



Project Optimus – Winning Strategies

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Table of Contents

- Introduction
- Study designs and development strategies
- Simulation scenarios
- How to execute simulation by using AI technology
- How to select the optimal strategy based on AI output

Introduction

Traditionally, dose selection in Oncology trials was based on identifying the Maximum Tolerated Dose (MTD)

- This approach may lead to selection of a dose that results in excess toxicity without additional gains in efficacy

Introduction

In 2021, the FDA launched Project Optimus, with objective of promoting more thorough assessment of dose response at early stages of Oncology development.

- This development paradigm, while not new in other therapeutic areas, is new to Oncology
- It requires application of more sophisticated approaches, including innovative designs and clinical trial simulations

Introduction

The FDA Guidance on Optimizing the Dosage in Oncology was published in 2024, from which we will cover the following messages:

- Recommended trial design is a randomized, parallel dose-response trial
- Multiple dosages should be compared
- The trial should be sized to allow for sufficient assessment of safety and antitumor activity for each dosage
- The trial does not need to be powered to demonstrate statistical significance
- This should lead to a broader use of Bayesian methods
- Adaptive designs should be considered

Study Designs – Differences from Traditional Approach

Phase 1

- Traditionally 3+3 design has been utilized the most because of its simplicity. This design has very poor operating characteristics
- The focus was on toxicity and identifying the MTD
- Only one dose was selected to proceed into further development.

Study Designs – Differences from Traditional Approach

Phase 1

- Gradually but slowly, with development of tools, other designs received more considerations. Such as:
- Modified Ji Bayesian Design
- CRM (continual reassessment method)
- And more recently , BOIN (Bayesian optimal interval design) has become very popular. It has better operating characteristics than 3+3 and is easier to implement than CRM.

With project Optimus the focus is shifting from MTD to Optimal Biological Dose (OBD). BOIN 1/2 design integrates efficacy and toxicity through utility functions.

Study Designs – Differences from Traditional Approach

Phase 2

- This must be a randomized, controlled trial.
- More than one dose should be taken from Phase 1. This will usually be OBD and another dose.
- The trial does not need to be powered for statistical significance.
- This should lead to increased use of Bayesian methods

Reasons for Increased Use of Bayesian Methods

- Greater flexibility for setting decision criteria
- Probabilistic outputs, which are more interpretable by non-statistical team members
- Updating knowledge and decision criteria as more data are collected
- Ability to incorporate prior information or historical data when appropriate.

Adaptive Designs

A variety of adaptive designs can be applied for dose selection such as:

- Dose pruning
- Adaptive Randomization
- Seamless Phase 2/3

Scenarios

OLD

BOIN + Phase 2/3 with single active arm

NEWER

BOIN 1/2 + Phase 2/3 with single active arm

NEW

BOIN 1/2 + “True” Seamless Phase 2/3

- Phase 2/3 trial “powered” for HR=75% (median survival of 8 vs. 6 months)
 - Need 387 events; number set for all simulations
- Power then calculated for different efficacy scenarios
- For Seamless trial; Dose selected by BOIN 1/2 + dose one level below

Scenarios

OLD & NEWER

BOIN or BOIN 1/2



Phase 2/3 with single active arm; can be a GSD

NEW

BOIN 1/2



Seamless
Phase 3

Interim Analysis

Dropped Dose

Selected Dose

Criteria

- Maximum Toxicity 0.35
- Minimum efficacy 0.25
- Utility split: Efficacy 2/3; Safety 1/3

Toxicity/Efficacy Scenarios

Dose (mg)	Toxicity	ORR 1	OS 1	ORR 2	OS 2
Dose 1	0.10	0.20	7	0.20	7
Dose 2	0.15	0.35	10.5	0.30	9
Dose 4	0.25	0.30	9	0.35	10.5
Dose 8	0.50	0.25	8	0.40	12

BOIN + Single Dose Phase 2/3

Dose (mg)	% times selected	Scenario 1		Scenario 2	
		Phase 3 PoS	Weighted PoS	Phase 3 PoS	Weighted PoS
Dose 1	4%	36%	1.5%	36%	1.5*%
Dose 2	14%	~100%	14%	97%	13.5%
Dose 4	53%	97%	51.5%	~100%	53%
Dose 8	28%	0	0	0	0
Total			67%		68%

BOIN I/II + Single Dose Phase 2/3

Dose (mg)	Scenario 1			Scenario 2		
	% times selected	Phase 3 PoS	Weighted PoS	% times selected	Phase 3 PoS	Weighted PoS
Dose 1	26%	36%	9.5%	30%	36%	9.5%
Dose 2	52%	~100%	52%	38%	97%	37%
Dose 4	20%	97%	19.5%	27%	~100%	27%
Dose 8	2%	0	0	5%	0	0
Total			81%			73.5%

BOIN I/II + Two Doses Phase 2/3

Dose (mg)	Scenario 1			Scenario 2		
	% times selected	Phase 3 PoS	Weighted PoS	% times selected	Phase 3 PoS	Weighted PoS
Dose 1 + 2	78%	95%	75.5%	68%	75%	51%
Dose 2 + 4	20%	95%	17%	27%	95%	25.5%
Dose 4 + 8	2%	65%	1.5%	5%	21%	1%
Total			94%			77.5%

Conclusions from these simulations

- Adding efficacy to decision criteria improves Phase 1 dose selection
- This is particularly true with non-monotonic dose selection
- For the most part, inclusion of efficacy prevented from selecting too high (toxic) dose.
- Sometimes, our selected criteria stopped short of the optimal dose.
 - This can be addressed by more explicit specification of utility criteria
- Seamless design further improves PoS
- While every situation is different, our simple simulations do show improvements with strategies proposed under Project Optimus

Thank You