sanofi

Statistical Considerations for Dosage optimization in Oncology

Christelle Lorenzato, Sanofi, Global Head Oncology Biostatistics*

SMAC – March 16th 2023

*Christelle Lorenzato is Sanofi employee and may hold shares and/or stock options in the company.

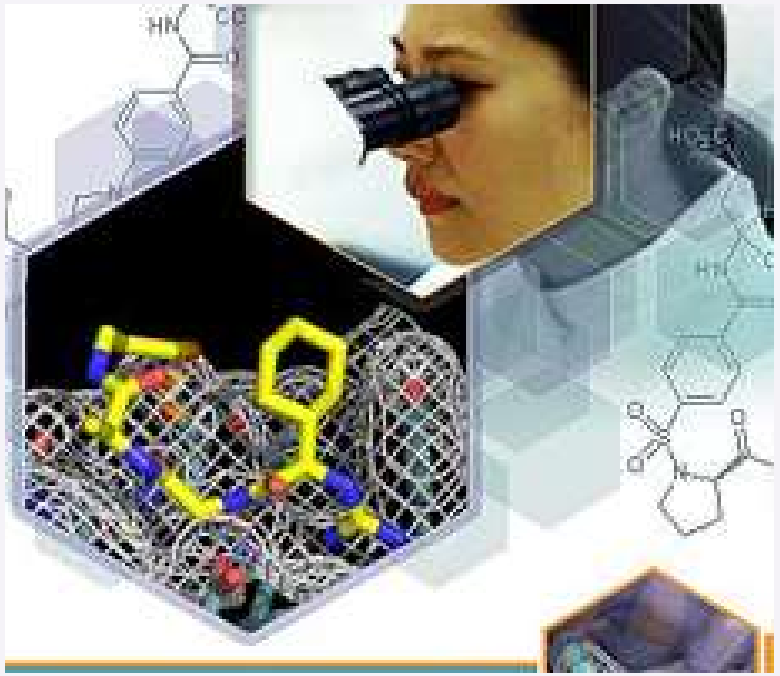
Agenda

01 Background

02 FDA's Project Optimus and some selected related publications

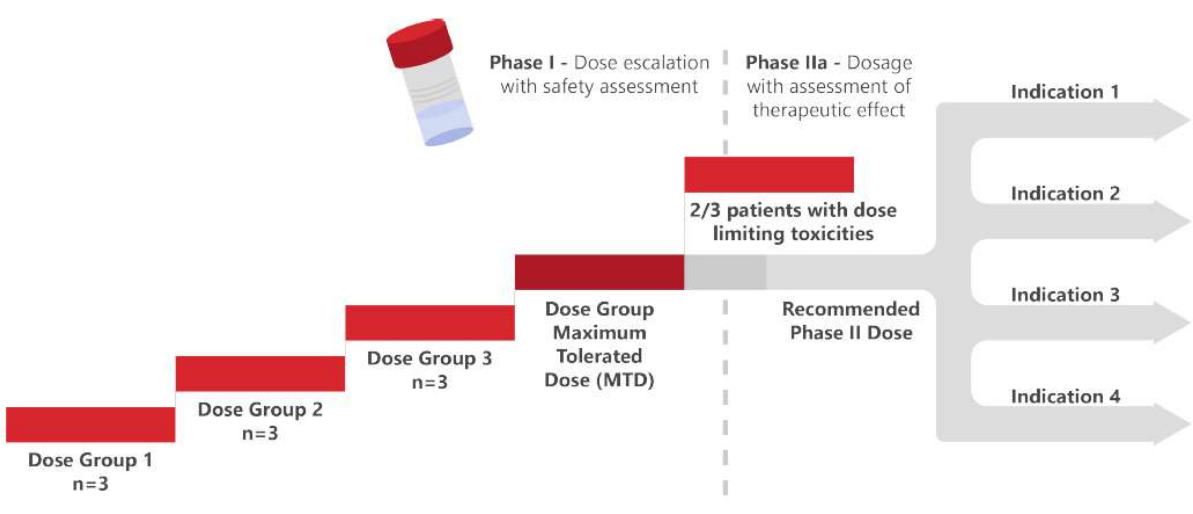
03 Key Statistical Considerations for Dosage Optimization

04 Discussions



01 Background

Background: Maximum tolerated dose (MTD) as historical paradigm for recommended dose in oncology

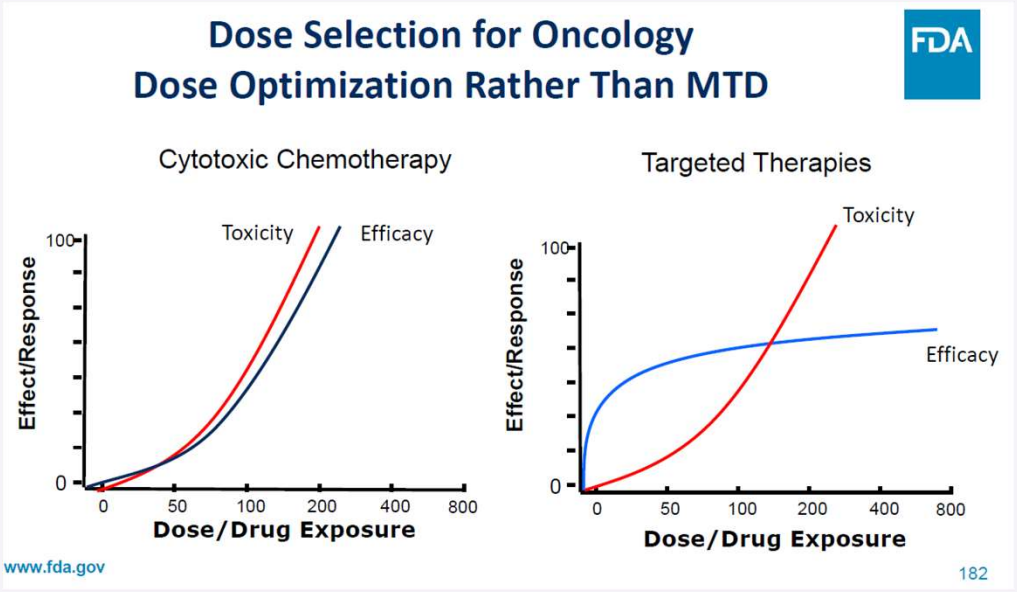


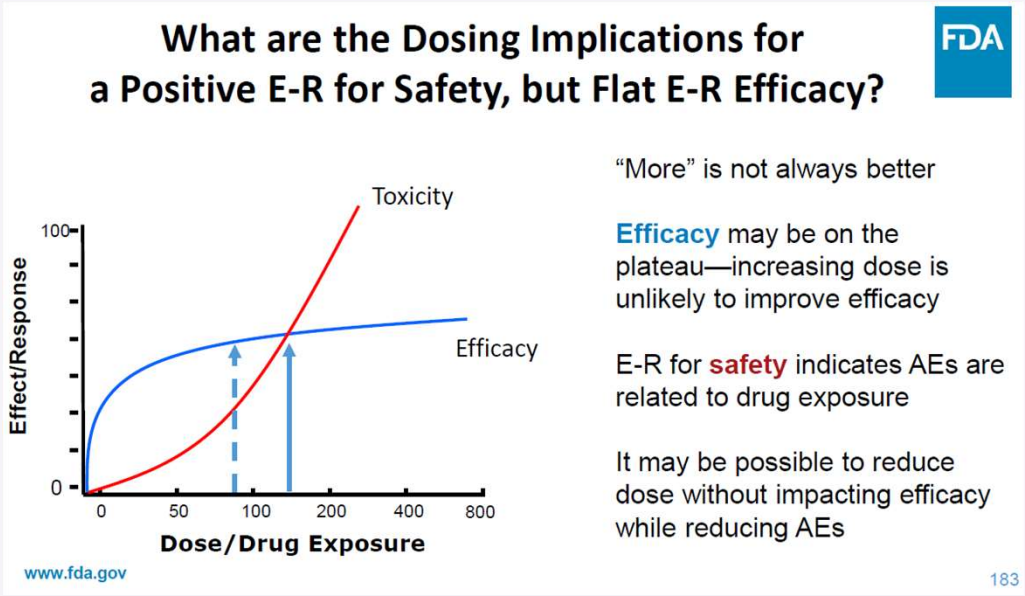
- The **MTD strategy** doesn't work with targeted cancer therapies; a higher dose does not necessarily result in improved anti-tumor activity
- Focuses on **cycle 1 toxicities**. However, patients take immunotherapies for longer periods of time, and often in combination with other treatments
- Even though **other endpoints** are considered, dose selection is dominated by DLT observation. Need to include the totality of evidence (e.g. PD biomarker, activity, safety) for dose finding

Diapositive 4

JL0 Maybe we can say the other endpoints are considered, but dose selection is dominated by DLT observation
Ji Lin; 2023-03-06T13:27:35.462

Challenges with Exposure-Response for Targeted Therapies





Different types of agents may have *wider or narrower therapeutic index* depending on the mechanism of actions

02 FDA’s Project Optimus

AND SOME SELECTED RELATED PUBLICATIONS

FDA's OPTIMUS project history

FDA in their 10th year of thinking about how to determine the best dose/schedule for oncology drugs

2021- FDA getting more serious about requiring to conduct dose-finding studies early (rather than after approval)

FDA article, NEJM 2021

Perspective

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.

Article Figures/Media Metrics

5 References 21 Citing Articles

In May 2021, the Food and Drug Administration (FDA), where we work, approved sotorasib (Lumakras) for metastatic non–small-cell lung cancers (NSCLCs) harboring the KRAS p.G12C mutation. Sotorasib, which was approved on the basis of the phase 2 portion of the CodeBreaK100 trial, is the first drug to target KRAS, which had been considered "undruggable" and was investigated unsuccessfully for decades.[1] Despite this achievement, the drug's development was hampered by a lack of robust dose exploration, which led the FDA to require the sponsors to conduct a

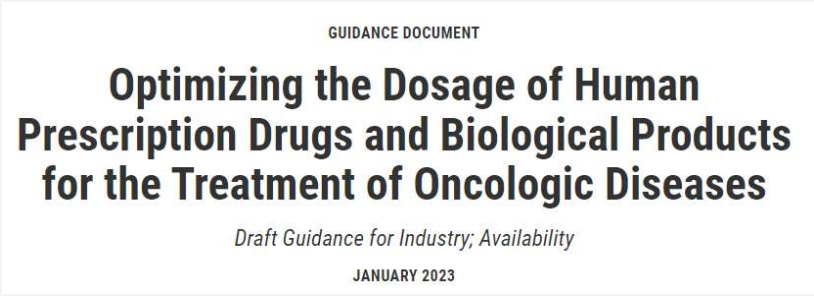
ARTICLE | REGULATION

Pazdur rings bell for dose optimization, wants to modernize clinical tox

FDA oncology chief tells sponsors to move beyond the era of MTD, says patients define tolerability: a conversation at ASCO22

2022 - FDA repeated those messages through Oncologic Drugs Advisory Committee (ODAC) meetings, public workshops, and conferences

January 2023 – FDA issued draft guidance



GUIDANCE DOCUMENT

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

Draft Guidance for Industry; Availability

JANUARY 2023

Goals of OPTIMUS project

Communicate expectations for dosage optimization

(via Guidance, workshops, public meetings)

Encourage sponsors to meet with FDA Oncology Review Divisions early

(well before conducting trials intended for registration)

Develop strategies that leverages the totality of **nonclinical and clinical data**

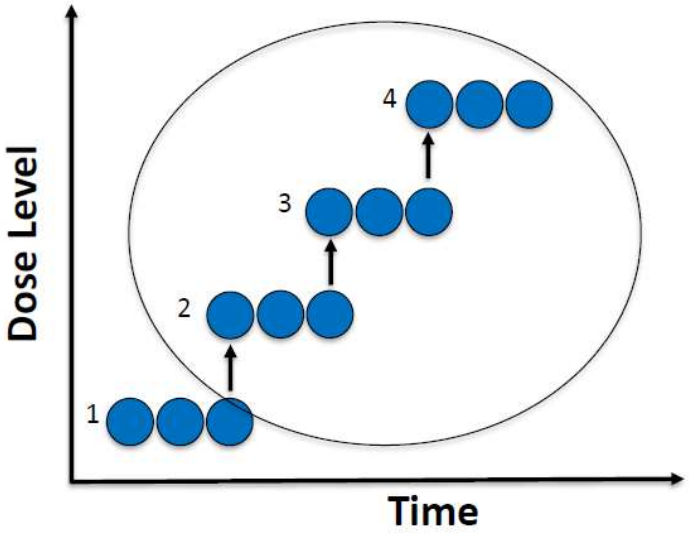
(toxicity, tolerability, activity, PK, PD marker, Exposure Response modeling)

Dosage optimization approaches to be considered as early as possible in the development and as efficiently as possible

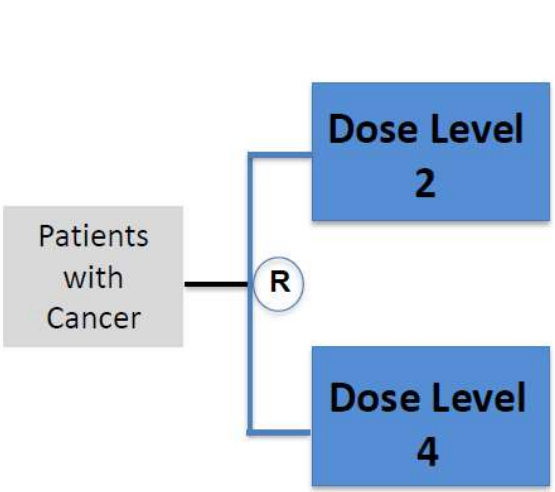
sanofi

Project Optimus' Impact on Dose Selection Paradigm

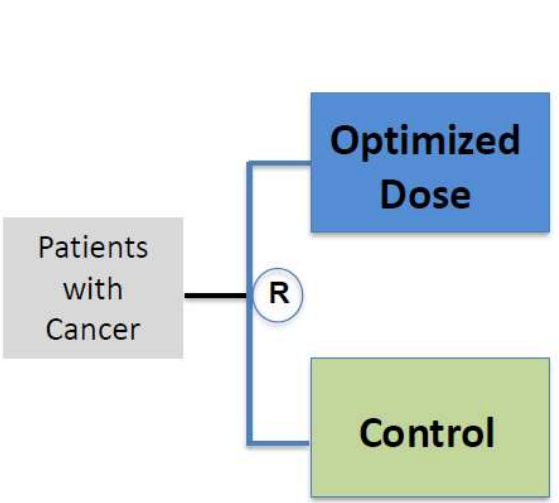
Updated Dose Selection Strategy



Select Several Dosages



Further Evaluate Dosages



Compare to Standard of Care

Some selected publications on OPTIMUS

N Engl J Med 2021; 385:1445-1447. Oct. 14, 2021

- *"We believe this practice [**small cohorts** of patients assessed for **DLTs** for **one treatment cycle** to identify the **MTD**] should be **reexamined** for targeted drugs and biologic therapies."*
- *"Dose selection for registration trials should be guided by PK and PD 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 PD markers and subsequently **evaluated in a randomized trial**."*
- *"Sponsors should carefully evaluate **exposure-response, efficacy**, and **safety** data from early trials to inform dose selection, **rather than automatically selecting the MTD**. "*

Nov. 5, 2021

- *"Ideally, the pre-registrational dose-finding study would be **randomized**, compare **at least two doses**, and **confirm the dose selected** for the registrational trial, which is the dose that maximizes benefit-risk by measuring efficacy among **a sizeable number of patients**.*
- *"The randomized dose-finding trials **do not necessarily need to be powered to conduct a rigorous statistical comparison across doses**; however, it is important that the trial is **sufficiently sized** to understand the general shape of the dose/exposure-activity/toxicity relationships, including the minimally active dose."*
- *"The **study design** for determining the optimal dose will **differ** depending on the product, the target population, and the data that are available."*

sanofi

Some selected publications on OPTIMUS

J Clin Oncol 40:3489-3500. American Society of Clinical Oncology –2022

- *"We reviewed US FDA initial approvals (2019- 2021) of small molecules and antibody-drug conjugates for oncologic indications to determine the proportion with a* ***recommended dosage at the MTD*** *or the maximal administered dose, to characterize the use of* ***randomized*** *evaluations of* ***multiple dosages*** *in dose selection, to describe the* ***frequency of dose modifications at the recommended dosage, and to identify case examples that highlight key principles for premarket dose optimization during drug development.***
- *Although there has been some* ***progress, dose optimization through randomized dose evaluation in oncology trials is not routinely conducted.***

- *The Methodology for the Development of Innovative Cancer Therapies (MDICT) Taskforce to develop a practical guide for dosage optimization in oncology phase I trials.*
- *Need for* ***robust nonclinical data*** *to inform trial design*
- *Health authorities should be consulted early and regularly.*
- *Strategies such as* ***randomization***, ***intrapatient dose escalation***, *and real-world eligibility criteria are encouraged*
- *Endpoints should include consideration of all* ***longitudinal toxicity***.
- *The phase I dose escalation trial should define the* ***recommended dose range*** *for later testing in randomized phase II,* ***rather than a single recommended phase II dose***, *and consider scenarios where different populations may require different dosages.*

sanofi

08 Statistical Considerations for Project Optimus

Overview of dosage optimization strategies and timing*

Dose optimization in dose escalation

- Define **design** based on key drug characteristics & MoA (e.g. BLRM, PoD-BIN, intra pt dose escalation …) and consider adding:
- **Backfilling:** additional patients in relevant DLs
- **Modeling:**
  - **PK/PD modeling**
  - **Safety-PD Biomarker / joint modeling**
- **BOIN12, Stage 1 of DROID**
- …

Dose optimization just *AFTER dose escalation*

- **Randomized phase 2** (e.g. Pick-the-Winner, stage 2 of DROID)
- Modeling including efficacy/safety/biomarker can be updated in ph 2

Delay dose optimization *AFTER preliminary efficacy signal*

- **Two stage phase 2 design:** small expansion cohort followed by randomized part (if efficacy signal in part 1)

Phase 2/3

- Operational/Adaptive inferential seamless phase 2/3 design
- Multi-arm randomized phase 3 design

Recommended Dose Range, to be tested in ph 2, based on all available data (rarely directly RP2D) → **Define the Recommended Dose (& Schedule) for pivotal study**

**Disease Modeling could also help to inform dose optimization during all phases*

sanofi

Backfilling

Figure 2. Backfilling to dose-levels where evidence of efficacy (e.g. tumor shrinkage or clearance of ctDNA) and safety (e.g. clearance of DL per dose-escalation study) has been demonstrated parallel to the dose escalation which will allow the accrual of more patients, saving time and resources.

From ESMO 2022 paper

- **Principle:** Backfiling is not a design. It consists in enrolling additional patients at relevant lower and safe dose Levels (DLs) during dose escalation, to collect additional information on safety and activity

- **Dose allocation of backfill patients:**
  - Allocation (potentially randomization) to a dose-level below the current one
  - Randomization to the dose-levels below the current one that have not been discarded due to lack of efficacy (1)

- **Use of backfill patients to guide dose-escalation and recommend a dose range to be tested in phase 2**
  - Increase correct selection of the MTD using model-based dose-escalation designs (2)
  - Prerequisite: dose escalation design needs to consider key drugs characteristics (MoA, expected safety profile, e.g. delayed toxicity, need for intra pt dose escalation …)

- Might be used to define a RP2D if the dose escalation population is similar to dose expansion, with very strong results (activity) & strong E-R modeling ?

(1) Dehbi et al. Contemporary clinical trials. 2021. (2) Barnet et al. ArXiv. 2022

Safety-PD Biomarker Joint Modeling

- Scenario: when efficacy biomarker is available in dose escalation phase to select biologically optimal dose level → Explore, identify and incorporate emerging biomarker data to facilitate decision-making (e.g. ctDNA)
- Proposal: Joint modeling the dose relation to toxicity and efficacy biomarker (e.g. latent probit regression):
  - Define target interval for toxicity (pic below), threshold for efficacy/biomarker, and overdose control level

    - Binary toxicity, target interval to ensure toxicity still drives the dose escalation e.g., ltox= 0.16 utox=0.33
    - Ordinal efficacy endpoint $Y_E = \{0,1,2\}$ for none, medium, and high response. E.g., response (1 or 2) threshold = 0.2
    - Over toxic control level, say 0.4
  - Selection rules
    - Target: maximize joint posterior probability for toxicity and efficacy/biomarker satisfying certain constrain. E.g. toxicity within a target interval, efficacy/biomarker above/below a threshold
    - Over-dose variability control: control posterior probability of over toxicity to be below some value.
    - Next dose recommendation: among non over dosed, find dose level with MAXIMUM target posterior probability
- Limitation: in many cases, a BM for dose optimization is unavailable (e.g., threshold of ctDNA level that translates into clinical efficacy) and/or may be difficult to observe activity in DE population

Very active stat research on OPTIMUS: some selected publications, more to come in 2023 !

BIOMETRIC METHODOLOGY | Full Access

DROID: Dose-ranging approach to optimizing dose in oncology drug development

Beibei Guo, Ying Yuan

First published: 20 February 2023 | https://doi.org/10.1111/biom.13840

- In the first stage, patients are sequentially enrolled and adaptively assigned to investigational doses to establish the **therapeutic dose range (TDR)** (vs MTD and RP2D), defined as the range of doses with acceptable toxicity and efficacy profiles, and the recommended phase 2 dose set (RP2S)
  - TDR: from MAD (minimum active dose based on the mnim acceptable PD threshold) to MTD
  - Finding TDR algorithm Consists of 2 dose exploration processes/models
- In the second stage, patients are randomized to the doses in RP2S **to assess the dose-response relationship and identify the optimal dose** using a **Bayesian dose-ranging inferential framework**

sanofi

Very active stat research on OPTIMUS: some selected publications, more to come in 2023 !

ORIGINAL REPORTS | Precision Medicine

BOIN12: Bayesian Optimal Interval Phase I/II Trial Design for Utility-Based Dose Finding in Immunotherapy and Targeted Therapies

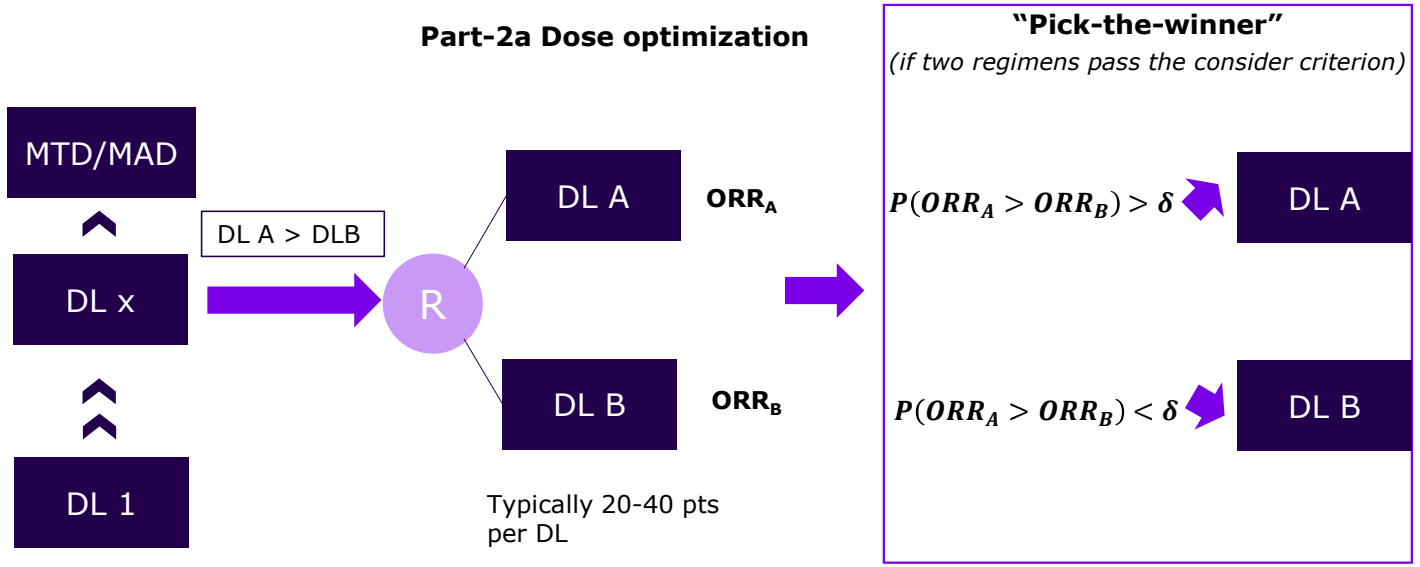
Check for updates

Ruitao Lin, PhD[1]; Yanhong Zhou, PhD[1]; Fangrong Yan, PhD[2]; Daniel Li, PhD[3]; and Ying Yuan, PhD[1]

- Decision of dose escalation and de-escalation by **simultaneously taking account of efficacy and toxicity** and adaptively allocates patients to the dose that **optimizes the toxicity-efficacy trade-off**
  - Based on utility measure

- “Compared with existing phase I/II dose-finding designs, the BOIN12 design is simpler to implement, has higher accuracy to identify the Optimal Biological Dose (OBD), and allocates more patients to the OBD. One of the most appealing features of the BOIN12 design is that its adaptation rule can be pretabulated and included in the protocol.”

Dose optimization after in dose expansion: randomized phase 2 with Pick-the-Winner approach



		DL A		
		No-Go	Consider	Continue
DL B	No-Go	No-Go	Consider DL A	Go DL A
	Consider	Consider DL B	Pick-the-winner for consider	Pick-the-winner for Go
	Continue	Go DL B	Pick-the-winner for Go	Pick-the-winner for Go

Optimal dosage defined based on the totality of evidence (activity, toxicity, E-R)

Discussions

- Other questions to be addressed, offering opportunities for alternative designs:
  - How to handle multiple indications ? Dosage by indication or for ALL indications ? If multiple indications, could we borrow information across indications (basket trial approach) ?
  - What about combination therapies ?
  - When do we really need randomization ?

- It is just a start: need to continue to explore and assess design options (e.g. simulations to compare operating characteristics) and pilot into clinical studies

- Need to gain more experience with FDA on projects: e.g. do we need to define the optimal dose before pivotal study or before submission ?

Thank you

Abstract

In 2021, the Food and Drug Administration (FDA) Oncology Center of Excellence announced “Project Optimus” focusing on dosage optimization for oncology drugs and recently issued a draft guidance entitled “Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases” (January 2023). Indeed, current strategies for determining the recommended dose(s) and schedule of anticancer agents for evaluation in registration trials are often based on a historical drug development paradigm developed for cytotoxic chemotherapies. For cytotoxic chemotherapies, higher doses of the drug were thought to have greater antitumor activity. In contrast, most anticancer agents currently in development are targeted or Immuno-Oncology therapies. Higher doses of targeted or I/O therapies may not have greater effect-safety ratio, and patients may stay on these therapies for long periods of time, increasing the importance of tolerability. In this context, new approaches to optimize the dosage of targeted anticancer agents are needed and should be based the totality of data generated (e.g. toxicity, activity, PK, PD marker, exposure response relationship).

The FDA’s draft guidance on dosage optimization will be summarized. Several options of designs and statistical approach to support dosage optimization in clinical development will be discussed, including back-filling in dose escalation, randomized phase 2, dose response modeling and multiple arms phase 3 trials.