Utilizing Randomization, Backfill and Expansion Cohorts to Gain Greater Understanding in Phase I trials

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Disclosure Information

Alexia Iasonos

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Intellectual Property Rights

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Professional Services and Activities

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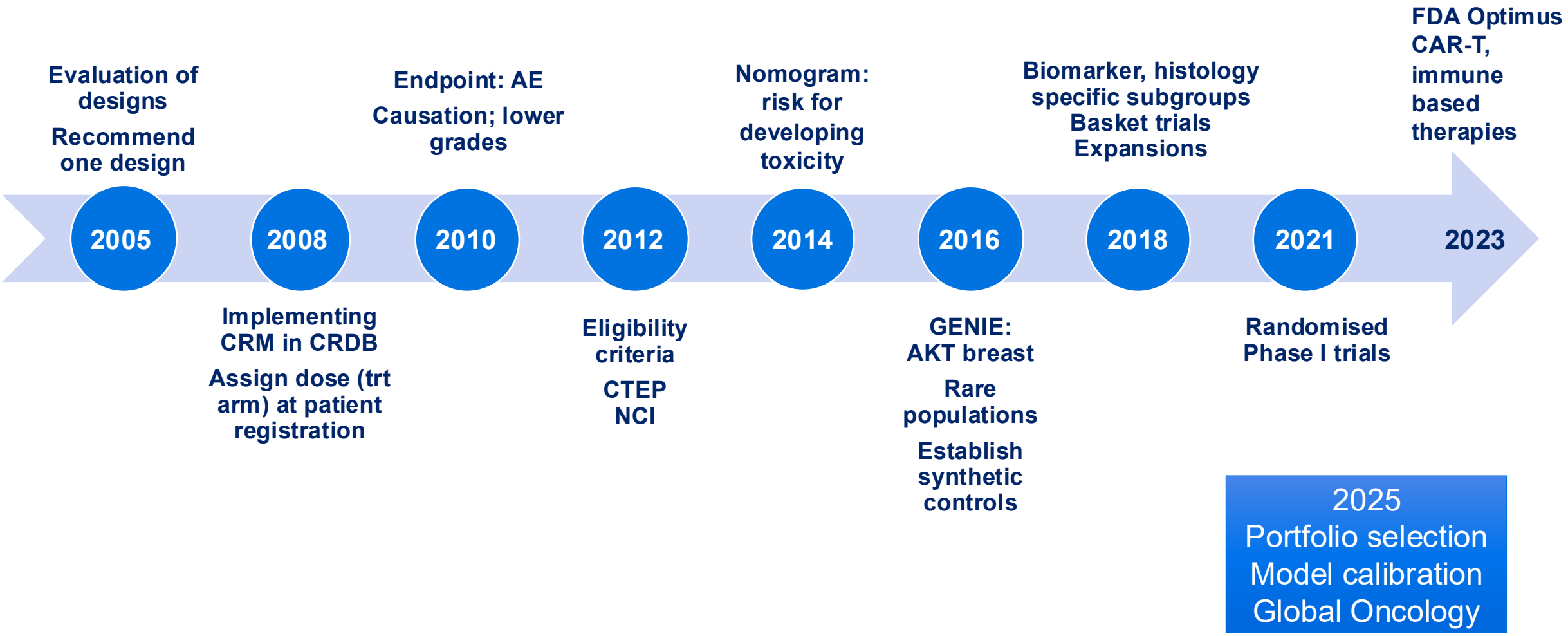
MSK Phase I research program



Acknowledgements

BJC British Journal of Cancer www.nature.com/bjc

REVIEW ARTICLE

Randomised Phase 1 clinical trials in oncology

Alexia Iasonos[1] and John O'Quigley[2]

The aims of Phase 1 trials in oncology have broadened considerably from simply demonstrating that the agent/regimen of interest is well tolerated in a relatively heterogeneous patient population to addressing multiple objectives under the heading of early-phase trials and, if possible, obtaining reliable evidence regarding clinical activity to lead to drug approvals via the Accelerated Approval approach or Breakthrough Therapy designation in cases where the tumours are rare, prognosis is poor or where there might be an unmet therapeutic need. Constructing a Phase 1 design that can address multiple objectives within the context of a single trial is not simple. Randomisation can play an important role, but carrying out such randomisation according to the principles of equipoise is a significant challenge in the Phase 1 setting. If the emerging data are not sufficient to definitively address the aims early on, then a proper design can reduce biases, enhance interpretability, and maximise information so that the Phase 1 data can be more compelling. This article outlines objectives and design considerations that need to be adhered to in order to respect ethical and scientific principles required for research in human subjects in early phase clinical trials.

British Journal of Cancer (2021) 125:920–926; https://doi.org/10.1038/s41416-021-01412-y

Professor John O'Quigley
University College London

Matthieu Clertant, PhD
Sorbonne University, Paris

Hakim Moulay- Dehbi, PhD, UCL

Optimizing dosages for oncology drug products: approaches to select dosages for clinical trials

CLINICAL CANCER RESEARCH

ABOUT ARTICLES FOR AUTHORS ALERTS NEWS CANCER HALLMARKS WEBINAR

Article Contents

Abstract

PERSPECTIVES IN REGULATORY SCIENCE AND POLICY | OCTOBER 02 2025

FDA-AACR Strategies for Optimizing Dosages for Oncology Drug Products: Early Phase Trials Using Innovative Trial Designs and Biomarkers

Olanrewaju O. Okusanya; Gabriela I. Patilea-Vrana; Anthony Sireci; Alexia Iasonos; Brad A. Davidson; Jiang Liu; Stacy S. Shord; Patricia M. LoRusso; Timothy A. Yap

+ Author & Article Information

Clin Cancer Res (2025)

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Abstract

Dosage selection for oncology drugs has traditionally relied on initial dose-finding trials to determine a maximum tolerated dose (MTD), which is then further evaluated in approval-supporting registrational trials. While this approach may have established optimized dosages for cytotoxic chemotherapeutics, many modern oncology drugs developed through this approach have been poorly optimized, requiring additional dosage optimization efforts in the post-market setting. Recent initiatives of the U.S. Food and Drug Administration outline the unsustainability of this approach, instead recommending the identification of a potentially optimized dosage at earlier stages through direct comparison of multiple dosages before marketing application submission. The selection of dosages for further investigation outside of the MTD requires fit-for-purpose techniques that address the specific promises and concerns of the drug under investigation. Although such strategies have been developed, they are currently rarely applied in favor of the MTD

FDA AACR Public workshop 2024

Objectives of early phase trials

1. How do we define a successful trial?
2. What are the ethical constraints?
3. What is the optimal design?

Trial concept

Whom to treat?	Patient population
When to treat?	Eligibility
How are we going to treat?	Treatment

→ Measurable endpoint

→ Design’s objectives

A successful trial

- Scientifically rigorous
- Maximizes information -no information wasted, timely design, efficient, feasible
- Adheres to ethical principles
  - Cannot expose too many patients to futile drugs
  - Cannot under-dose or over-dose

Research or state of the art, best treatment care?

"……. something is either research or standard care; it cannot be both"
(Miller and Rosenstein, NEJM 348: 2003)

Versus

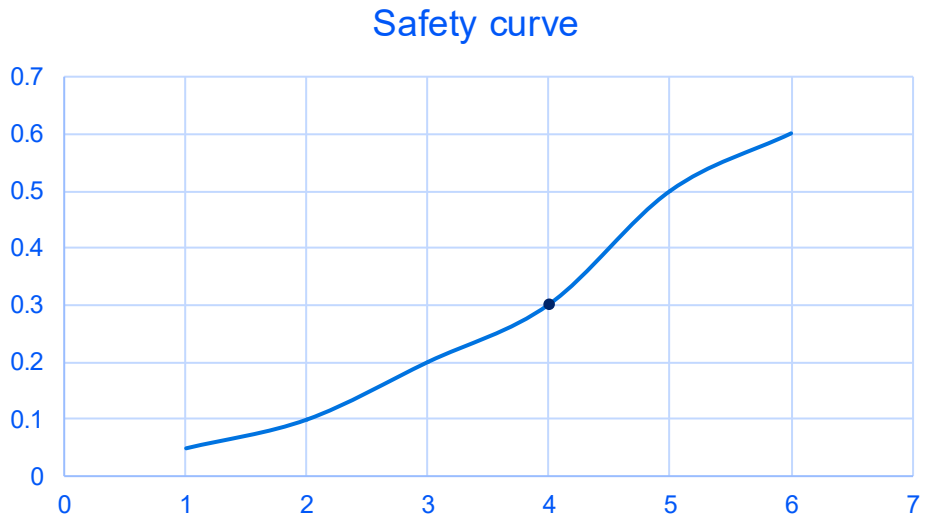
"Enrollment on an investigational study is state-of-the-art care for many patients in oncology today" (ASCO, NCCN, advocacy organizations, etc.)

Much of the treatment-related research we do is performed in a care-delivery context with characteristics of both care and research.

New therapies – new ways of dosing

Chemotherapy

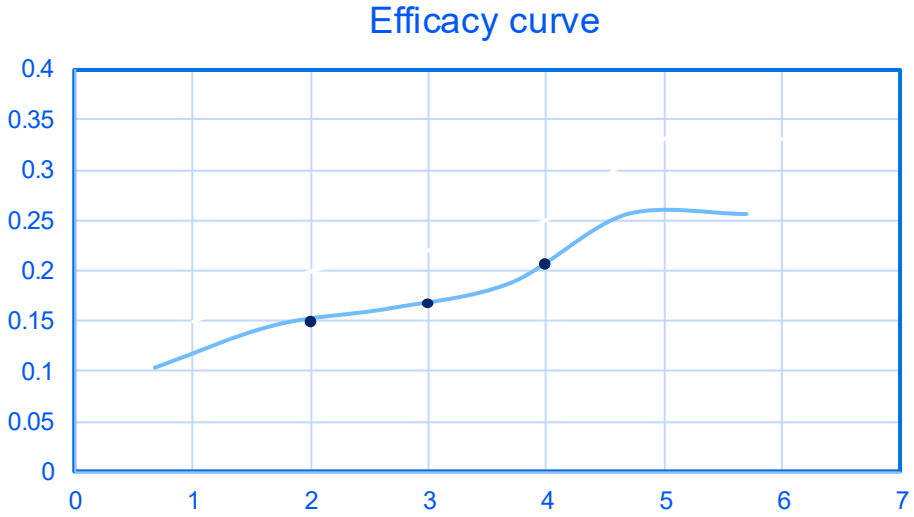
More is better



Dose escalation
Dose elimination
Find a Single dose MTD

New mechanisms of action

Less is more



Dose ranging
Dose exploration
More than 1 dose

Controlled backfill, Hakim Dehbi et al 2022, 2023

Randomized expansion cohort

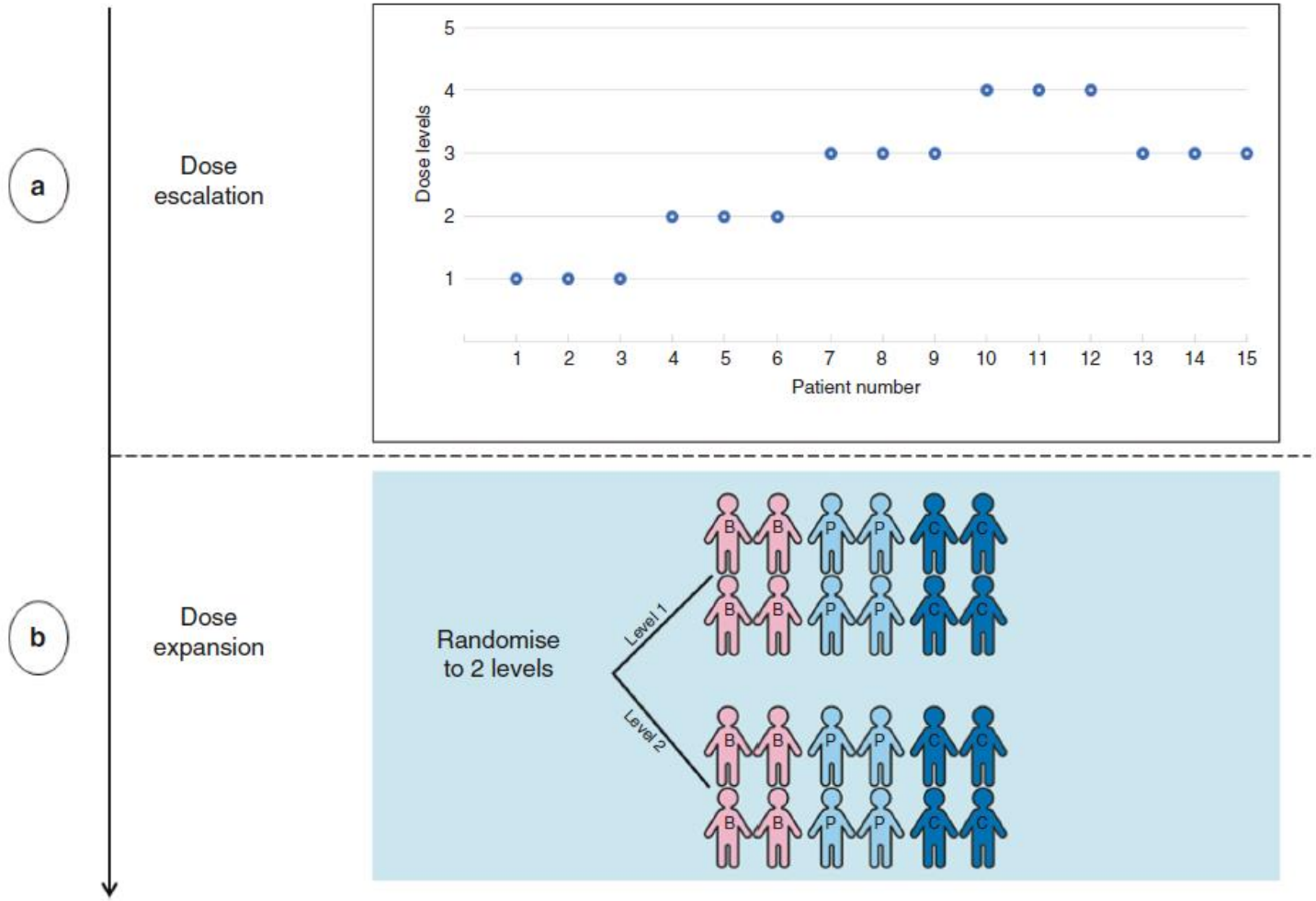


Fig. 1 **Dose escalation (carried out in cohorts of 3 patients) followed sequentially by dose expansion after the maximum-tolerated dose (MTD) has been determined.** Dose expansion randomises subjects equally to two dose levels in molecular- or disease-specific patient populations (denoted by B: breast, P: prostate and C: colon cancer). **a** shows the dose escalation. **b** shows the dose expansion.

- 2-step approach
  - Dose escalation first
  - Dose expansion via randomization afterwards
- Limitation: focus on 2 dose levels chosen in escalation phase/part

Iasonos, A., O'Quigley, J. Randomised Phase 1 clinical trials in oncology. *Br J Cancer* **125,** 920–926 (2021).

Backfill cohorts

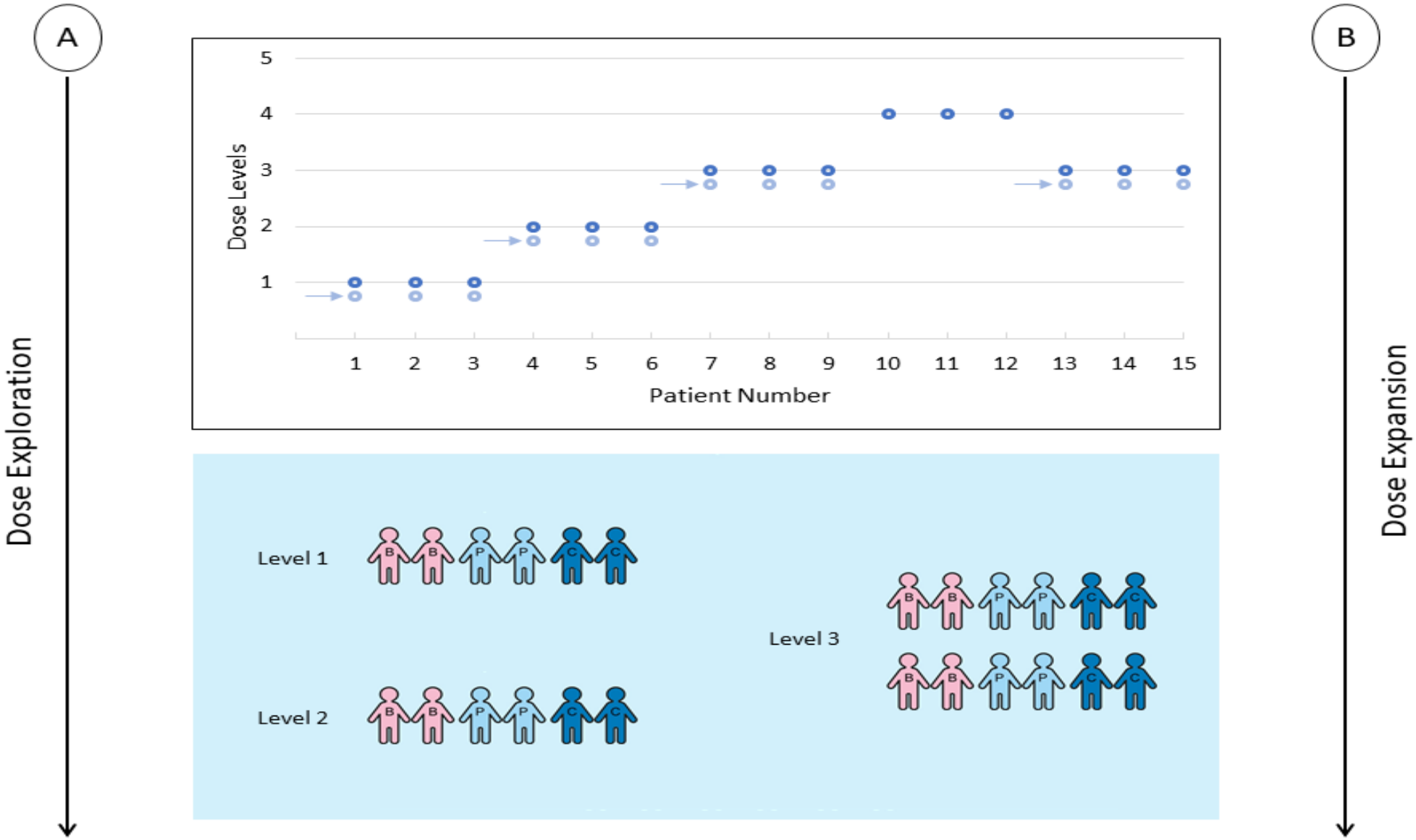


Figure 2. Simultaneous dose exploration

Design 1 Simple dose escalation	Design 2 Dose escalation + dose expansion	Design 3 Dose escalation + dose expansion or backfill **Amplification**
1. Identify the MTD and establish the safety profile in a heterogenous patient population (safety only)	1. Identify the MTD in a heterogenous patient population (dose escalation; safety)	1. Identify the MTD in a heterogenous patient population (dose escalation)
	2. Identify whether the drug shows promising efficacy and in which disease groups (DEC)	2. Identify whether the drug shows promising efficacy and in which disease groups (DEC; efficacy)
	3. Identify the appropriate patient population for drug development (DEC and dose escalation)	3. Assess whether the drug works uniformly or whether there are differences in response within subgroups (disease heterogeneity and drug activity)
		4. Identify patient populations, dose and treatment schedule
		5. Identify which drugs need to be eliminated early because they are ineffective and which drugs to take forward because of promising activity (DEC and dose escalation)

How many patients?

How many dose levels? How many patients per dose level?

Patient heterogeneity:

- Disease (e.g. melanoma, gynecological, breast) – dose escalation
- Dose (3 levels) - backfill in heterogenous groups
- Efficacy: disease specific or marker specific cohorts (dose expansion)

Subgroups become small very fast 18 subgroups times 20 pts = 360;

How do we determine the total sample size given that, per dose level *n* is still underpowered to address the question(s) of interest?

Patient heterogeneity and sample size

The answer is on the number of questions being addressed

Hierarchy in the questions

- Primary
- Secondary
- Exploratory

Collect rigorous data to understand

- why it failed
- where it is working, where it is not going to work

Move the field forward -inform next study

Eliminate systematic biases (randomization)

Role of randomization in phase I trials

Eligibility criteria define the patient population only up to **known risk factors**

To balance the patient population with respect to

- Comorbidities
- Prior treatment
- Advanced disease
- Factors not controlled by eligibility criteria

  - Risk factors that remain unknown
  - Patient population may be different due to these unknown factors
  - At the conclusion of the study, a higher efficacy in one cohort could be
    - a function of the treatment or the differences in patient populations?

Randomize or not

Pros:

- With a randomized design have a concurrent comparison group
- Uniform evaluation criteria - controlled eligibility criteria
- Risk factors (known and unknown) tend to be balanced between treatment groups
- Can be used to evaluate additional questions: e.g. biomarkers, PK/PD

Cons

- Are there sufficient resources?
- What is the anticipated accrual/ duration?
- Does it increase the total sample size?

Stop a futile drug (dose) early or Expand a safe/active drug to more patients

Probabilistic statements in clinical trials

Probabilistic estimates of getting the correct answer

- Phase III setting: getting the right drug (power)
- Phase I setting: getting the right dose or dose levels (or schedule)

Stopping rules decrease the total N

- Savings seem small (3-6 patients), it allows allocating resources elsewhere:
  - End the trial one year earlier or expand another dose level
  - Compare PK/PD in another cohort of 6 patients

Clinical Impact: Many drugs to choose from, what is next?

Dynamic Stopping Rules

1. **Posterior Probability;** Iasonos and O'Quigley (2016)
2. **Tree-based evaluation;** O'Quigley and Reiner (1998)
3. **Allocation;** Goodman et al (1995)

Original Research Article

SMMR
STATISTICAL METHODS IN MEDICAL RESEARCH

Stopping rules for phase I clinical trials with dose expansion cohorts

Sean M Devlin[1], Alexia Iasonos[1], and John O'Quigley[2]

Statistical Methods in Medical Research
1–13

DOI: 10.1177/09622802211064996
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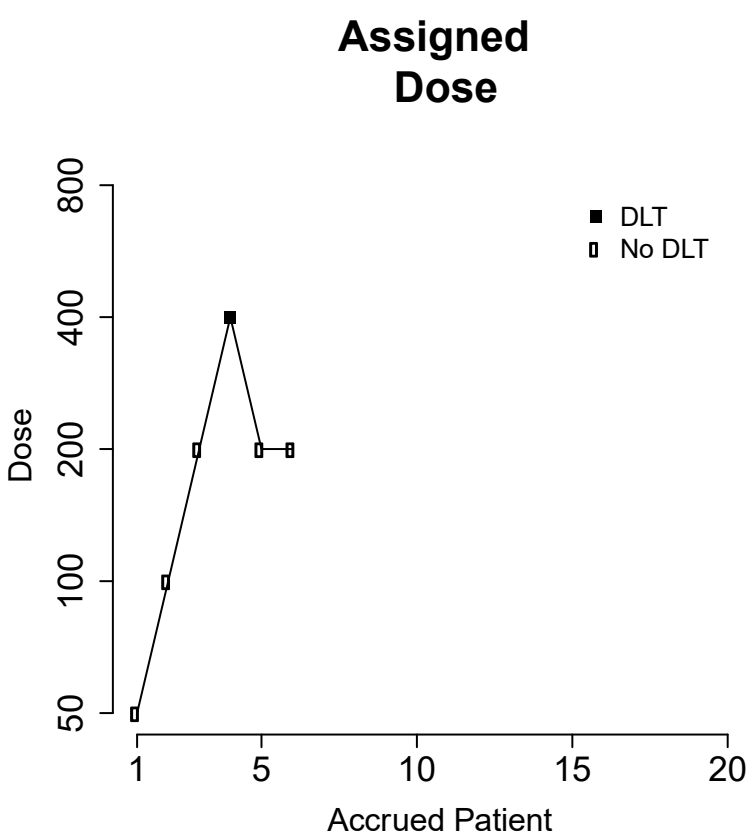
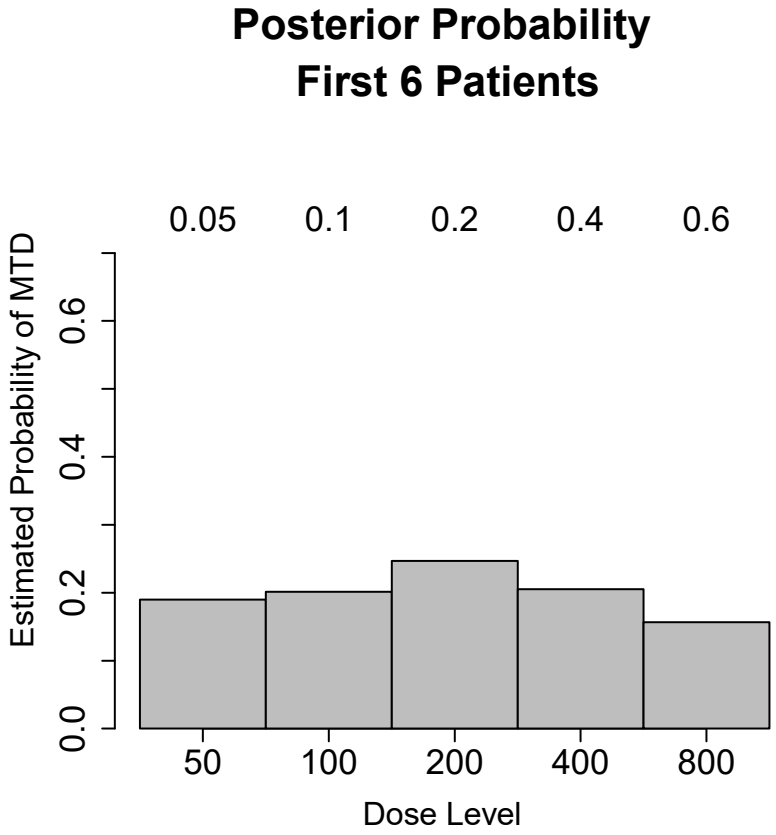
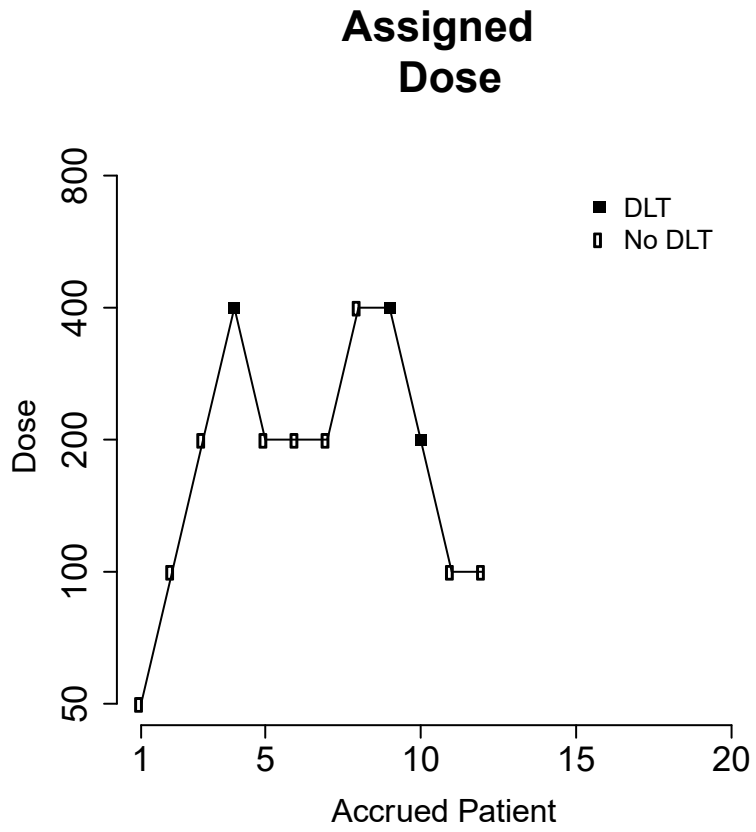
SAGE

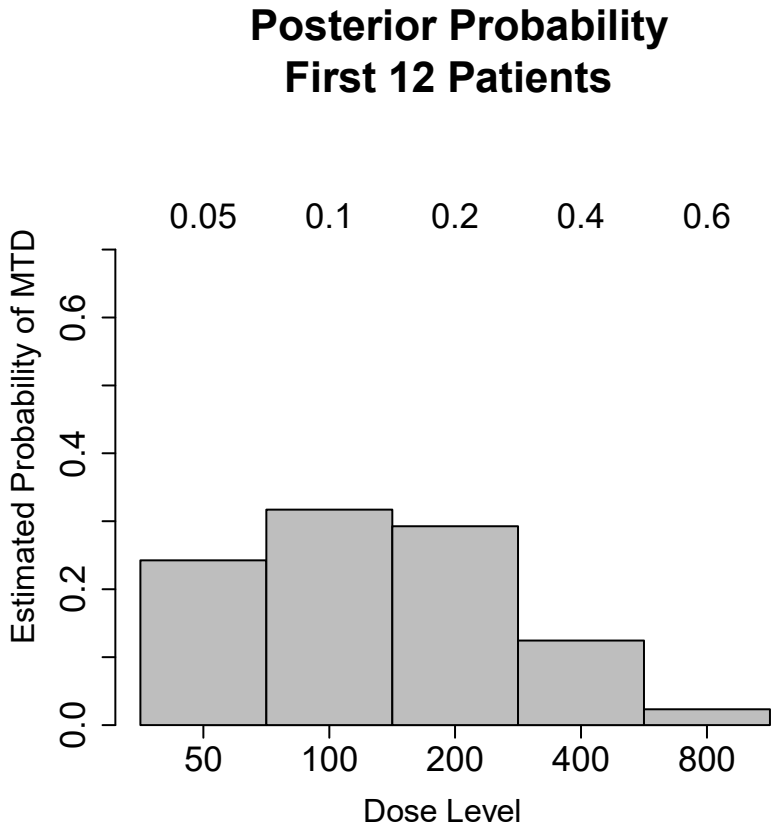
Posterior Probability Rules



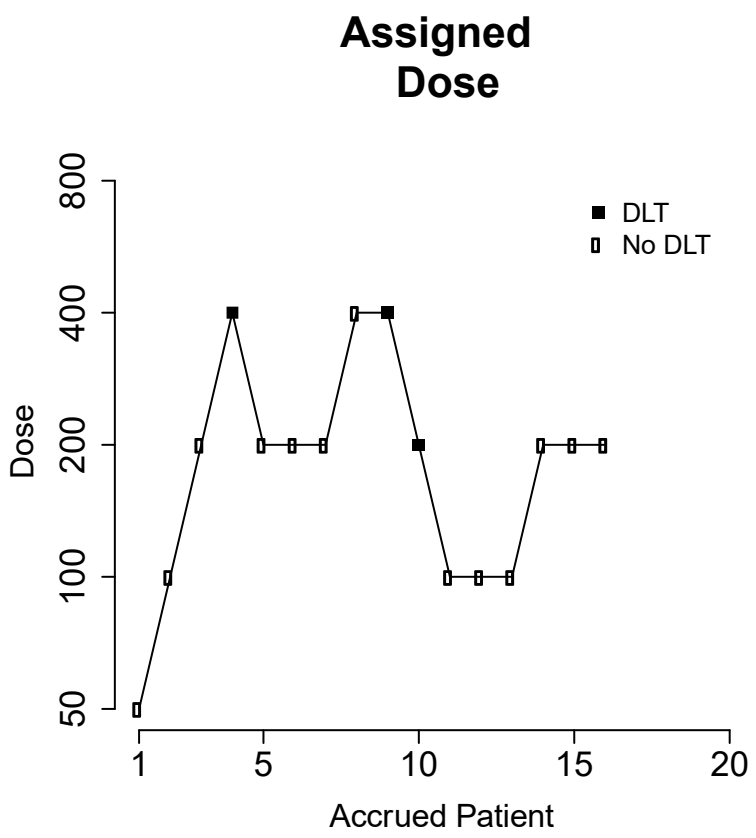


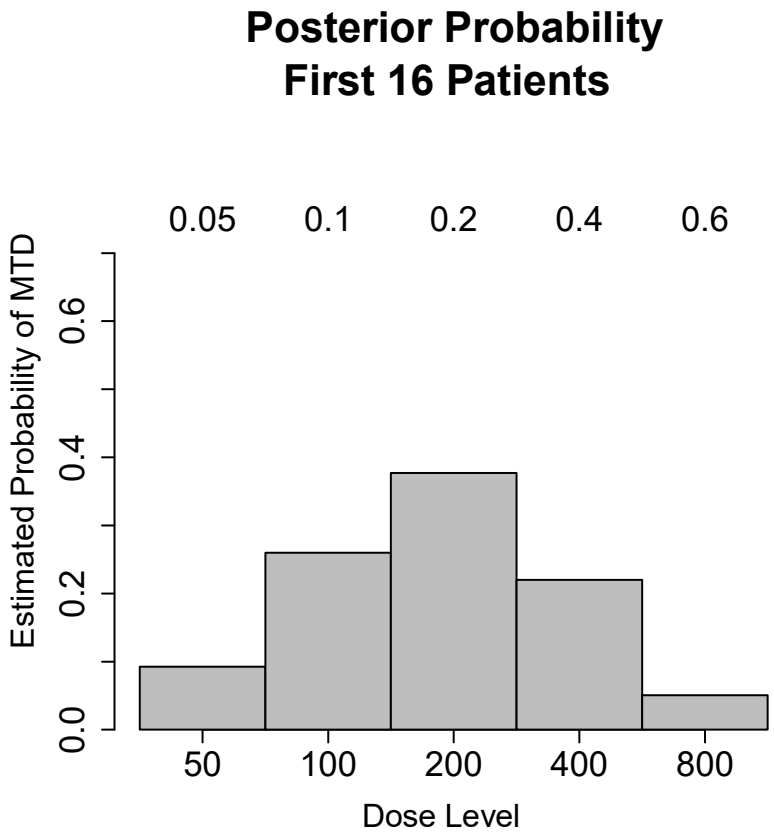
Posterior Probability Rules



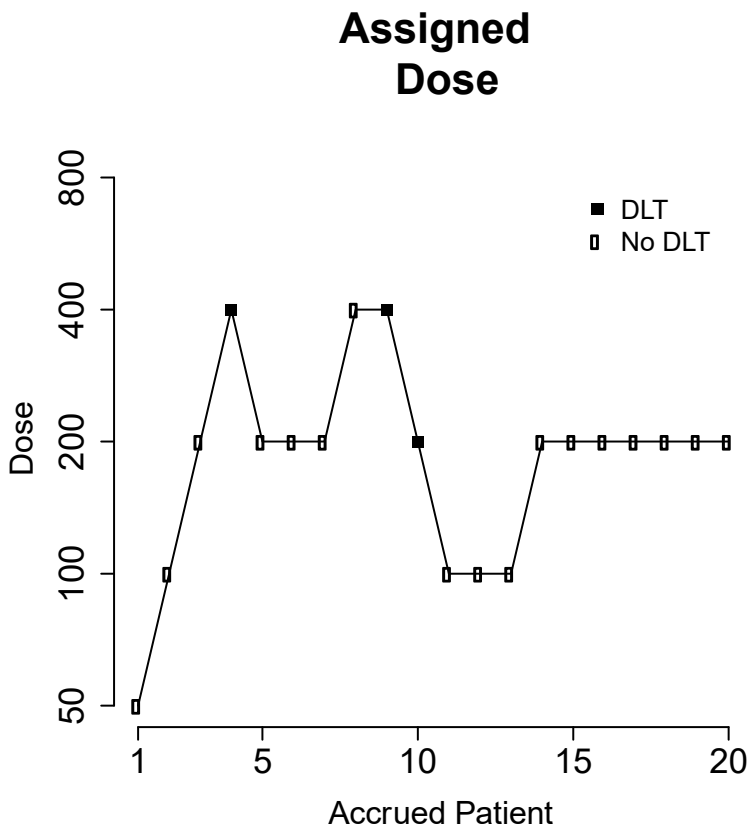


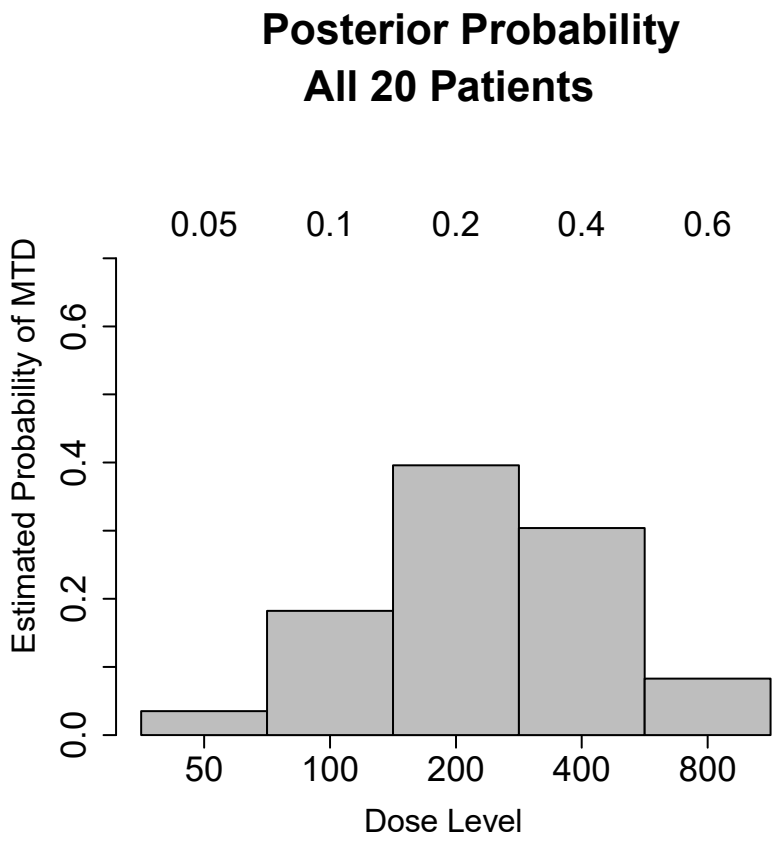
Posterior Probability Rules





Posterior Probability Rules





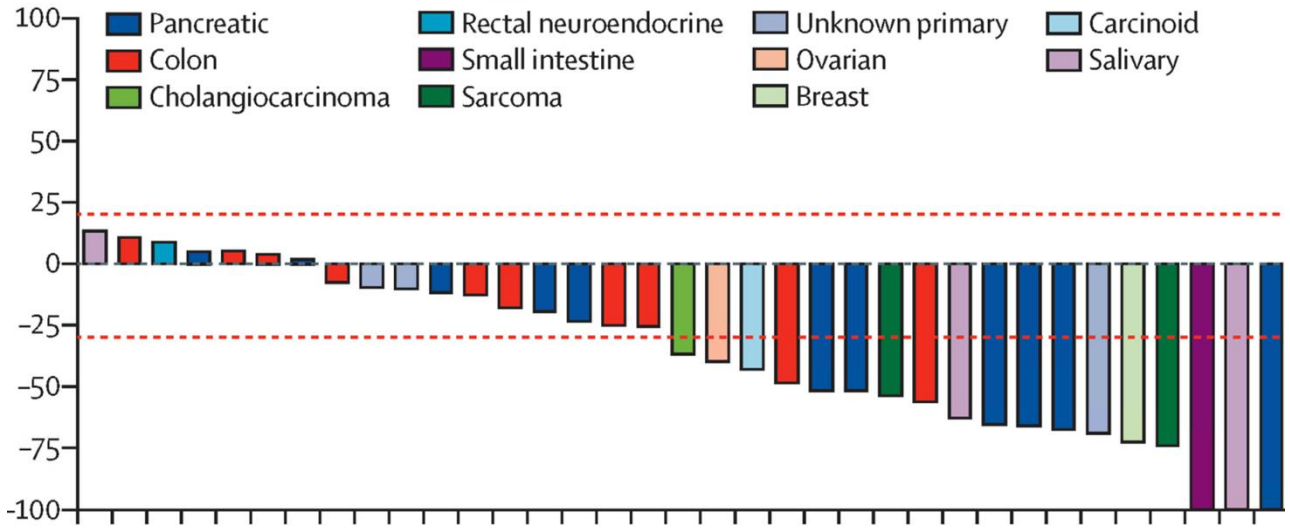
Portfolio selection and regulatory approval

MSK EDD led programs that pave the way for the tumor-agnostic regulatory approval of several drugs

<u>Tumor agnostic drug approvals</u>

Pembrolizumab MSI-H/dMMR 2017
Larotrectinib *NTRK* fusion 2019
(MSK IRB #15-183)
Entrectinib *NTRK* fusion 2019
(MSK IRB #16-026)
Pembrolizumab TMB-H 2020
Dostarlimab dMMR 2021
Dabrafenib Trametinib $BRAF^{V600E}$ 2022
Selpercatinib *RET* fusion 2022
(MSK IRB #17-256)
Repotrectinib *NTRK* fusion 2024
(MSK IRB #17-084)
Trastuzumab deruxtecan HER2+ 2024

Phase 1/2 basket trial of **selpercatinib**
(LIBRETTO-001) for any cancer with a ***RET* fusion**



Multiple studies in the EDD continue to invest in the "basket trial" approach to patient accrual.

Dr Drilon's slide

Concluding remarks

There is no boilerplate design that can address all the clinical objectives

The research questions being addressed, and the hierarchy of importance would determine the optimal design

Each trial has unique elements based on preclinical, clinical and emerging data; patient population and available treatments

What information do we want to get?

How can we maximize the information?

Limited resources for rare cancers:

Cancer Discov. 2024 Jun 3;14(6):909-914. doi: 10.1158/2159-8290.CD-24-0368.

Optimus–Era Dose Finding for Rare Cancers

Yonina R Murciano-Goroff [1], Sean M Devlin [1], Alexia Iasonos [1], Alexander Drilon [1 2]

Concluding remarks

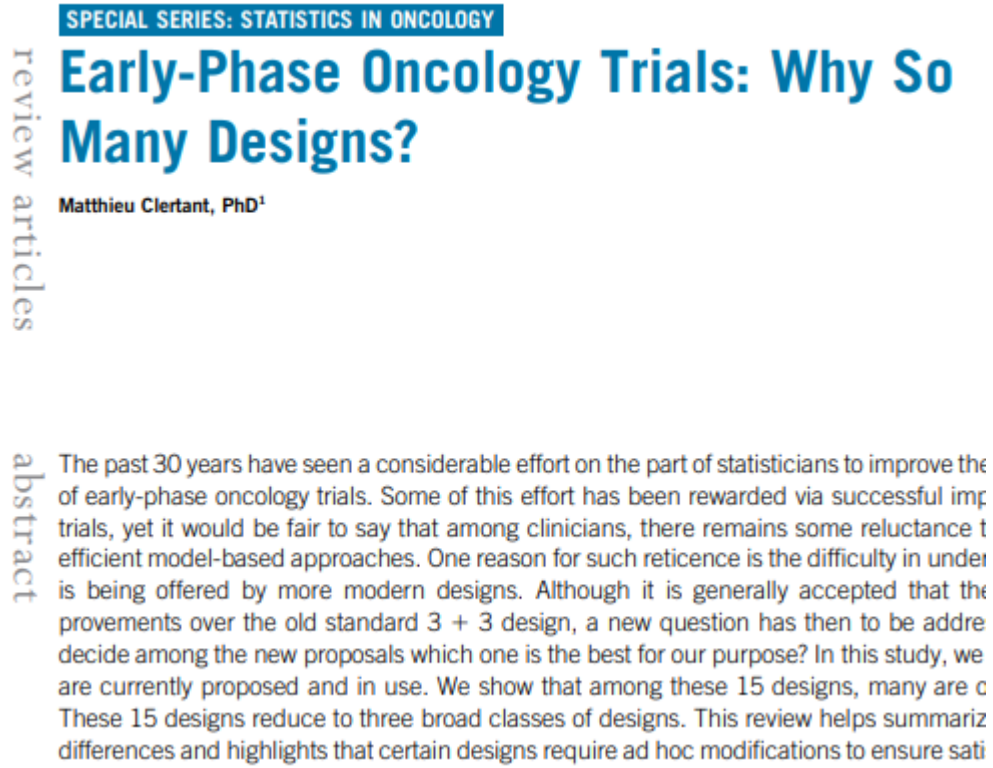
Available and well established, studied tools exist and can be used (or modified) to address challenges posed by new therapies

Randomization is an established tool

Adaptive, model-based designs provide solutions to the current clinical challenges

Sequential designs Probabilistic estimates of the correct answer

Small, dose escalation phase I designs still have an important role



review articles

SPECIAL SERIES: STATISTICS IN ONCOLOGY

Early-Phase Oncology Trials: Why So Many Designs?

Matthieu Clertant, PhD[1]

abstract

The past 30 years have seen a considerable effort on the part of statisticians to improve the
of early-phase oncology trials. Some of this effort has been rewarded via successful imp
trials, yet it would be fair to say that among clinicians, there remains some reluctance t
efficient model-based approaches. One reason for such reticence is the difficulty in under
is being offered by more modern designs. Although it is generally accepted that the
provements over the old standard 3 + 3 design, a new question has then to be addre
decide among the new proposals which one is the best for our purpose? In this study, we
are currently proposed and in use. We show that among these 15 designs, many are c
These 15 designs reduce to three broad classes of designs. This review helps summariz
differences and highlights that certain designs require ad hoc modifications to ensure sati

EXTRA MATERIAL

Ongoing research

Address FDA project OPTIMUS requirements:

less is more

Cancer is a long term, chronic disease
Patients need to maintain QoL, work, deal with financial toxicity
New treatment types (immune, cell, targeted based) – long term use and less toxic

Patient tolerability PRO / QoL;
Patient choice; patient's tolerance – pediatrics application - consortia paper Julia Glade Bender et al 2023
Design calibration – causal inference in Phase I trials
Address Industry protocols (research team)

- Hakim Dehbi, Backfill/amplification, University College of London
- Matthieu Clertant, Sorbonne, (calibration of various designs, heterogeneity)
- John O'Quigley, randomized Phase I trials, expansion / backfill cohorts

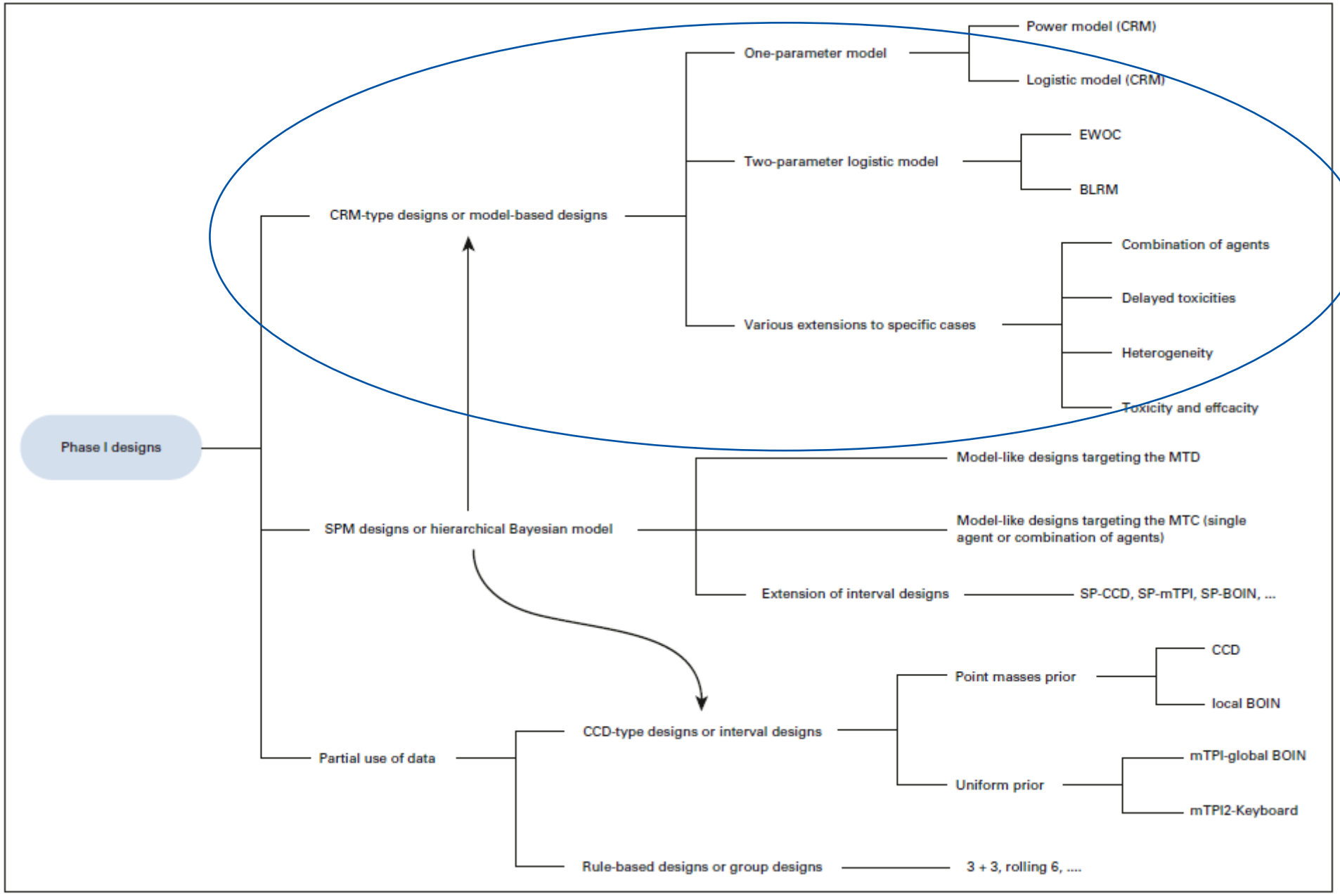
Rare patient population

In rare patient populations, a long-term drug development process that studies the drug in distinct phases of three clinical trials including a comparative follow-up study might not be feasible.

Thus, results from early phase trials, in terms of dose, treatment schedule and patient population, will inform registrational studies.

Although the sequential entry of patients eliminates some biases, randomisation will enhance our chances of avoiding imbalances in patients from specific categories being treated at particular doses or schedules.

Eliminating the chance of patients receiving an ineffective or unsafe dose


Phase I designs
CRM-type designs or model-based designs
One-parameter model
Power model (CRM)
Logistic model (CRM)
Two-parameter logistic model
EWOC
BLRM
Various extensions to specific cases
Combination of agents
Delayed toxicities
Heterogeneity
Toxicity and effcacity
SPM designs or hierarchical Bayesian model
Model-like designs targeting the MTD
Model-like designs targeting the MTC (single agent or combination of agents)
Extension of interval designs
SP-CCD, SP-mTPI, SP-BOIN, ...
Partial use of data
CCD-type designs or interval designs
Point masses prior
CCD
local BOIN
Uniform prior
mTPI-global BOIN
mTPI2-Keyboard
Rule-based designs or group designs
3 + 3, rolling 6, ...
model
Interval