Paper AS11

Project Optimus – Winning Strategies

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Abstract

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. 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. This paper explains how to utilize Artificial Intelligence (AI) to efficiently select the optimal dose through following steps:

1. Outline study designs and development strategies
2. Specify simulation scenarios
3. Execute simulation by using AI technology
4. Select the optimal strategy based on AI outputs

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.

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.

The FDA Guidance on Optimizing the Dosage in Oncology was published in 2024. In this paper we will focus on the following messages from this guidance:

- 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. However, this design has very poor operating characteristics. Gradually but slowly, with development of tools, other designs received more considerations. Such as:

- Modified Ji Bayesian Design
- CRM (continual reassessment method)
- Lately, BOIN (Bayesian optimal interval design) has become very popular. It has better operating characteristics than 3+3, and is easier to implement than CRM.

The focus of Phase 1 was on toxicity and on identifying the MTD. Only one dose was selected to proceed into further development.

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, and as such searches for the OBD.

Phase 2

According to the Project Optimus Guidance this must be a randomized, controlled trial. More than one dose should proceed from Phase 1 to further development. This will usually be the OBD and another dose. Some additional considerations are that:

- 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

Following are reasons that Project Optimus would require greater use of Bayesan statistics:

- 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 Design

A large variety of adaptive designs can be applied for dose selection as a response to this Guidance. Some of the most obvious choices are:

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

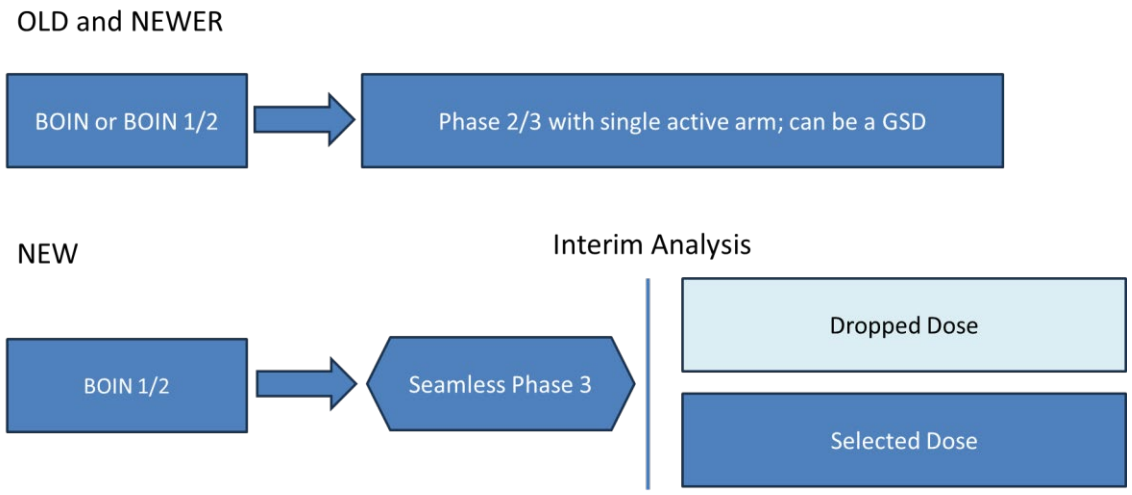
Scenarios

In this presentation three different strategies were compared.

- The OLD, or traditional strategy will have Phase 1 focused on toxicity only. The Phase 1 design will be BOIN. This design will be followed by a Phase 2/3 design with a single active arm.
- The NEWER strategy will have Phase 1 that is simultaneously addressing toxicity and efficacy by applying BOIN 1/2 design. This Phase 1 will be followed by a Phase 2/3 design with a single active arm.
- The NEW strategy will also be applying BOIN 1/2 to address toxicity and efficacy simultaneously. Phase 1 will be followed by a Seamless Phase 2/3 design that will have two active arms.

Of note is that above strategies are relatively straightforward, compared to scenarios that sponsors may have to consider. The reasons for this are (1) it is impossible to address all possible scenarios in a simulation study that is not focusing on a specific program, and (2) we are addressing segments of overall strategy that are most affected by the new Guidance.

Here is the graphical presentation of the three strategies:



Criteria

The following criteria will be applied for dose selection in Phase 1.

- Maximum toxicity is 0.35
- Minimum efficacy measured by the Overall Response Rate (ORR) is 0.25
- The Utility split is Efficacy 2/3 to Safety 1/3. This means that there is twice more weight on efficacy than on safety. The utility needs to be defined for BOIN 1/2, and not for BOIN.
- Toxicity is monotonically increasing with increased dose.
- Two efficacy scenarios are proposed. One with monotonic increase with dose, and other with inverse U-shaped relationship of efficacy with dose.
- Based on these scenarios the best dose will be selected for the OLD, and the NEWER strategy.

- For the NEW strategy, dose selected by BOIN or BOIN 1/2 and dose one level below will be taken to the Phase 2/3

The sample size (in terms of number of events) is selected such that there is 80% power for hazard ratio (HR) of 75%, or median survival of 8 months vs. 6 months. The approximate relationship between the ORR (which is studied in Phase 1) and Overall Survival (which is the primary endpoint for Phase 2/3) was derived from published studies. Using these assumptions 387 events are needed. For simulations all trials, including the seamless Phase 2/3 trials, will be fixed at 387 events, and then probability of success will be calculated. All scenarios are presented in Table 1.

Table1. Toxicity/Efficacy scenarios

Dosage	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

Results

Results are summarized in Tables 2-4 below.

Table 2. BOIN + single dose Phase 2/3

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

Table 3. BOIN I/II + single dose Phase 2/3

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

Table 4. BOIN I/II + two doses Phase 2/3

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

Conclusions

- Adding efficacy to decision criteria improves Phase 1 dose selection
- This is particularly true with non-monotonic dose-response
- 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

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