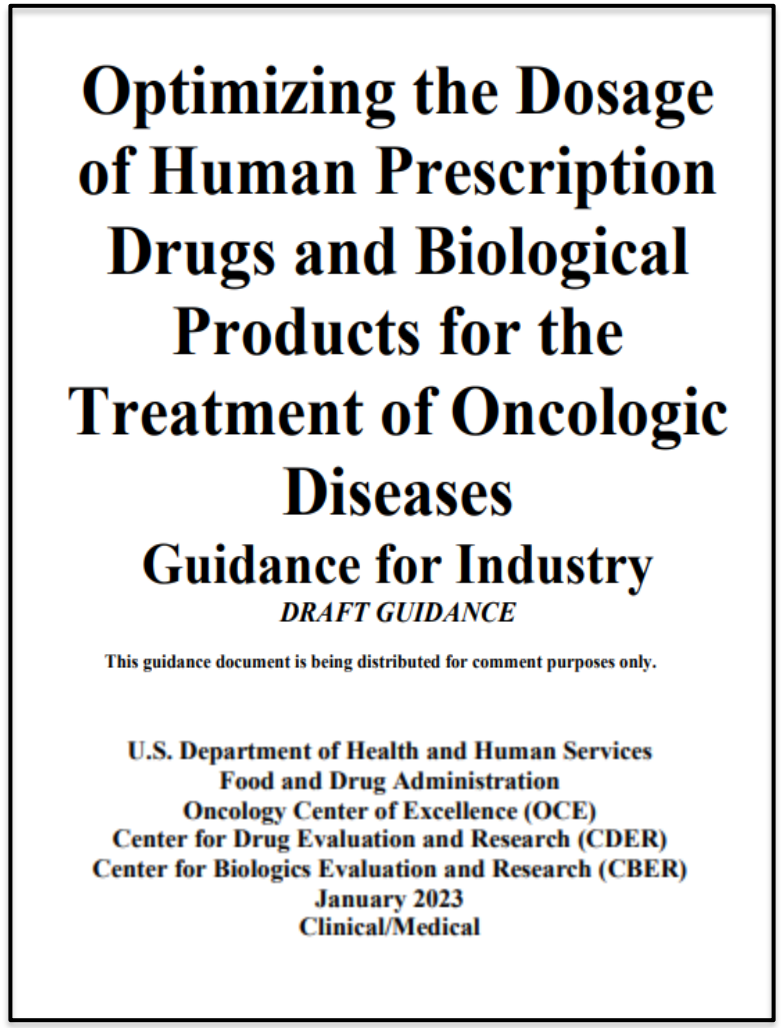
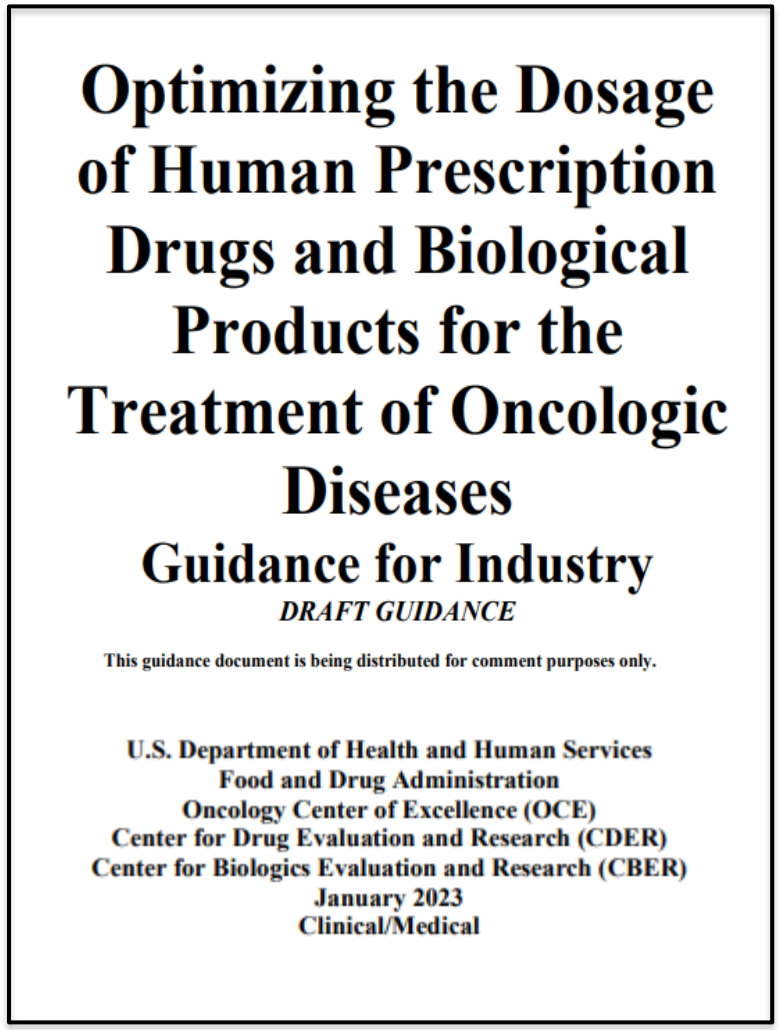


2003



2023

Oncology Dosage Optimization Draft Guidance



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.

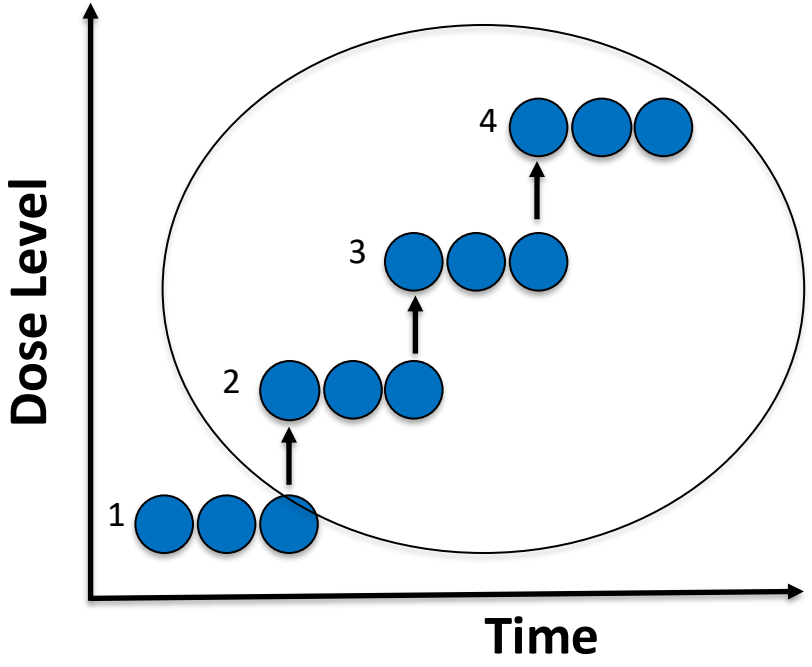
U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
January 2023
Clinical/Medical

2023

- Dosages must have justification appropriate to the stage of development
- 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) → more on next slide
- Safety assessments to include low-grade symptomatic toxicities which affect tolerability
- Dosage optimization important for all products, including those with anticipated rapid development timelines

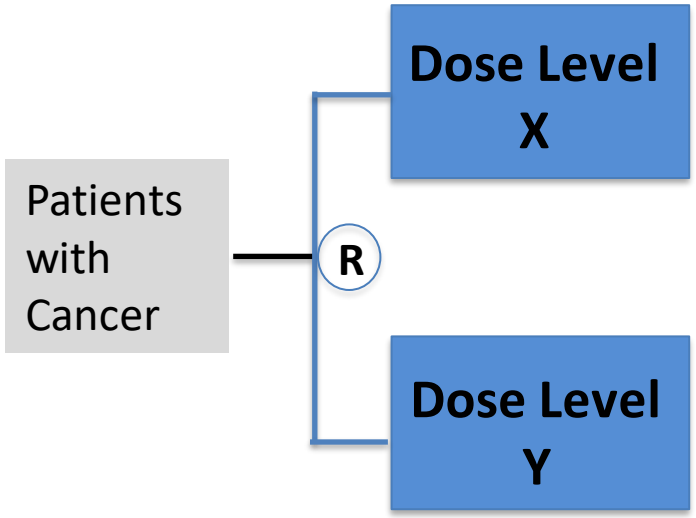
Updated Dosage Selection Strategy

Dose Escalation



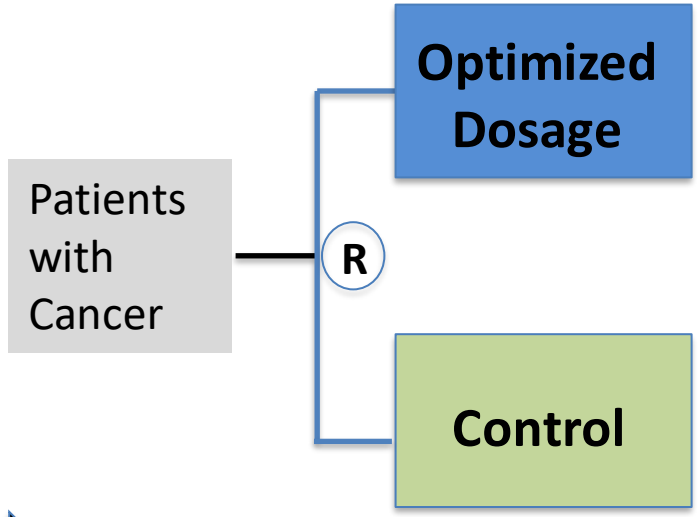
Select Several Dosages

Dosage Optimization



Further Evaluate Dosages

Registration



Compare to Standard of Care

Project Optimus Recipe for Success

Patients and Advocates

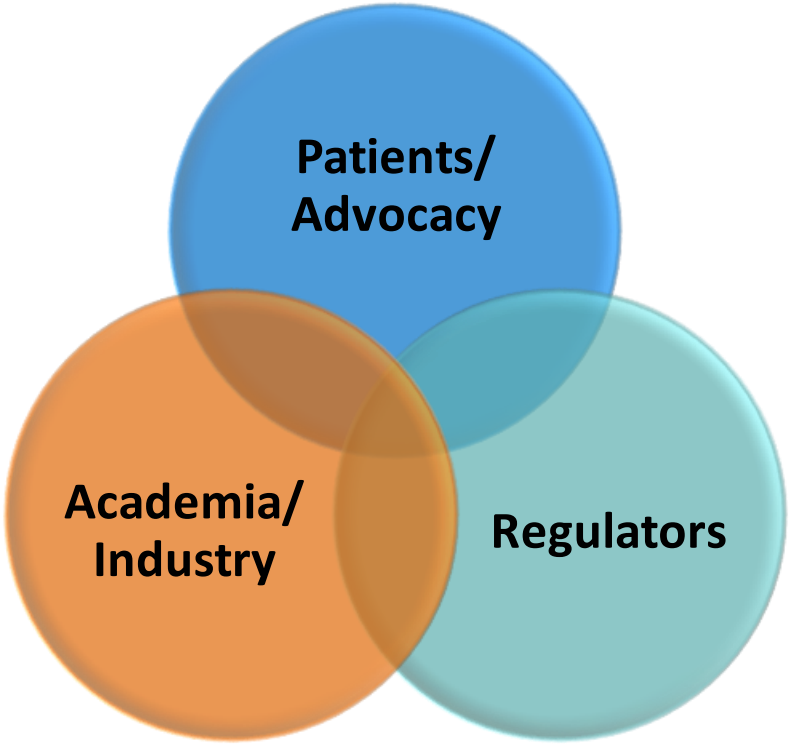
- Communicate expectations
- Provide input on trial design
- Participate in dosage optimization trials

Academics and Industry

- Plan for dosage optimization early
- Design and conduct trials for dosage optimization throughout clinical development
- Seek input from regulators

Regulators

- Provide guidance
- Facilitate interactions to discuss dose optimization
- Be flexible and support innovation



Key Points

- It is important to consider the totality of data (nonclinical, PK, PD, efficacy, safety) at each step in dosage selection
- Randomized trials allow selection of a dosage optimized for benefit-risk
- No one size fits all; flexibility is key
- Meet with FDA early, and again as needed

Dosage Optimization Resources

FDA

- Available for product-specific advice through relevant review division as early as preIND meeting
- Dosing Tool Kit pilot for products with Breakthrough Therapy Designation (coming soon)

Multi-Stakeholder Meetings

- Friends of Cancer Research White Paper 2021
- FDA- ASCO Workshop: "Getting the Dose Right"

Publications

- The Drug-Dosing Conundrum in Oncology- When Less is More

Guidance Documents

- ICH E4: Dose-Response Information to Support Drug Registration
- Exposure- Response Relationships
- Optimizing the Dosage for Treatment of Oncologic Diseases

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