The Challenges of Dose-Optimization

Industry Perspective

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Early Clinical Development

Disclaimer

The opinions expressed in this presentation are solely those of the presenter's and not necessarily those of Seagen Inc. or Seagen International GmbH

The presentation focuses on key challenges associated with dose optimization in early drug development, not on specific treatment options/products

Objectives

- Reflect on challenges and open questions related to FDA's Project OPTIMUS from the drug developer's perspective
- Discuss some considerations for implementation in oncology early clinical studies from industry perspective

Historical Background

FIERCE Biotech

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Virtual Events FiercePharma Jobs Resources Webinar

Biotech

FDA's renewed focus on oncology dosing spooks investors, but companies say they're ready

by Annalee Armstrong | Jun 28, 2021 11:58am

Pink Sheet

Informa Pharma Intelligence

US FDA's 'Project Optimus' Will Encou… Away From Conventional Dose-Findi… Cancer Therapies

26 May 2021 | ANALYSIS

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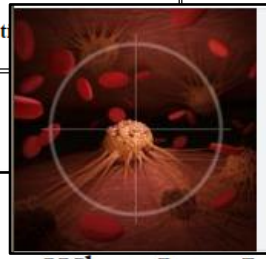
Dose Response Information to Support Drug Registrat…

Step 5



PHARMACYTIMES.COM

The Impact of the FDA's Project Optimus on Oncology Drug Trials

In an interview with Pharmacy Times®, Maria Whitman, Global Head of the Pharmaceutical and Biotech Practice at ZS, discusses the FDA's Project Optimus,…

The NEW ENGLAND JOURNAL of MEDICINE

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

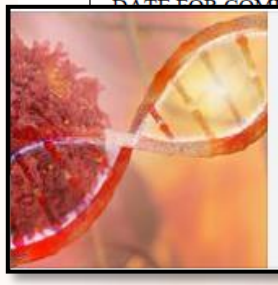
Mirat Shah, M.D., Atiqur Rahman, Ph.D., Marc R. Theoret, M.D., and Richard Pazdur, M.D.

Pink Sheet

US FDA Plans To Get Tougher On Oncology Optimization

16 Jun 2021 | ANALYSIS

APPROVAL BY CPMP
DATE FOR COMING INTO OPERATION



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How New FDA Guidance Project Optimus May Affect Future of Oncology Clinical Trials, Drug Pipeline

Julie Bullock, VP, global head of clinical pharmacology and translational medicine at Certara, discusses the…

…cology Drug Developers: Step Back, …And Find The Right Dose

13 Aug 2021 | ANALYSIS

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.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Mirat Shah at 301-796-8547 or Stacy Shord at 301-796-6261.

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

Rethink Conduct of Early Clinical Development in Oncology

- Number of approved anti-cancer medicines in Europe more than doubled from 2015 to 2020[1]
- Targeted and immuno-oncology agents represent a considerable group
- >6,000 active clinical trials investigating novel immunotherapies
- Targeted therapies often developed for continuous use until relapse/PD – short term follow-up insufficient to identify chronic toxicities
- Goals of dose optimization:
  - Improve tolerability, reduce dose modifications and enable longer treatment duration
  - Accelerate patient access to new cancer medications
  - Avoid dose optimization in phase 3 and post-marketing

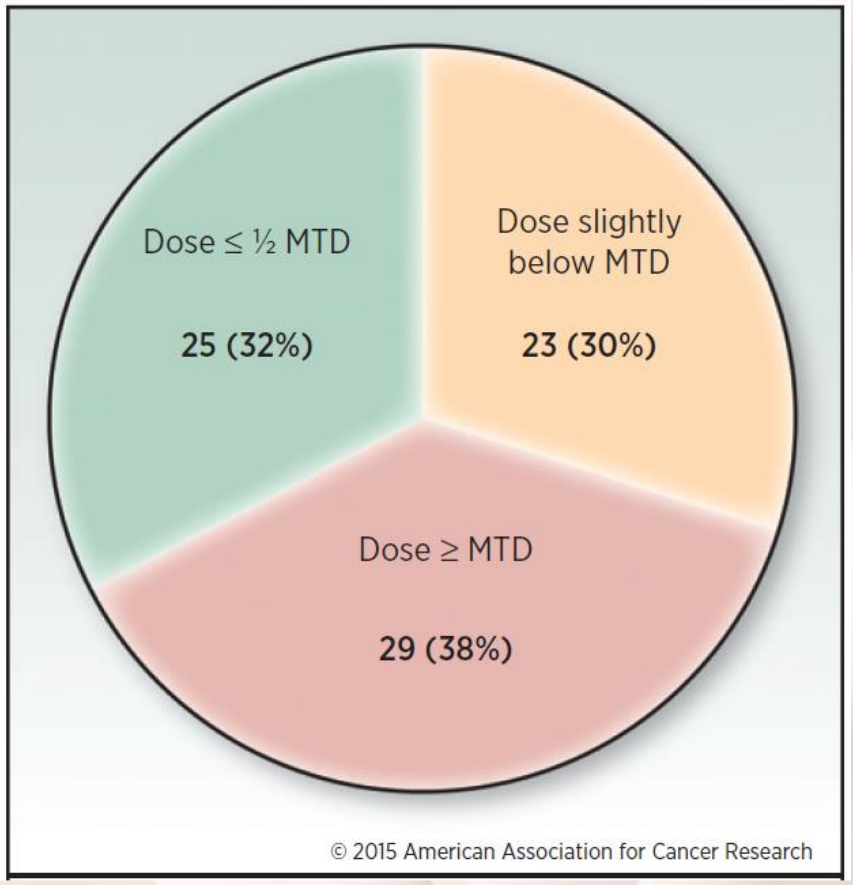
1 – Falcone R et al. Cancers 2022, 14(4), 889

Dosing Challenges in Era of Targeted Therapies

- Of 1'221 patients with metastatic breast cancer, 86% reported significant ADRs, with 43% missing ≥1 dose, 20% requiring hospital admission[1]
- Long term use of less tolerable doses, when lower doses would suffice, may cause poorer compliance and lower efficacy:
  - 24 phase 1 studies at MDACC: Substantially higher drop-outs due to toxicity with no improvement in response over doses that were roughly half of the MTD[2]
  - Only 30% of 201 phase 1 trials reported objectively quantifiable/clinically gradable AEs. More subjective AEs (e.g., pain, fatigue) often not sufficiently reported, adding to ambiguity in DLT determination[3]
- Roughly 2/3 of monotherapies have approved doses less than MTD
- For 30% of compounds, MTD is not within 20% of approved dose[4]

1 - Patient-Centered Dosing Initiative. Accessed at: https://www.therightdose.org
2 - Jain RK et al. Clin Cancer Res 2010;16:1289–97
3 - Penel N et al. Invest New Drugs 2011;29:1414–9
4 - Jardim DL, et al. Clin Cancer Res 2014;20:281–8.

MTDs and Approved Doses



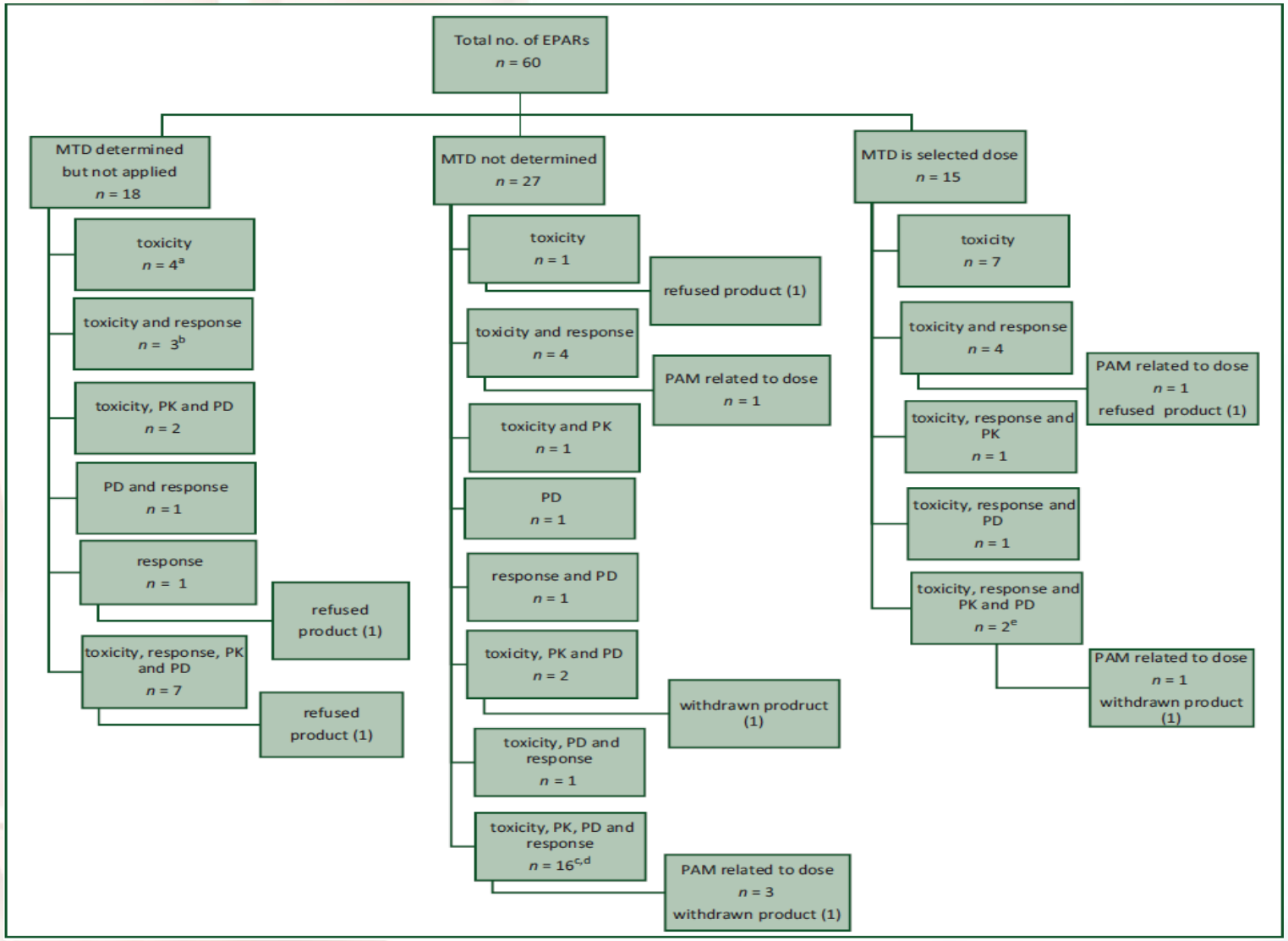
Sachs JR et al. Clin Cancer Res 2016;22:1318–24

Examples of successful non-MTD development by:

- Modelling and simulation-based methods
- (Bio-) Marker-based dosing approaches

These strategies have been successfully implemented, resulting in doses substantially less than MTD

Overview of Observed Dose Selection Criteria for 60 Agents in EPARs (2015 – 20)[1]



[1] Maliepaard M et al. ESMO Open 2021;6:1 - 10

EPARs, European Public Assessment Reports
MTD, maximum tolerated dose
PAM, post-authorisation measure
PD, pharmacodynamics
PK, pharmacokinetics

Moving from MTD to Minimally Reproducible Active Dose (MRAD)

- Project OPTIMUS: More robust understanding in impact of different doses on efficacy and toxicity (including chronic/persistent low-grade)
- Targets may be saturated below MTD → less on-target toxicity; activity-toxicity relationship not closely linked
- Randomised comparisons: Minimal biologically active dose (estimated from PK-PD modelling) to highest tolerable dose to rule out a differential benefit with acceptable tolerability
  - Not powered, but sufficiently sized to understand general shape of dose - exposure, PD, toxicity relationship
  - *Need more patients, increased heterogeneity, more time …*

Heterogeneity of Study Population and Data Interpretation

- Enroll appropriately broad population to assess impact of covariates on PK, safety and efficacy
- Adequately characterise PK to support PopPK, dose- and exposure-response analyses
- MRAD not always consistent across different populations, including:
  - Tumour type (additional signalling pathways)
  - Mutations (drug affinity and inhibitory activity), reduced affinity for resistance mutations
- Analysis plan for PD and PGx data to be considered if appropriate

How to balance need for more data from broader population without confounding but strengthening data interpretation?

Added Complexity due to new Study Designs

- Recommended design: Randomized, parallel dose-response trial
- Intervals between dose cohorts may have to be increased to capture PD and longer-term toxicities
- Model-based systems integrating later data to be considered, e.g., TiTE-CRM → *more resources required*
- Ensure similar population and interpretability of dose- and exposure-response analysis → *in contrast to ask for broader population enrolled*
- Dose-finding models required to deal with associated complexity of integrating data on broad tolerability (not just DLTs), PD and activity measures

Complexity due to Demands on Study Designs

- Timing and prioritisation of dose comparisons to be reconciled with other expansion priorities such as population optimisation (refining tumour types, biomarker selection)
- Needed before dose-efficacy relationship can be explored in an adequately sensitive population
- Using real-time PK data and early validation of PD biomarkers to inform development decisions
- Adaptive designs with interim analyses to allow early stopping of one or more arm

Study Endpoints and Biomarker Validation

- ORR / DOR may not be adequate where response rates are lower. PD endpoints will support this data but may require increased tumour biopsies

  → *Leverage advances in radiographic, ctDNA and blood biomarkers, at multiple timepoints, less variability, and greater accessibility and acceptability than biopsies*

- Validated biomarkers enabling optimal patient selection and PK-PD decision-making will require earlier and more extensive biomarker development (plus added complexity of IVDR?)

  → *Implications on resources and costs*

Additional Points to Consider

- Alternative dosing strategies (e.g., step-wise dosing, tapering to tolerability)
- Include PROs, engage with patients
- Frequency and impact of symptomatic reactions (incl. Gr 1-2)
- Consider backfilling into lower escalation dose levels

Subsequent Indications and Usages:

- Consider nonclinical and clinical data ("Totality of the evidence")
- Strong rationale needed for dose selected for registrational trial, especially in diseases not adequately represented in early development

… Speed …

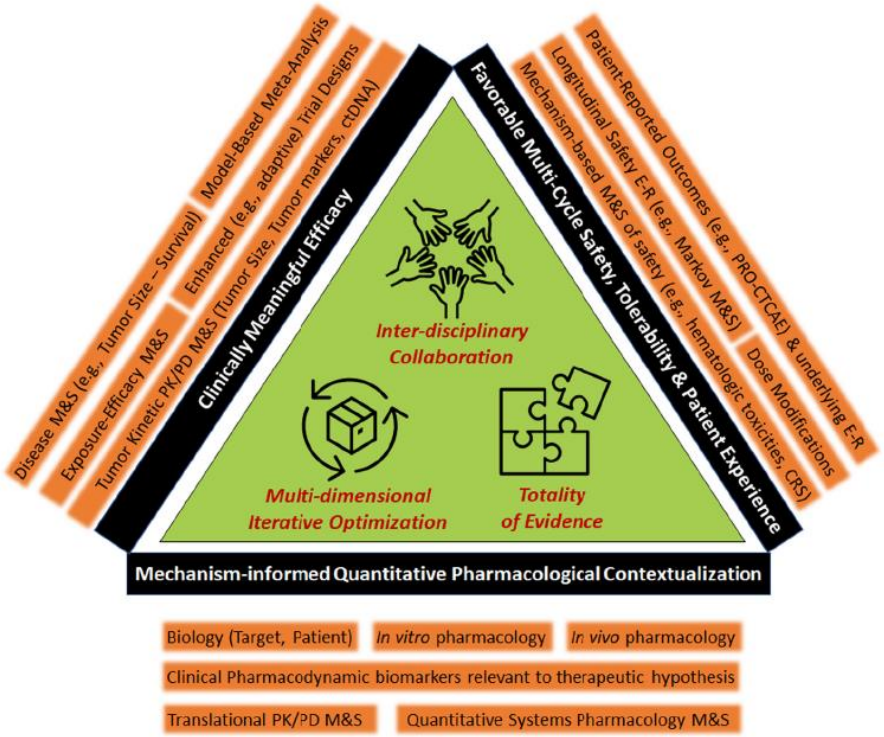
- Overall duration of drug development may be affected by need for increasingly rigorous dose characterization
- May be balanced by yielding more optimal dosing for registration studies
- Further dose comparisons could impact fast track agents, whereas they might have proceeded previously to registration
- Could streamlined regulatory interactions such as Fast Track (US), ILAP (UK), and PRIME (EU) overcome challenges of increased timelines?

… and Costs

- Increased initial cost of drug development has implications on long term affordability (and access)
- Changes in trial design, data requirements and costs may have marked funding implications for biotechs
- Difference between larger pharmaceutical companies and smaller biotech which often have less flexibility to rapidly increase budgets
- Opportunity in developing smarter trial designs to utilise generated data most efficiently and amplifying available data via intra-patient comparisons of PK - PD

Conclusions

- Primary goal: support paradigm shift from using MTD as default approach for oncology drug development to a randomised exploration of optimal dosing
- Rigorous selection of dose schedules to help patients gain increased benefit from systemic treatment, thereby improve individual Risk:Benefit ratio
- Multi-stakeholder engagement needed to address dose optimisation challenges, to ensure high adoption rate, low barriers, and effective exchange between clinicians, patients, regulators, and industry



Venkatakrishnan K (2022) Clin Pharm Therap 112(5);927-32