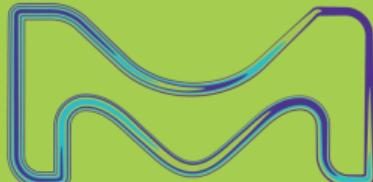


Lecture 3: Project Optimus and the framework of Complex Innovative Designs

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Recap of course learning objectives

- Understand the potential benefits and drawbacks of using adaptive designs.
- Learn about the breadth and depth of the toolbox offered by adaptive designs.
- Know where to search for more information on adaptive designs.
- Understand the difference between using Bayesian methods for design and/or inference.
- Learn about the current regulatory environment regarding Bayesian methods.
- See real-life examples of using Bayesian methods for clinical trials.
- Learn about key aspects of complex innovative designs and their practical implementation.
- Understand the operation of different dose-finding methodologies and how they differ.
- Learn about key aspects of Project Optimus and the importance of Bayesian adaptive designs in early phase dose escalation/optimization trials.
- Understand the relation between design, implementation and analysis aspects of complex adaptive designs (through an example using Bayesian response-adaptive randomization).

Complex Innovative Trial Designs

Definition: Clinical trial designs aiming to facilitate and advance the use of complex adaptive, Bayesian, and other novel clinical trial design methodologies to enhance trial efficiency.

Examples of CIDs: Master protocols including umbrella, basket and platform studies, Complex Adaptive Design including Response Adaptive Randomization or Bayesian Adaptive Design requiring design simulations.

Examples of Designs that are not CIDs: Dose escalation designs that include Bayesian design (eg: BLRM, mTPI, BOIN etc.), oncology phase Ib cohort expansions, *The Project Optimus Initiative*.

CIDs may vary but often share similar operational and design requirements:

1. Complex design, set-up, data management, patient randomization.
2. Complex study governance and decision-making.
3. Requirement for significant regulatory involvement.(CID Paired Meeting Program)
4. Need for experienced staff.

Key Criteria for Complex Study Designation

- Tests multiple hypotheses within a single study organized into sub-studies (e.g., master or core protocol)
 1. **Basket Design:** Testing a single therapy against multiple indications
 2. **Umbrella Design:** Testing multiple therapies against a single indication
 3. **Platform Design:** Testing multiple therapies and/or combinations against an indication using shared infrastructure and a common control arm

AND/OR

- Incorporates prospective adaptive elements
 1. Response Adaptive Randomization (RAR).
 2. Covariate-Adjusted Response Adaptive Randomization (CARA).
 3. Early stop for futility or efficacy.
 4. Bayesian or frequentist designs.
 5. Adaptive dose-ranging studies.



Define a core of master protocol, independent of the organization of the documents via appendices or sub-protocols

A linking document and elements that remain constant across any planned sub-study, arm, cohort, or sub-protocol for complex innovative designs

Which elements should always be included in the master protocol?

Which elements should be duplicated in the sub-study or sub-protocol?

Informational Elements

- Rationale
- Background
- Risk benefit analysis
- Disease or pathology specific information
- Definitions
- Objectives and common end points

Administrative Elements

- Registration and PI information
- Synopsis
- Study schema
- Common schedule of assessments
- Inclusion/ exclusion criteria
- sub-study organization

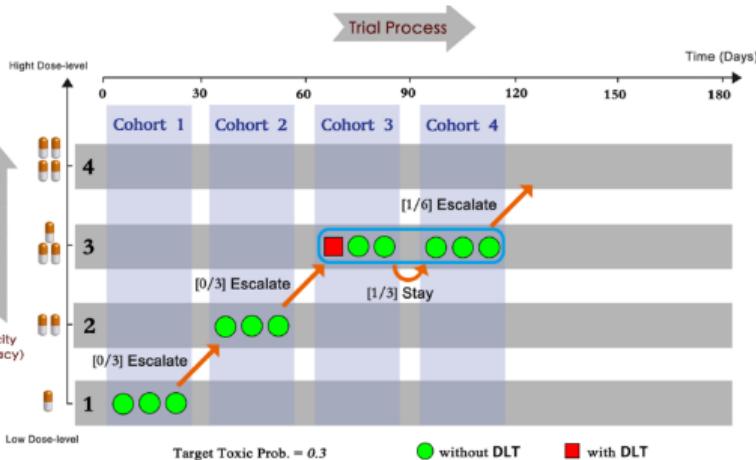
Statistical Elements

- Statistical simulations (if using)
- Power analysis
- Core SAP

Design Elements

- Key hypothesis
- Prospective adaptations
- Planned sub-studies and sub-study organization
- Common control arms (if using)
- Blinding
- Type of design

Traditional Dose Escalation Approach Targeting MTD

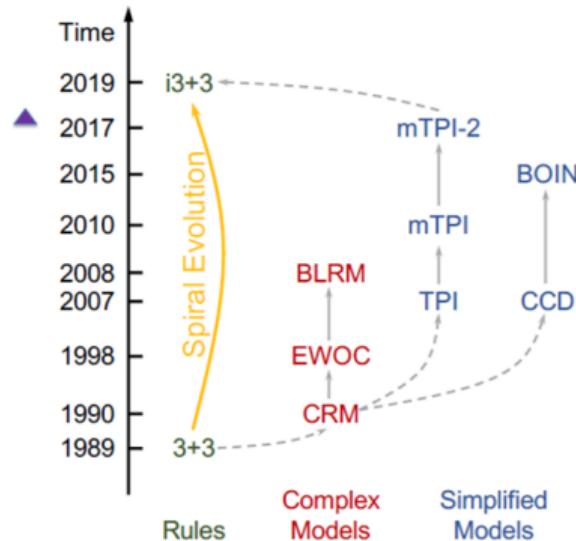
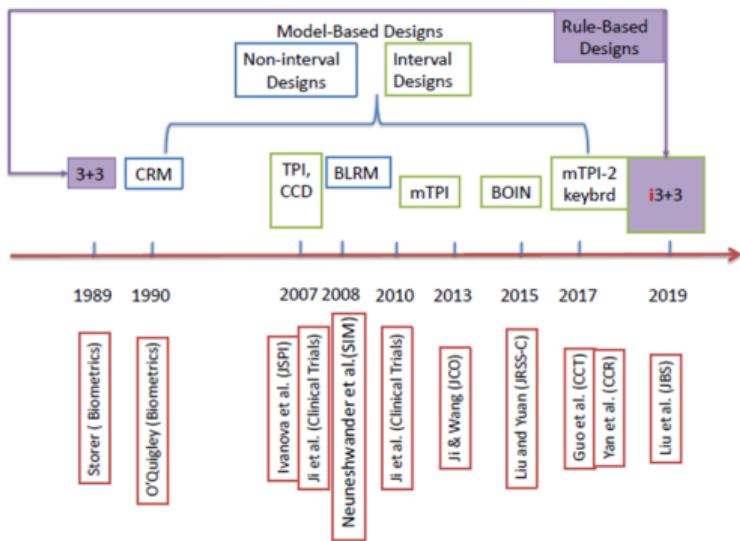


- **Goal** To establish the recommended dose and/or schedule of new drugs or drug combinations for phase II trials.
- Dose-limiting toxicities (DLTs) traditionally are defined by the occurrence of severe toxicities (grade 3 and above) during the first cycle of systemic cancer therapy.
- **Maximum Tolerated Dose (MTD)** The highest dose of a drug or treatment that does not cause unacceptable (DLTs).
- The MTD is determined in clinical trials by testing increasing doses on different groups of people until the highest dose with acceptable side effects is found.

Adaptive Dose Escalation Methods for Cytotoxic Chemotherapies

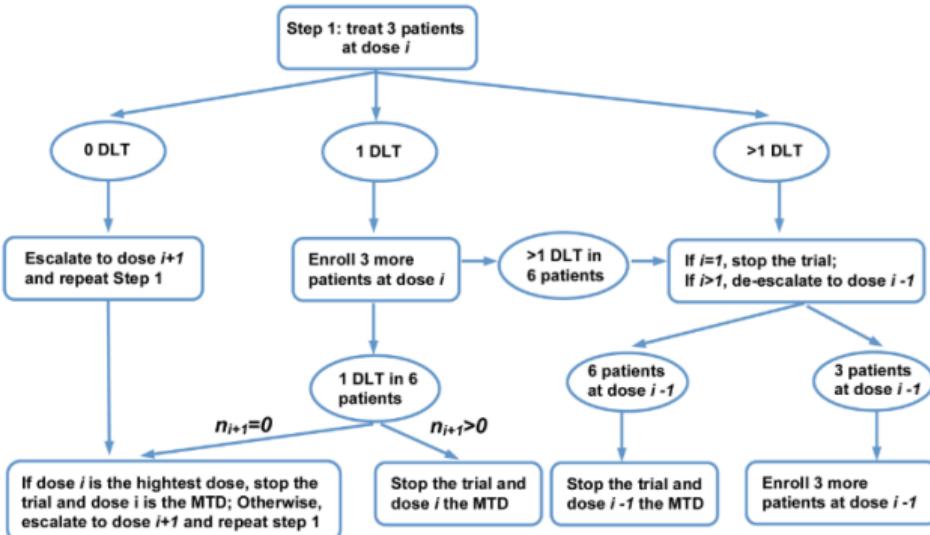
Dose-finding designs over last 30 years

- So many designs are available now.
Which one to use?



Rule Based Design : The 3+3 Method

- A Rule Based Design
- No statistical models needed to implement in practice
 - Societal Acceptance
 - Easy to implement
 - Transparent escalation rule
- Naive and Rigid rule
 - ≤ 6 patients per dose level
 - MTD wide range ($\frac{1}{6}$ to $\frac{1}{3}$)
 - Large variabilities in MTD identification
 - Often little data supporting RP2D choices
- Often identifies a subtherapeutic dose as the MTD



Model Based Dose Finding Methods as an Improvement

The CRM & BLRM designs

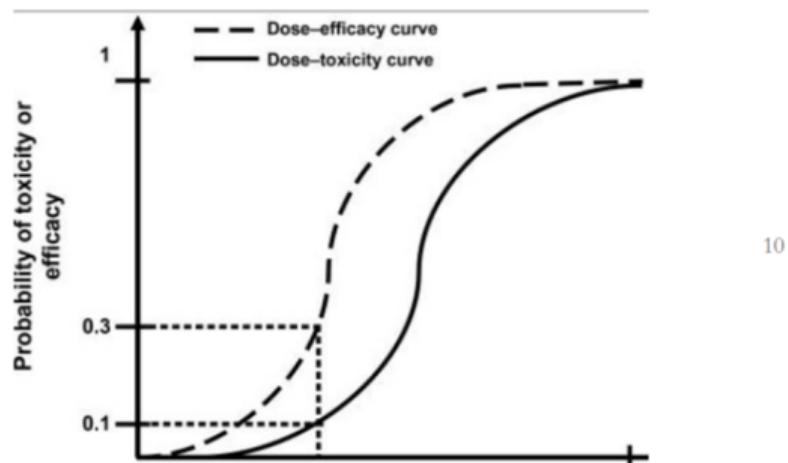
- MTD: a target rate p_T
- BLRM: probability intervals
- Dose-response curve
- $p(x) = p_0(x)\exp(\alpha)$ or $\text{logit}^{(-1)}(x\beta)$
 - $\alpha \sim N(0, 1.34)$; or $\beta \sim \text{prior}$
 - $p_0(x)$ is the “skeleton”
 - Next dose = $\text{argmin}|\hat{p}(x) - p_T|$ or based on posterior prob. of intervals
- Operation
 - Need a statistical expert for inference and decision making
 - Too complex for the clinical team
 - SMC may override dosing decision
 - Ad-hoc rules for over-dose control

- Model based

- Account for variability
- Dose response curves
- Flexible and powerful

- Lots of modifications

- Over-dose control
- Bayesian models
- # of parameters
- Black box, complex, costly



Model Assisted Design : Bayesian Optimal Interval Design (BOIN)

- At a dose j , n_j (e.g., =3, 6, 9) patients are treated, and y_j DLTs observed.
- Let the target DLT rate be ϕ , and ϕ_1 be the lowest toxicity rate below which a dose is considered sub-therapeutic, and ϕ_2 the highest toxicity rate above which a dose is considered excessively toxic. Let p_j denote the true toxicity probability of dose level j .
- Let, $H_1 : p_j = \phi$; $H_2 : p_j = \phi_1$; $H_3 : p_j = \phi_2$ and let $\{\pi_{ij} = P(H_i)\}_{i=1}^3$
- Therefore, $\lambda_e = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right) + n_j^{-1} \log\left(\frac{\pi_{2j}}{\pi_{1j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)}$ and $\lambda_d = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right) + n_j^{-1} \log\left(\frac{\pi_{1j}}{\pi_{3j}}\right)}{\log\left(\frac{\phi_2(1-\phi_1)}{\phi(1-\phi_2)}\right)}$
- $\lambda_e = \text{argmax}_{(y_j/n_j)}(P(H_2|n_j, m_j) > P(H_1|n_j, y_j))$ and $\lambda_d = \text{argmin}_{(y_j/n_j)}(P(H_3|n_j, m_j) > P(H_1|n_j, y_j))$.
- When setting $\pi_{1j} = \pi_{2j} = \pi_{3j} = 1/3$, the BOIN design is long-term memory coherent in the sense that the probability of dose escalation (or deescalation) is zero when the observed toxicity rate at the current dose is higher (or lower) than the target toxicity rate ϕ (Theorem 2, Liu and Yuan, 2015).

FDA Fit-for-Purpose BOIN



For FDA's Fit-for-Purpose BOIN (10th December 2021), compare $\frac{y_j}{n_j}$ with intervals

- If $\frac{y_j}{n_j} \leq \lambda_e$, Escalate
- If $\frac{y_j}{n_j} > \lambda_d$, Deescalate
- If $\lambda_e < \frac{y_j}{n_j} \leq \lambda_d$, Stay at the same dose level.

* DLT rate =
$$\frac{\text{Total number of patients who experienced DLT at the current dose}}{\text{Total number of evaluable patients treated at the current dose}}$$

The Sotorasib (Lumakras) Trial

Sotorasib (Lumakras) for NSCLC

Approved in May 2021 for patients with NSCLCs harboring KRAS p.G12C mutation (based on a phase 2 trial)

The first drug successfully targets KRAS, a historically “undruggable” and yet important cancer biomarker

However, a postmarketing trial is required by FDA to further explore lower doses than the approved one

This is due to lack of sufficient dose exploration in early-phase development (e.g., phase 1 with small sample size; dose selection under MTD-regime)

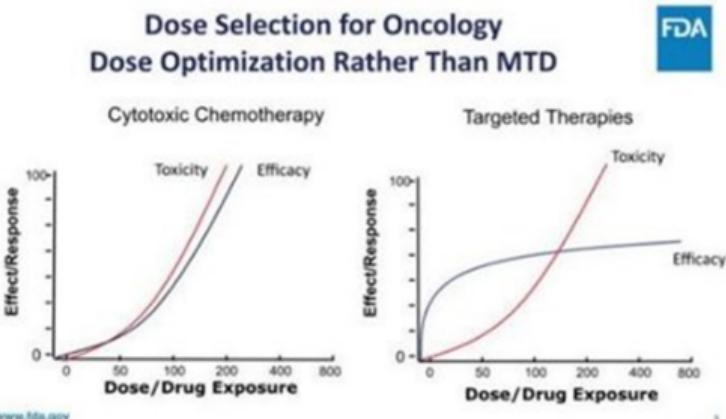
Oncology drugs with post-market dose modification

Examples of Drugs Whose Doses or Schedules Were Modified for Safety or Tolerability after Approval.*			
Small-molecule drugs			
Drug	Initial Dose and Trials	Modified or Added Dose and Trials	Reason for Modified or Added Dose
Ceritinib (Zykadia)	750 mg PO daily fasted (ASCEND-1)	450 mg PO daily with food (ASCEND-8)	Reduce gastrointestinal toxic effects
Dasatinib (Sprycel)	70 mg PO twice daily (CA180013, CA180005, CA180006, and CA180015)	100 mg PO daily (CA180034)	Reduce hematologic toxic effects and fluid retention
Niraparib (Zejula)	300 mg PO daily (NOVA)	200 mg PO daily (PRIMA)	Reduce thrombocytopenia in patients with a lower platelet count or lower body weight
Ponatinib (Iclusig)	45 mg PO daily (PACE)	45 mg PO daily, then 15 mg PO daily once $\leq 1\%$ BCR-ABL is achieved (OPTIC)	Reduce vascular occlusive events
Chemotherapy			
Cabazitaxel (Jevtana)	25 mg/m ² IV every 3 wk (TROPIC)	20 mg/m ² IV every 3 wk (PROSELICA)	Reduce hematologic toxic effects and infections
Antibody-drug conjugates			
Gemtuzumab ozogamicin (Mylotarg)	9 mg/m ² IV on days 1 and 15 (Study 201, Study 202, and Study 203)	3 mg/m ² IV on days 1, 4, and 7 (Mylofrance-1)	Reduce veno-occlusive disease and treatment-related mortality

* Adapted from the Food and Drug Administration.² IV denotes intravenous, and PO by mouth.

- All the listed drugs had to **reduce** their dose or schedule due to toxicity

Project Optimus in Oncology



- Landscape is moving away from cytotoxic chemotherapy into targeted therapies.
- Emphasis is now changing from solely identifying the MTD towards also determining an optimized dose level based on all available clinical data and the dose and exposure-response relationship.
- FDA's Project Optimus aims at finding the dose that balances the efficacy-toxicity profile.
- **Goal:** Educate, innovate, and collaborate with companies, academia, professional societies, international regulatory authorities, and patients to move forward with an unified dose optimization paradigm across oncology.

FDA Project Optimus Initiative for Dose Optimization

Collection and Interpretation of Clinical Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Data

- Integrate PK/PD/PG data with clinical data (safety and efficacy)
- Investigate effects in multiple populations when possible

Trial Designs to Compare Multiple Dosages

- Backfill patients on multiple doses before dose comparison
- Randomized dose comparison (adaptively and without considering frequentist error rates as the case for late-phase trials) – Bayesian?

Safety and Tolerability -- Endpoints

- DLT and low grade toxicity should be considered – Toxicity burden
- PRO

Subsequent Indications and Usages

- Different doses for different diseases should be considered

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

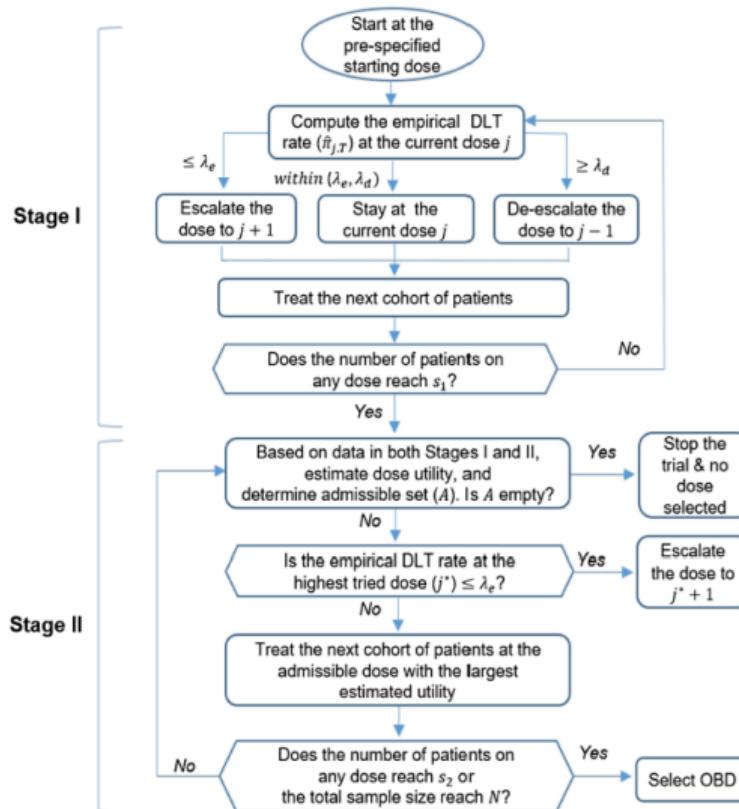
Guidance for Industry

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)

Adaptive Design Methods in Favour of Optimus

- Rule Based Design
 - Jointi3+3 (Lin and Ji, 2020)
 - Bi3+3 (Lie *et. al.*, 2024)
- Model Based Designs
 - EffTox (Thall and Cook, 2004)
 - Backfill CRM (Dehbi, O'Quigley and Iasonos, 2021)
- Model Assisted Designs
 - **U-BOIN** (Zhou *et. al.*, 2019)
 - **BOIN12** (Lin *et. al.*, 2020)
 - BOIN-ET (Takeda *et. al.*, 2018)
 - PRINTE (Lin and Ji, 2021)
 - Comb-BOIN12 (Lu *et. al.*, 2024)

The U-BOIN Design

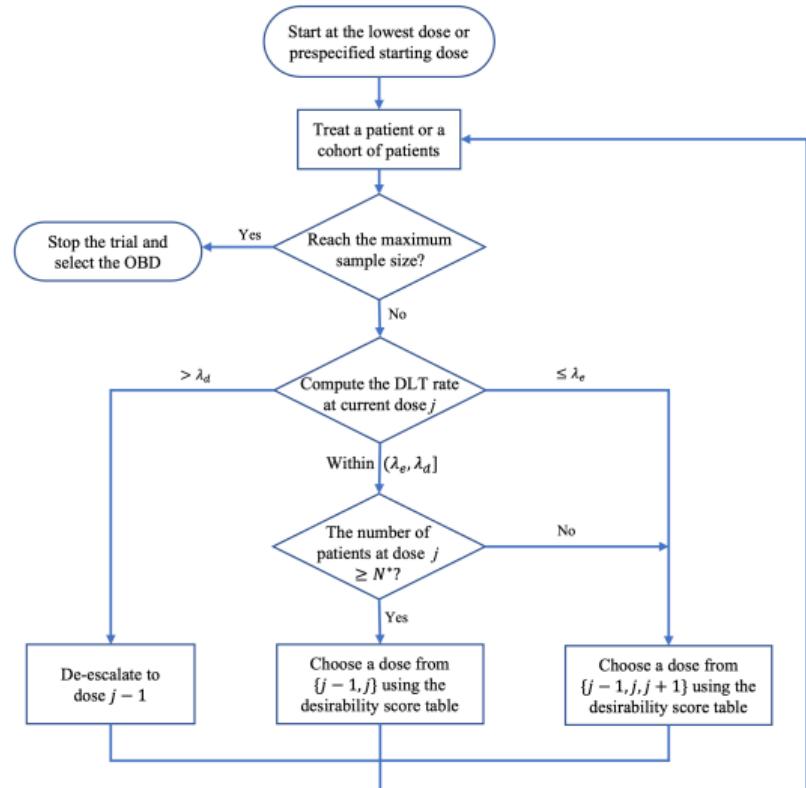


Boundaries	Target DLT rate (ϕ_T)					
	0.15	0.20	0.25	0.30	0.35	0.40
λ_e (escalation)	0.118	0.157	0.197	0.236	0.276	0.316
λ_d (de-escalation)	0.179	0.238	0.298	0.358	0.419	0.480

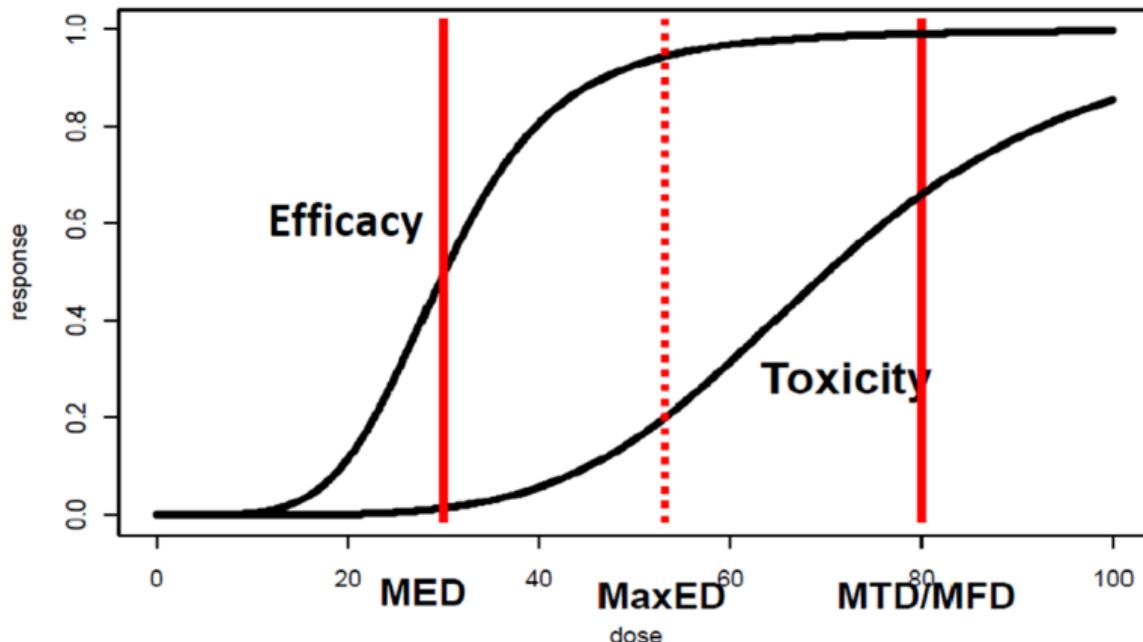
Toxicity	Efficacy	
	Yes	No
No	$u_1 = 100$	$u_2 = 40$
Yes	$u_3 = 60$	$u_4 = 0$

The BOIN12 Design

- Patients are adaptively assigned to the most desirable dose (OBD).
- $\lambda_e = 0.197$ and $\lambda_d = 0.298$. $N^* = 6$, $\phi = 0.25$, $\phi_T = 0.30$, $\phi_E = 0.35$.
- **Admissible dose** : Let $\hat{p}_j = y_j/n_j$.
 $P[\hat{p}_j > \phi_T | \text{data}] < 0.95$ and
 $P[\hat{p}_j > \phi_E | \text{data}] < 0.90$
- Reaching the maximum sample size :
 1. MTD : the dose level that has the isotonically estimated toxicity probability closest to ϕ_T
 2. The final OBD is chosen as the dose level that has the highest estimated utility among the doses that are not higher than the MTD.



Every Drug Has an Appropriate Dose



MED: Minimum Effective Dose

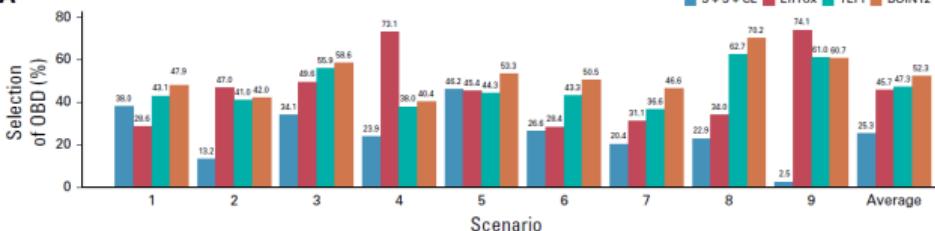
MaxED: Maximum Effective Dose

MTD: Maximum Tolerated Dose

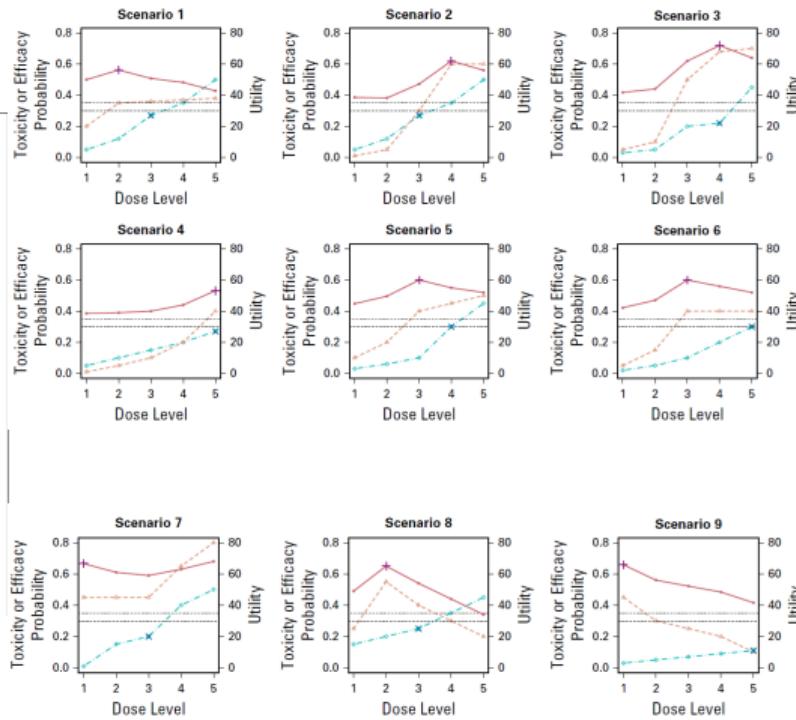
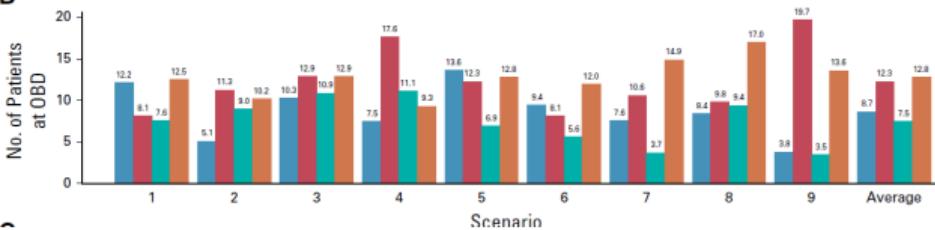
MFD: Maximum Feasible Dose

Simulation Study

A



B



A Real-Life Case Study

- Clark T, Mukherjee A, Lichtlen P, Sweeney J (2024) Bayesian Interval Based Designs for Phase I Dose-Escalation Trials: A Case Study in Oncology. *J Clin Trials.* 14:566
- The primary objective was to estimate MTD, based on the number of dose-limiting toxicities (DLTs) observed at a specific dose level.
- A BOIN design was used and comprised eight planned escalating dose levels; dose levels 1 to 8.



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Research Article

Bayesian Interval Based Designs for Phase I Dose-Escalation Trials: A Case Study in Oncology

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ABSTRACT

The objective of phase I dose-escalation clinical trials has generally been to determine the Maximum Tolerated Dose (MTD). However, with the advent of molecular targeted therapies this approach has changed, as dose limiting toxicities are less frequently observed. For this reason, the concept of Optimal Biological Dose (OBD) has been developed, which considers efficacy and toxicity. Several Bayesian model-assisted designs have been proposed to target the MTD more accurately and/or the OBD compared to traditional rule-based approaches such as the 3+3 design. These include the Bayesian Optimal Interval (BOIN) and the BOIN phase I/II (BOIN12) design. The BOIN design targets the MTD, while the BOIN12, which takes both efficacy and toxicity into account in decisions to escalate/de-escalate the dose, targets the OBD. In this article we use a real-life case study to compare the BOIN and the BOIN12 designs under different scenarios and showcase how each of the designs perform when the compound under investigation has a benign toxicity profile. We argue that both efficacy and toxicity should be taken into consideration when designing early-phase oncology studies.

Keywords: Bayesian adaptive designs; Dose escalation; Toxicity-efficacy trade-off; Optimal biologic dose; Phase I trials

A Real-Life Case Study (Continued..)

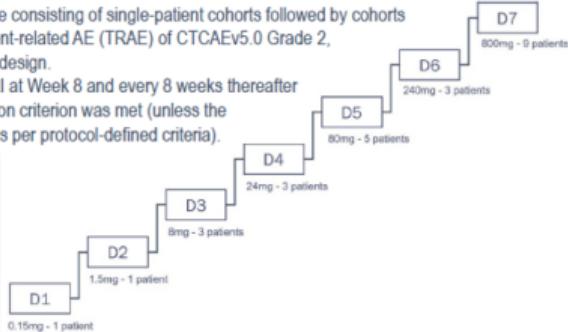
Dose escalation trial design

Treatment:

- Dose escalation started with an accelerated phase consisting of single-patient cohorts followed by cohorts of n≥3 patients upon occurrence of a first treatment-related AE (TRAE) of CTCAEv5.0 Grade 2, as guided by a Bayesian Optimal Interval (BOIN) design.
- Efficacy was assessed by on-treatment CT or MRI at Week 8 and every 8 weeks thereafter until disease progression or another discontinuation criterion was met (unless the investigator elected to treat beyond progression as per protocol-defined criteria).

Inclusion criteria

- ✓ 18 years of age or above
- ✓ Patients with metastatic/ unresectable solid tumors confirmed by pathology/ fresh biopsy, with progressing disease since last therapy and for whom there is no available standard of care
- ✓ Measurable disease according to RECIST 1.1
- ✓ ECOG PS 0–1
- ✓ Adequate renal, liver, and hematologic function



Objectives:

- The primary objectives of this dose escalation part of the trial were the characterization of the safety and tolerability profile of NM21-1480, the determination of its maximum tolerated dose (MTD) and the determination of dose level(s) for further evaluation of pharmacodynamics and clinical activity in expansion cohorts.
- The secondary objectives were the establishment of a pharmacokinetic profile and the evaluation of immunogenicity.
- Exploratory objectives comprised the assessment of anti-tumoral activity of NM21-1480, based on RECIST 1.1., the characterization of the pharmacodynamic profile of the compound, and the exploration of potential biomarkers of clinical response.

Methods:

- This is a first-in-human, multicenter, open-label, phase 1/2a trial of NM21-1480 in advanced solid tumors (NCT04442126) (Figure 2).
- The trial consists of two consecutive parts: dose escalation (phase 1 – Part A) and expansion (phase 2 – Part B).
- The dose-limiting toxicity (DLT) monitoring period was 28 days, comprising two full dosing intervals.

- A newly available pharmacodynamic (PD) data suggested that efficacy (DCR) may not increase monotonically with dose and that PD activity might plateau due to the affinity-balanced design of the molecule.
- At high concentrations the target engagers for the drug may become saturated resulting in “insulating effects” that restrict drug activity.

A Real-Life Case Study (Continued..)

- Scenarios

Dose level/ Scenario	1	2	3	4	5	6	7	8	Dose level/ Efficacy Scenario	1	2	3	4	5	6	7	8
S1	0.10	0.30	0.45	0.48	0.51	0.54	0.56	0.58	EFF S1	0.05	0.10	0.20	0.30	0.40	0.35	0.30	0.20
S2	0.04	0.06	0.11	0.16	0.29	0.47	0.55	0.60	EFF S2	0.05	0.20	0.30	0.35	0.40	0.45	0.48	0.50
S3	0.03	0.06	0.10	0.15	0.30	0.46	0.68	0.80	EFF S3	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40
S4	0.01	0.03	0.06	0.09	0.11	0.30	0.45	0.60									
S5	0.02	0.03	0.05	0.06	0.07	0.08	0.09	0.10									

- BOIN

TABLE 2 Sample Size Probabilities.

Sample Size/ DLT Scenario	6	9	12	15	18	21	24	27
DLT S1	0.04	0.06	0.12	0.19	0.30	0.29	0.04	0.06
DLT S2	<0.01	<0.01	0.02	0.04	0.06	0.88	<0.001	<0.001
DLT S3	<0.001	<0.01	0.01	0.03	0.07	0.88	<0.001	<0.001
DLT S4	<0.001	<0.001	<0.01	<0.01	0.02	0.96	<0.001	<0.001
DLT S5	<0.001	<0.001	0.03	0.01	0.01	0.98	<0.001	<0.001

Dose level/ DLT Scenario	1	2	3	4	5	6	7	8
DLT S1	0.14	0.65	0.17	0.03	<0.01	<0.001	<0.001	<0.001
DLT S2	<0.001	0.01	0.06	0.24	0.48	0.18	0.03	<0.001
DLT S3	<0.001	<0.001	0.05	0.25	0.49	0.19	<0.01	<0.001
DLT S4	<0.001	<0.001	<0.01	0.03	0.23	0.50	0.20	0.02
DLT S5	<0.001	<0.001	<0.01	<0.01	0.03	0.11	0.27	0.56

Sample Size/ Efficacy Scenario	3	6	9	12	15	18	21	24	27
EFF S1	<0.001	<0.01	<0.01	0.02	0.02	0.03	0.04	0.04	0.85
EFF S2	<0.001	<0.001	<0.01	0.02	0.02	0.02	0.02	0.02	0.89
EFF S3	<0.001	<0.001	<0.01	0.02	0.02	0.03	0.04	0.04	0.84

Dose level/ Efficacy Scenario	Early stop	1	2	3	4	5	6	7	8
EFF S1	0.18	0.38	0.28	0.11	0.04	0.1	<0.01	<0.001	<0.001
EFF S2	0.13	0.28	0.44	0.10	0.03	0.01	<0.01	<0.001	<0.001
EFF S3	0.18	0.39	0.27	0.10	0.03	0.02	<0.01	<0.01	<0.001
BOIN	0.99	0.14	0.65	0.17	0.03	<0.01	<0.001	<0.001	0.0

A Real-Life Case Study (Continued..)

One patient in the 80mg cohort died due to rapid disease progression.

Toxicity profile was extremely benign so the early stopping rule of a maximum of 12 patients exposed at any dose level was not met.

Table: Maximum Tolerated Dose (MTD) selection smoothed DLT rate is closest to the target DLT rate.

Dose Level	Number of Patients	Patients with DLTs	Posterior DLT Estimate	95% Credible Interval	Posterior Toxicity > 0.3
0.15 mg	1	0	0.01	(0.00 , 0.13)	0.03
1.5 mg	1	0	0.01	(0.00 , 0.13)	0.03
8 mg	3	0	0.01	(0.00 , 0.13)	0.03
24 mg	3	0	0.01	(0.00 , 0.13)	0.03
80 mg	5	1	0.01	(0.00 , 0.13)	0.09
240 mg	3	0	0.01	(0.00 , 0.13)	0.09
800 mg	9	0	0.01	(0.00 , 0.13)	0.09

The OBD was determined to be DL4 (24mg).

Table: Summary of Clinical Study Results

Dose Level/ Probabilities	DL1 0.15 mg	DL2 1.5 mg	DL3 8 mg	DL4 24 mg	DL5 80 mg	DL6 240 mg	DL7 800 mg
Pr(Toxicity=0,Efficacy=1)	0	0	0.33	1	0.4	1	0.44
Pr(Toxicity=1,Efficacy=1)	0	0	0	0	0	0	0
Pr(Toxicity=0,Efficacy=0)	1	1	0.67	0	0.4	0	0.56
Pr(Toxicity=1,Efficacy=0)	0	0	0	0	0.2	0	0
Pr(Toxicity)	0	0	0	0	0.01	0.01	0.01
Pr(Efficacy)	0	0	0.33	1	0.4	1	0.44
Mean Utility	46.67	46.67	56	80	54.29	80	63.64

Future Direction

- Delayed Efficacy
 - The measure of biological activity is often quickly observable after drug administration and correlated with the clinical response. For example, abundance of CD8+ T cells can predict response to anti-PD-1 therapy
 - Immune activity (Y_I) can be used to predict the likelihood of achieving a clinical response.

$$\text{logit} \left(\frac{\pi_{Ej}}{\gamma} \right) = \beta_0 + \beta_1 Y_I,$$

where π_{Ej} is the probability of efficacy, β_0 and β_1 are regression parameters and $0 < \gamma \leq 1$ is a plateau parameter used to reflect the probability of clinical response which often levels out after the immune activity reaches a certain level.

- Incorporating Patient Heterogeneity
- Identifying the Optimal Basket indication
- Extending the concept beyond oncology

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