

Early Phase Oncology design in the age of Project Optimus

William H.H. Reece

Director, Biostatistics

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Introduction



In 2022, the FDA introduced Project Optimus for Dose Selection in Early Phase Oncology studies.



Far-reaching impacts on any program with dose escalation:

Oncology Programs

Non-Oncology Programs



Impacts any program that may eventually include the USA

The immediate reaction

"This adds another step to the development program that adds cost and time and slows us up."

The exciting alternative

"This can be leveraged to speed up every step of the development program, reduce patient numbers, improve patient safety, and increase the chances of early approval."

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Overview

1. **Project Optimus changed everything**

   Escalation, expansion, decision rules, endpoints, etc.

2. **Sponsors must adapt**

   Not an option to ignore it.

3. **How to adapt escalation**

   Find a recommended dose range, not prove the exact dose.

4. **Designing the optimization phase**

   Randomized, flexible, interim-driven dose optimization directly evaluating full risk/benefit profile.

5. **Leveraging optimization for earlier approval**

   Earlier transition to target population, more powerful endpoints, leveraging optimization to demonstrate efficacy. Get the dose right!

Randomized dose optimization can be the information-generating core of the entire program.

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Project Optimus - Introduction

- https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus

- The goal of Project Optimus is to educate, innovate, and collaborate with companies, academia, professional societies, international regulatory authorities, and patients to move forward with a dose-finding and dose optimization paradigm across oncology that emphasizes selection of a dose or doses that maximizes not only the efficacy of a drug but the safety and tolerability as well.

- Specific Goals include:

[…]

  - Develop strategies for dose finding and dose optimization that leverages nonclinical and clinical data in dose selection, including randomized evaluations of a range of doses in trials. An emphasis of such strategies will be placed on performing these studies as early as possible in the development program and as efficiently as possible to bring promising new therapies to patients.

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Project Optimus - Implications

- Key elements:
  - ✓ Recommended Phase 2 Dose (RP2D) cannot be selected using Dose Limiting Toxicities (DLTs) alone.
  - ✓ Dose to be selected based on totality of Safety, PK, PD and Efficacy data.
  - ✓ Randomized dose-optimization phase supports dose selection.

- Practical implications are that:
  - FDA has rejected designs that expand a single dose without a randomized dose optimization phase.
  - FDA has rejected choice of dose for a later study because sponsor did not have randomized evidence.

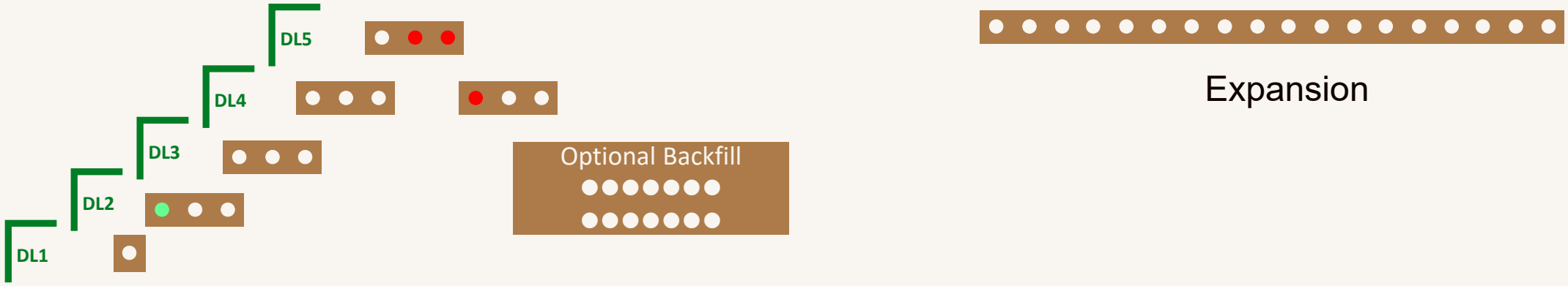
Development programs must adapt
How to adapt without Increasing cost?

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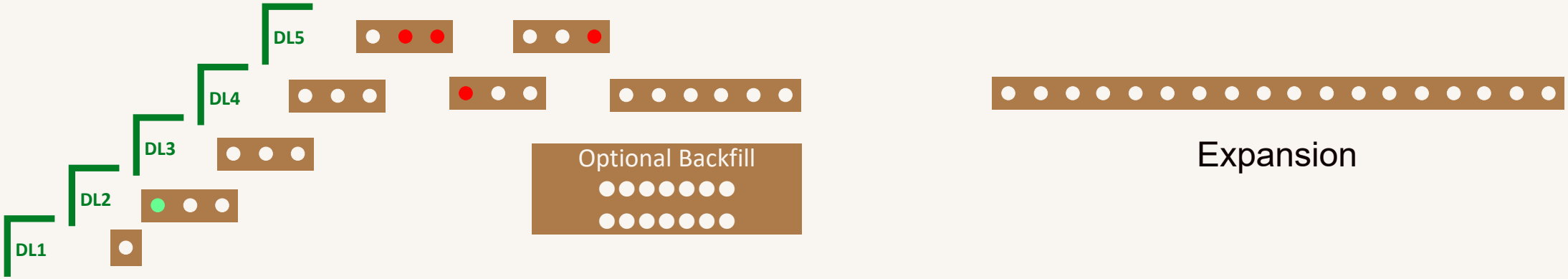
A re-look at escalation

Traditional Escalation identifies the Maximum Tolerated Dose

3+3



BOIN / mTPI-2



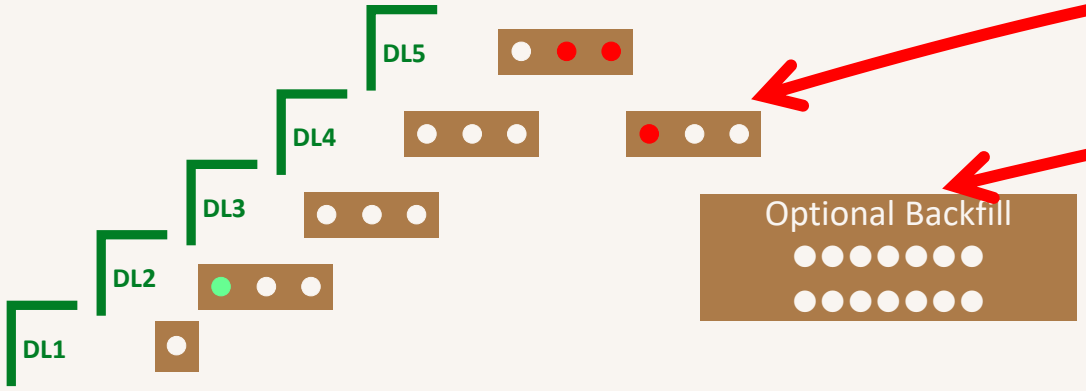
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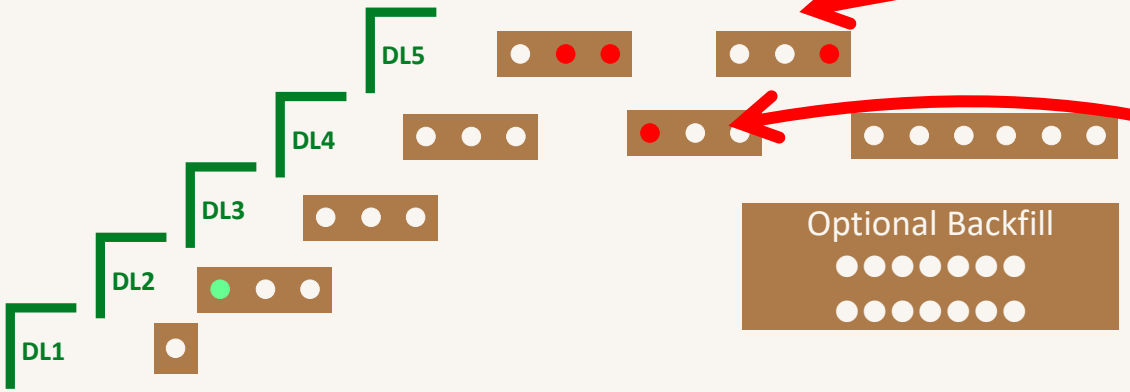
A re-look at escalation

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BOIN / mTPI-2



With Randomized Optimization

- No need to know the MTD before expansion
- Why backfill?
  - Insight into PK/PD/safety/initial view of efficacy?
  - Detail in Optimization phase; in escalation, keep it small
- Why re-test DL5?
  - Does DL4 demonstrate efficacy?
  - Is it better than a lower dose?
- Why confirm DL4?
  - Optimization does many more

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Key changes to Escalation phase

	Traditional	Under Optimus
Primary Objective	Identify the Maximum Tolerated Dose	Identify initial Recommended Dose Range (RDR)
Escalation Rule	3+3/mTPI/BOIN/CRM/BLRM	Stop once top of RDR is known. e.g. once a de-escalation boundary is hit
Primary Endpoint	DLT	DLT
Maximum number of patients per dose level	Up to ~12-15 to confirm the MTD	Up to ~6
Accelerated Titration	Optional	Optional
Intra-patient dose escalation	Optional	Optional
Total number of patients	15-40	10-20

Escalation phase no longer definitive, so can be smaller

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Demystifying the escalation rule

Standard escalation rules target the Maximum Tolerated Dose (MTD)

CRM and BLRM are model-based, and require relatively large numbers of DLT's before the model is informative. **Not suitable when DLT frequency is low**.

3+3, BOIN and mTPI are **very similar** at 3 & 6 pts.

Number of evaluable patients	3			6			9		
Dose Escalation rule	BOIN	3+3	mTPI-2	BOIN	3+3	mTPI-2	BOIN	3+3	mTPI-2
Escalate if # of DLT <=	0	0	0	1	1	1	1	NA	1
Stay if # of DLT =	1*	1	1	NA	NA	2	2	NA	2-4
De-escalate if # of DLT >=	2	2	2	2	2	3	3	NA	5
Eliminate if # of DLT >=	3			4			5	NA	

Personal preference: BOIN
(Rules work for any patient number, can be rolled through into optimization)

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Designing the Dose-Optimization phase

THERE ARE 2 LIKELY PATHS TO MARKET:

1. **Accelerated Approval** with non-comparative analysis.
   - Primary endpoint: Overall Response Rate (ORR) + Duration of Response (DOR)
   - Overall Survival (OS) and Progression Free Survival not acceptable without comparator arm.
   - Potentially achievable in an early phase study if ORR is exceptional and unequivocal

2. **Full Approval** from randomized Phase III study
   - Comparator is typically Standard of Care
   - Large study, with completely different design.
   - Difficult to seamlessly integrate with early phase study.

PRIMARY ANALYSIS:

- Pooled ORR across all doses

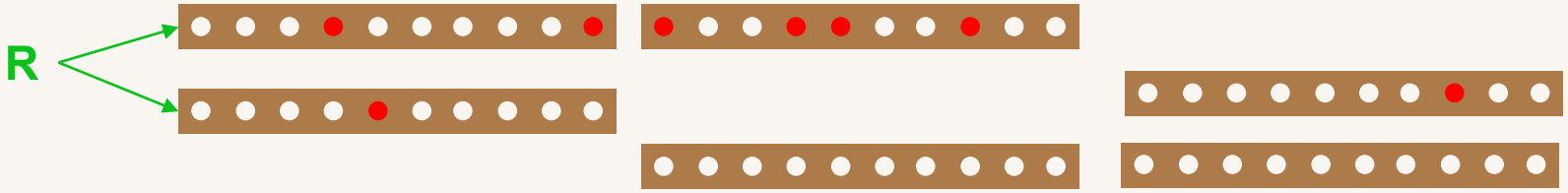
SAMPLE SIZE :

- Minimum of 10-20 pts per dose level.
- Multiple Interim Analyses for futility

Sample size may be further optimized to achieve desired success probabilities

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Designing Optimization/Expansion



Keep it flexible

- You don’t know the recommended dose – it replaces escalation/backfill.
- Continuous re-adjustment - interim Analysis every ~10-20 pts.
- 2 Doses at a time enriches target dose.
- Continue to monitor DLT’s - BOIN De-escalation boundary.
- Allow re-escalation if efficacy and safety support it.
- Open a lower dose if no difference in efficacy.

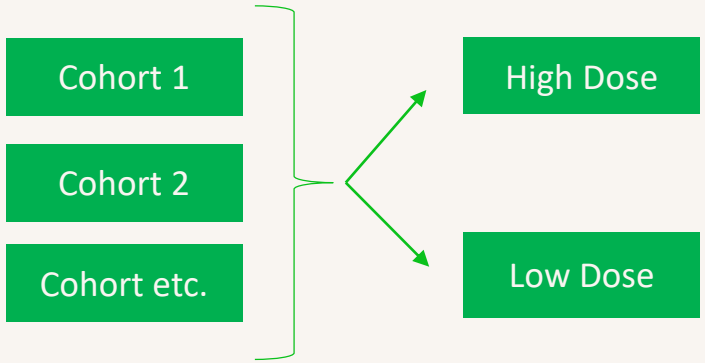
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Basket Trials & Multiple Cohorts

Don’t optimize dose in one cohort and then open the rest



Optimize the dose in parallel across cohorts.

Optimal dose may be different in different disease cohorts.

So you need to randomize all of them anyway.

- Primary:
  - All cohorts in the same model
  - Stratify by cohort
- Investigatory:
  - Cohort by Dose Interaction

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Leveraging Optimization for earlier approval

- **Randomized Dose Optimization opens a new pathway to claim efficacy**
  - If there is a statistically significant difference in efficacy between the two doses, then there is strong evidence that one of the doses has proven efficacy.
  - Effectively means that the alternative dose acts as a randomized control.

- **Implication for dose choice**
  - A wider spread of doses is more likely to show a difference, and may lead to earlier approval.

- **Implications for Statistical Section**
  - Even if not powering the study to detect a difference, formal comparisons between doses should be pre-defined and specified:
  - All efficacy endpoints are valid for the randomized comparison:
    - PFS
    - OS
    - ORR
  - Modelling should be pre-defined and robust:
    - Include randomization stratification factors in the model.
    - Stratify by all timepoints where the dose levels, or comparator arms changed in the randomization

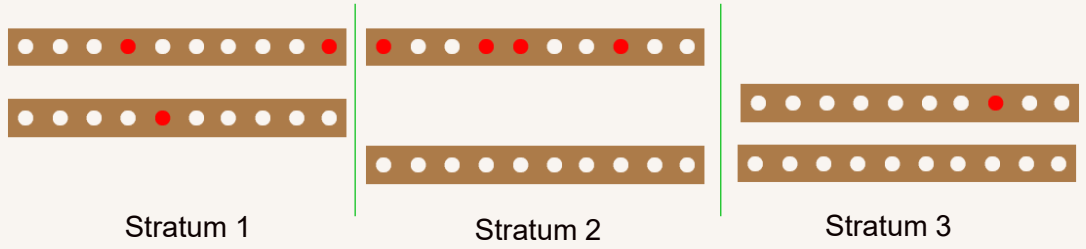
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Increasing power to detect dose differences

Comparisons between doses – simple summaries lose information, so use models

1. **Logistic Regression for ORR**
2. **Proportional Hazards for PFS/OS**

Stratify by change in randomization comparison.



Investigate baseline factors.

- **Demographics**
- **Lab parameters**
- **Disease diagnosis**
- **Biomarkers**
- **Etc.**

Modelling unlocks the power of the randomization

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Getting the Most Out of the Data

- More is possible than just reporting response rates
- Dose/Response analyses should be pro-actively defined in SAP:
  - Discover early whether the dose-response or dose-toxicity profile is predictable.
  - Err on the side of finding false positive predictive models. Confirm in later studies, if need be.
  - Logistic regression/Proportional Hazards variable selection framework allows:
    - Adjustment for baseline covariates to allow for non-randomized nature of comparison
    - Stratification by disease cohort
    - Investigation of whether dosing can be improved by considering height, weight, BMI, renal function.

Pro-active identification of exploratory analyses in the SAP can speed up development

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Summary

- Project Optimus has changed the way Oncology programs run, both within and outside US.

- Escalation and Expansion phases can now be smaller and faster.
  - The old escalation phases are no longer sufficient, and can be smaller.
  - The expansion phase can be randomized, stays the same size, and can now be more powerful.

- The randomized dose optimization phase creates new opportunities:
  - To prove efficacy with fewer patients.
  - To correctly identify the dose.

Unlock the power of Optimus!

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