Cancer Drug Development Forum Multi-Stakeholder Workshop

Status and Goals of Project Optimus

Stacy S. Shord, PharmD, BCOP, FCCP
Deputy Division Director
Division of Cancer Pharmacology II
Office of Clinical Pharmacology
OTS/CDER/FDA

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Disclaimer

Opinions presented are those of the speaker and should not be construed to represent FDA's views or policies.

Outline

- Introduce history and goals of FDA Project Optimus
- Describe past and upcoming activities associated with Project Optimus

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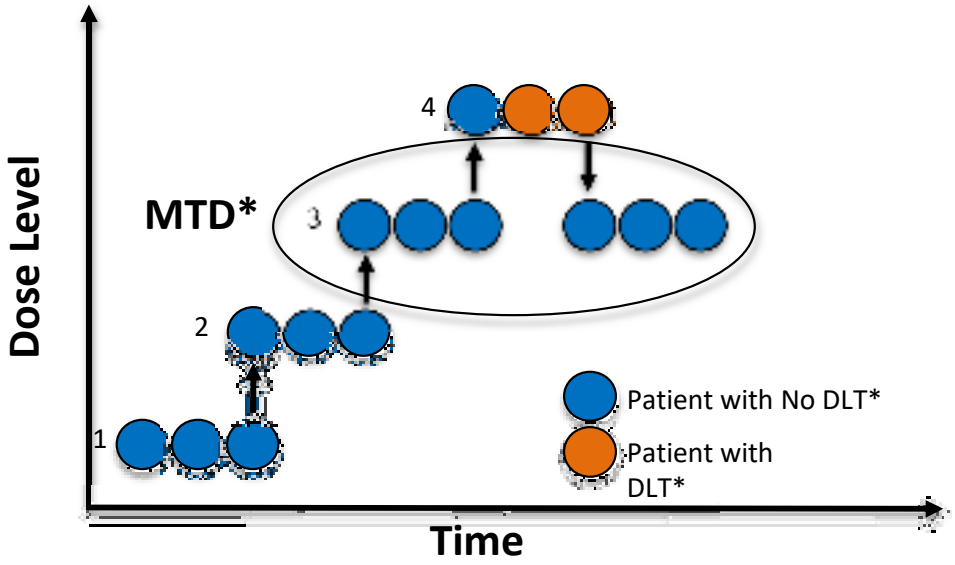
Historic Dose-Finding in Oncology



- MTD approach dominated oncology dose-finding paradigm
  - Based on underlying assumption that higher dose, greater likelihood of efficacy and toxicity with cytotoxic agents
- New molecular targeted and immune therapies challenge this paradigm
- Alternative dose-finding paradigms that balance risk and benefit is needed
- Project Optimus and other projects within FDA focus on supporting this much needed paradigm shift

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

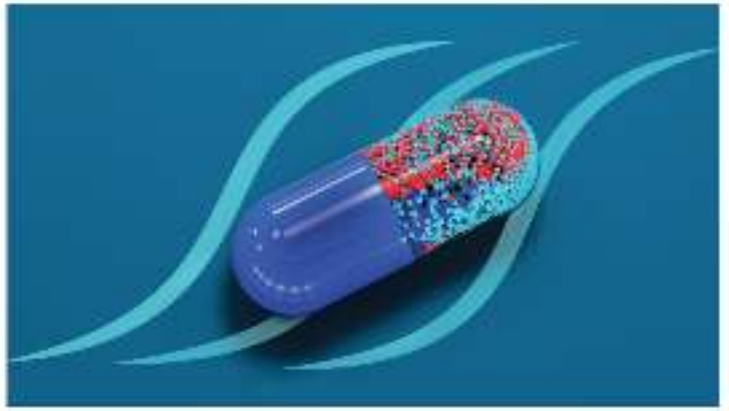
Oncology Center of Excellence

Project Optimus

What? Initiative to reform the dosage optimization and dose selection paradigm in oncology drug development

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

More Information: Project Optimus



Consequences of Not Optimizing Dosage Before Approval

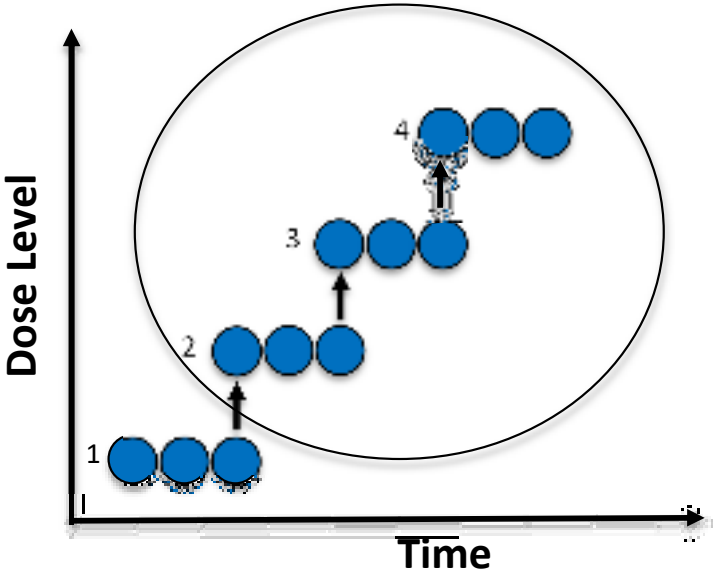
- Drug is poorly-tolerated at the approved recommended dosage
  - Patients may stop taking a potentially efficacious drug
  - Patients choose to try a different drug
- It takes a long time to evaluate alternative dosages following approval
  - Patients may not want to participate in trial if commercially available
  - Disease area moves on to other treatments
- Drug does not make it to market or must be withdrawn from the market

Emphasizing Dosage Optimization **Prior to Approval**

- Patients receive 'optimized' dosage which
  - Improves tolerability and adherence
  - Reduces dosage modifications (i.e., discontinuations)
  - And potentially increases likelihood of response to treatment
- More efficient to evaluate multiple dosages early in development
- Earlier understanding of dose- and exposure-response relationships may allow for more rapid development of new therapies
  - combination regimens, new dosing regimens & new formulations
- Challenging to conduct dosage optimization trials post-approval

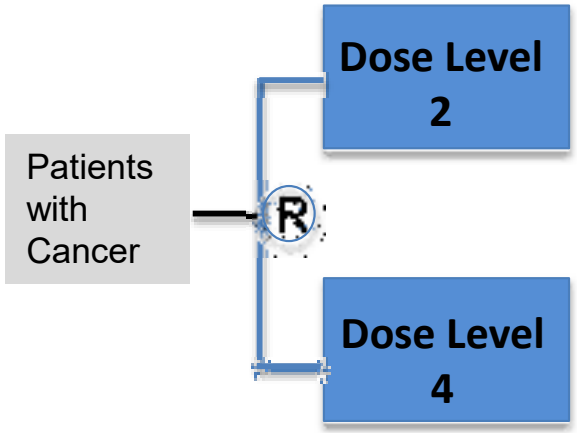
Updated Dosage Selection Strategy

Dose Escalation



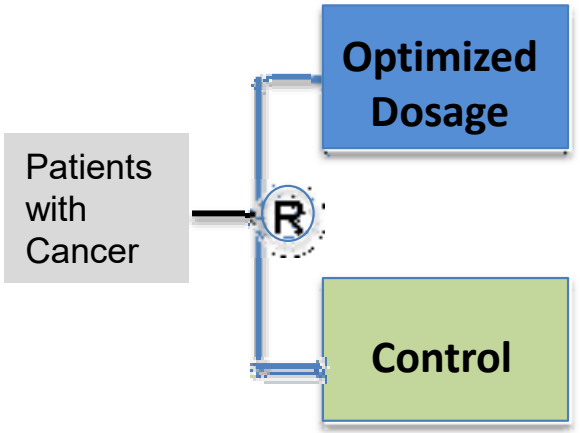
Select Dosage for Further Exploration

Dosage Optimization



Evaluate Several Dosages

Comparison to Standard-of-Care



Comparison to Standard-of-Care

Project Optimus: Summary

- Dosage optimization is essential to safety and effective anti-cancer therapies
- Project Optimus is focused on reforming dosage selection in oncology drug development by
  - Striving to move dosage optimization before the marketing application
  - Considering novel approaches to dosage selection – not one size fits all; and
  - Recommending the Sponsors meet with FDA early and as needed

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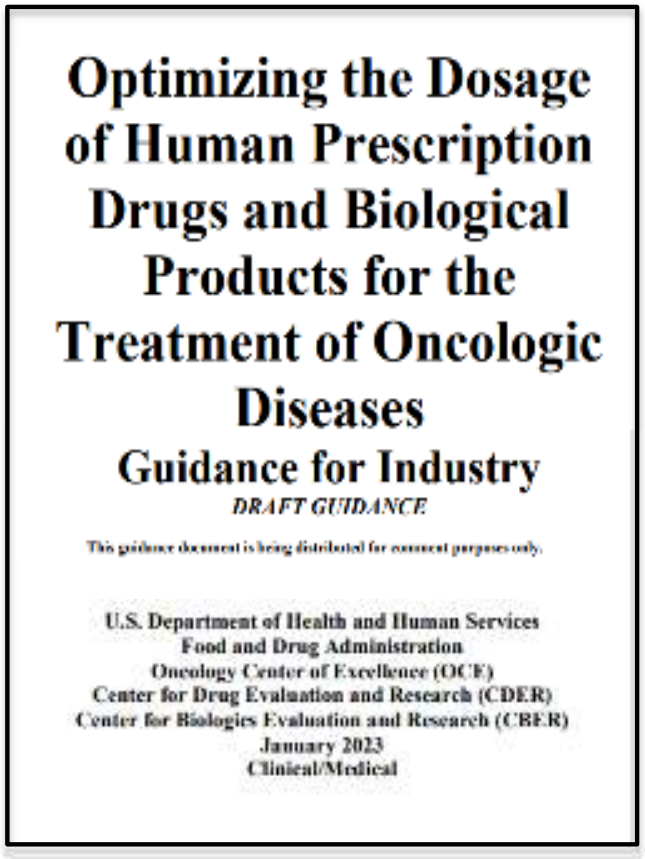
Project Optimus: A year in review

- Engaged sponsors in discussions around arriving at a “better” dosage during the pre-IND meeting/initial IND submission and later milestone meetings
- Published reviews, perspectives and other papers to discuss improving dosage optimization processes
- Participated in multiple national and international meetings to highlight Project Optimus
- Developed and supported multiple meetings to engage with external stakeholders
- Published draft guidance regarding oncology dosage optimization

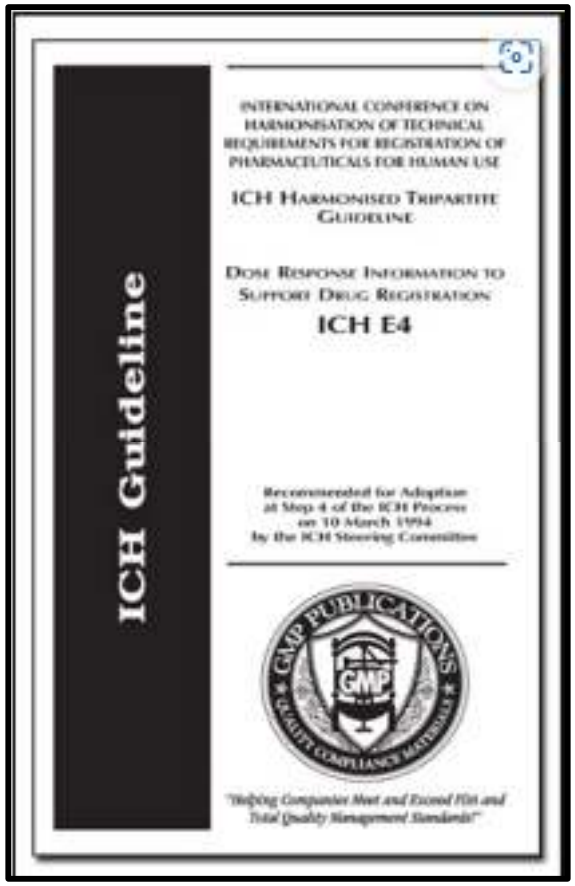
Oncology Dosage Optimization Draft Guidance

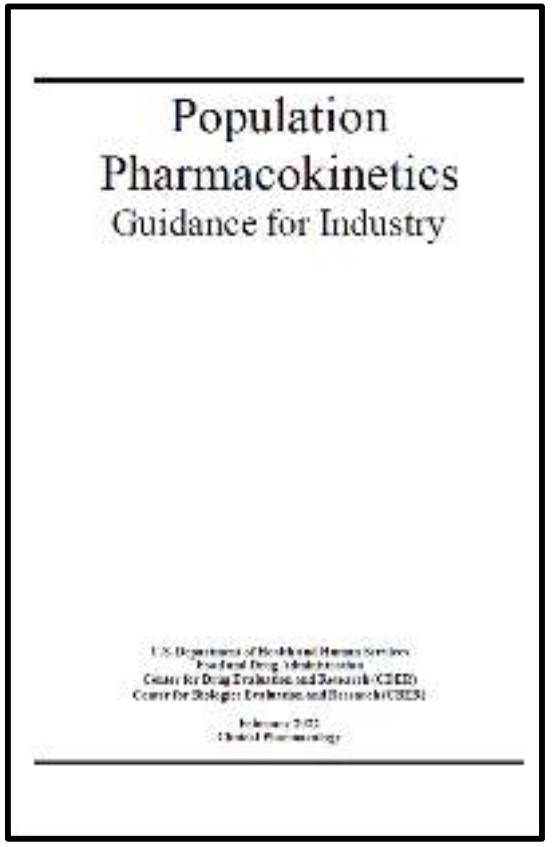


2023

- Dosages must have justification appropriate to the stage of development
- Evaluate all data for to select and support dosages
- Randomized comparisons support identification of optimized dosage(s)
- Safety assessments should include low-grade symptomatic toxicities
- Important for all products, including those with anticipated rapid development timelines

Other Guidance Documents Supporting Dosage Optimization





Opportunities to Engage with FDA

- PIND Meetings and EOPX Meetings
  - Justify dosage(s) selected for clinical trial(s), including dosage modifications
  - Consider all available relevant nonclinical and clinical data

- Type D Meetings (new under PDUFA VII)
  - Two focused topics only
  - Granted within 14 days, occurs within 50 days

- MIDD Paired Meeting Program

Engaging with Stakeholders

Multi-Stakeholder Meetings

- Friends of Cancer Research Annual Meeting 2021 and White Paper
- Conversations on Cancer: More Isn't Always Better
- AACR Annual Meeting 2022
  - Dose Optimization for Antibody Drug Conjugates
  - Using Patient-Generated Data to Optimize the Dose for Oncology Drugs
- FDA-ASCO Virtual Workshop 2022: Getting the Dose Right: Optimizing Dose Selection Strategies in Oncology
- ACCP Annual Meeting 2022
  - Revisiting Oncology Dose Finding: Striking the Optimum Balance Between Efficiency & Robustness
- American Conference on Pharmacometrics 13 (2022):
  - Oncology Drug Development - Getting Ready for Project Optimus
- Society for Immunotherapy of Cancer 2022
  - Assessment of Combination Therapies Regarding Safety, Dose, Contribution of Component

Publications

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

Project Optimus: Moving Forward

Committed to continuing to develop the framework for dosage optimization in oncology

- Advancing regulatory science for dosage optimization
- Enhancing communication with Sponsors throughout premarket drug development
- Engaging with external stakeholders. Coming Soon – Workshops for Fall 2023

Acknowledgements

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