Clinical Trials in Oncology Europe

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Tailored Trial Designs for Precise Outcomes

Optimisation and selection of dose in early phase oncology trials

Adaptive designs

Accelerated titration & backfill strategies

Biomarker integration

Project Optimus

• Project Optimus is FDA Oncology Centre of Excellence (OCE) initiative to reform the dose optimisation and dose selection model in oncology drug development.

• The goal is to move forward with a dose-finding and dose optimization model across oncology that emphasises the selection of doses, that maximise the efficacy of a drug as well as its safety and tolerability.

Two Doses Into Phase II

- Multiple dosages should be compared in a clinical trial designed to assess activity, safety, and tolerability.

- Do not delay dose optimization until after approval – may result in patients being exposed to a poorly tolerated dosage or one without maximal clinical benefit.

- Nonclinical and clinical data provide initial understanding of dose and exposure response relationships for activity, safety, and tolerability.

- A recommended trial design to compare these dosages is a randomized, parallel dose response trial.

Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases - Guidance for Industry (FDA - August 2024)

Direct Feedback from the FDA

Additional Clinical Pharmacology Comments:

1. In general, dose-finding trials include a limited number of patients exposed to an investigational drug for a relatively short duration and frequently do not sufficiently evaluate the safety, tolerability, exposure, and anti-tumor activity over a wide dosage range.
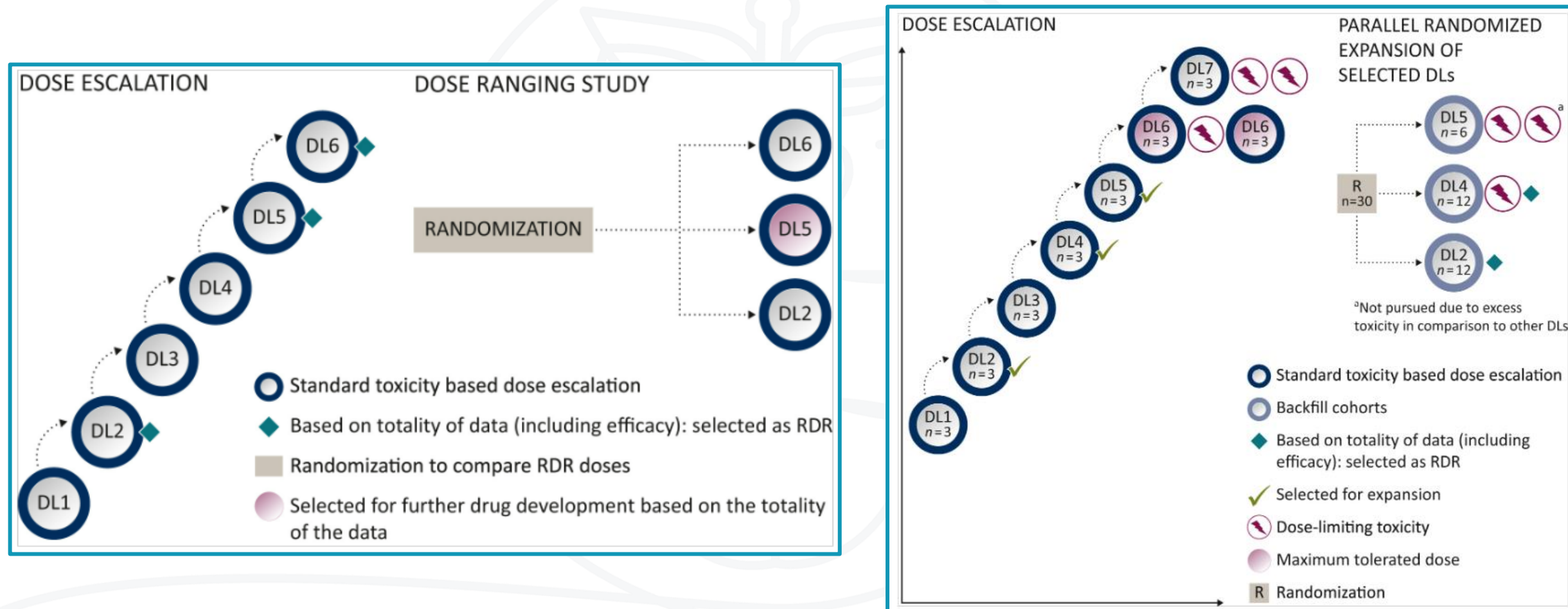
    To select and support the proposed dosage(s) to be investigated in clinical trials, you should plan to investigate multiple dosages early in clinical development and conduct further dosage exploration beyond your initial dose-escalation phase in a sufficient number of patients with adequate follow up. This may include evaluating additional dose cohorts, investigating multiple dosages in an expansion phase, and conducting a randomized, parallel dose-response trial.

    You should evaluate relevant data that provide a preliminary understanding of dose- or exposure-response relationships. Available clinical data should include safety and tolerability, anti-tumor activity or efficacy, pharmacokinetic data, and pharmacodynamic data. You should also consider using modeling and simulation to integrate the relevant data with the model updated as new data become available.

    Inadequately justified dosage(s) could result in a clinical hold if sufficient information at the proposed dosage(s) is NOT available to assess the risks to patients in clinical trials.

- MDICT Taskforce (supported by the European Society of Medical Oncology (ESMO))

Adapted from Seymour et. al. Annals of Oncology Vol 34, Issue 1 2023

Multi-Step Dose Finding

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Stage 1: Gather information – determine active dose levels

Stage 2: Confirm dosage for pivotal efficacy studies

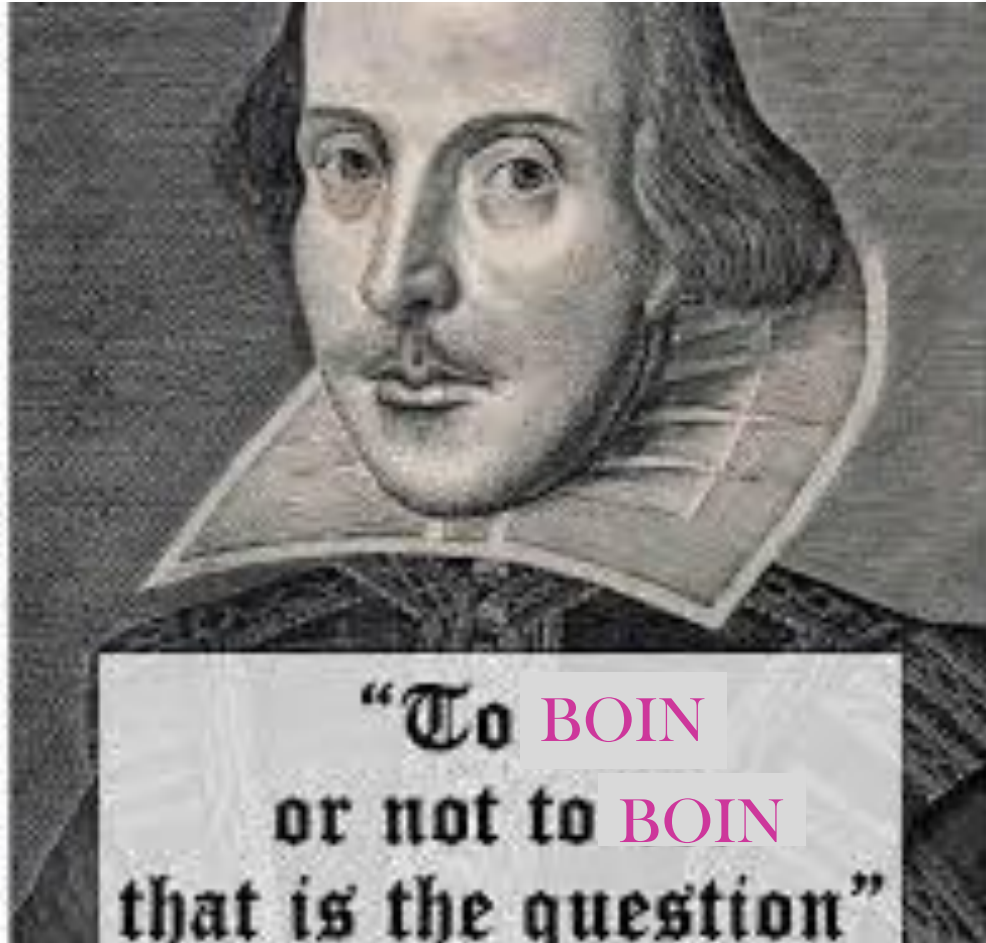|	Escalation (Ia)	Expansion (Ib)	Dose Finding (2a)
Design	BOIN or 3+3	Backfill or expansion cohorts	Randomized 2 dose levels
Population	All comers or tumor-specific	Tumor-specific or subtype	Tumor-specific or subtype
Objectives	Safety PK/PD Activity	Activity Safety PK/PD	Efficacy Safety PK/PD
Dose Informed by	ICH-S9 or MABEL	Nonclinical Escalation Data Modeling	Esc/Exp data Modeling

MABEL = minimum anticipated biological effect level
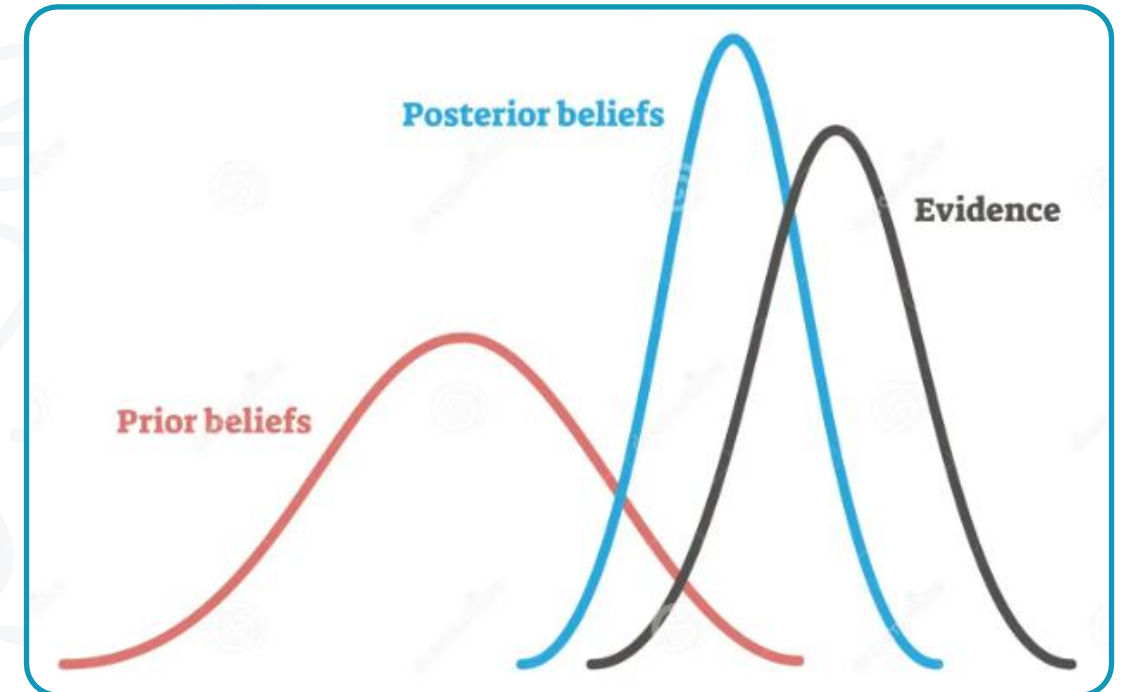
*Adapted from Certara

Domains to Consider for Expansion/Dose Finding

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Domain	Supporting Evidence
Translational	• Is there pharmacological evidence (e.g., target engagement, MOA, outcome-based biomarkers, tumor volume) in the relevant pre-clinical species? • Is the dose-PK relationship established in the non-clinical species (i.e., is the PK dose proportional)? • Are the pharmacological/efficacious target concentrations for patients defined? • Is the dose/exposure-response (i.e., biomarkers, tumor size, etc.) relationship identified from the in vitro cellular systems or the in vivo animal models?
Pharmacokinetics (PK)	• Is the dose-PK relationship well established (i.e., is the PK dose proportional)? • Do the PK characteristics (accumulation, half-life) justify the dosing interval? • Are there any intrinsic or extrinsic factors (e.g., food, body weight, immunogenicity) that would majorly influence PK (i.e., if these warrant dose adjustments in a subset of patients)? • Was the PK variability considered when selecting a dose that would achieve target exposure for most patients?
Efficacy, Pharmacodynamics (PD) and Exposure Response (ER)	• Well-defined biomarkers to support dose-response relationship? • Dose-exposure-response and PK/PD relationship? • Is dose schedule justified based on PK, PK/PD, or Quantitative Systems Pharmacology modeling? • Relevant exposure metrics for efficacy e.g., AUC, Cmax, Receptor Occupancy
Safety and ER	• Is there increased rate of dose interruption or discontinuations with increasing doses/exposures? • Are there dose-exposure-safety relationships? • Will there be overlapping toxicities with concomitant therapies or combination treatments? • If acute/transient toxicities observed, were alternative dosing schedules considered? • Is it a narrow therapeutic window drug but with monitorable toxicities e.g, biomarkers, BP, HR?

Adapted from Friends of Cancer Research – Optimizing Dosing In Oncology Drug Development 2021

Beyond the 3+3

"To BOIN or not to BOIN that is the question"

- Model-based design that assumes a fixed set of variables for the dose–toxicity curve and then based on the incoming trial data, continuously updates the estimate of the curve to guide the dose assignment e.g. Continual Reassessment Method (CRM)

- Model-assisted designs combine the performance of model-based designs with the ease of algorithm-based designs. Dose-escalation and de-escalation rules are set out in the protocol e.g. Bayesian Optimal Interval (BOIN) design
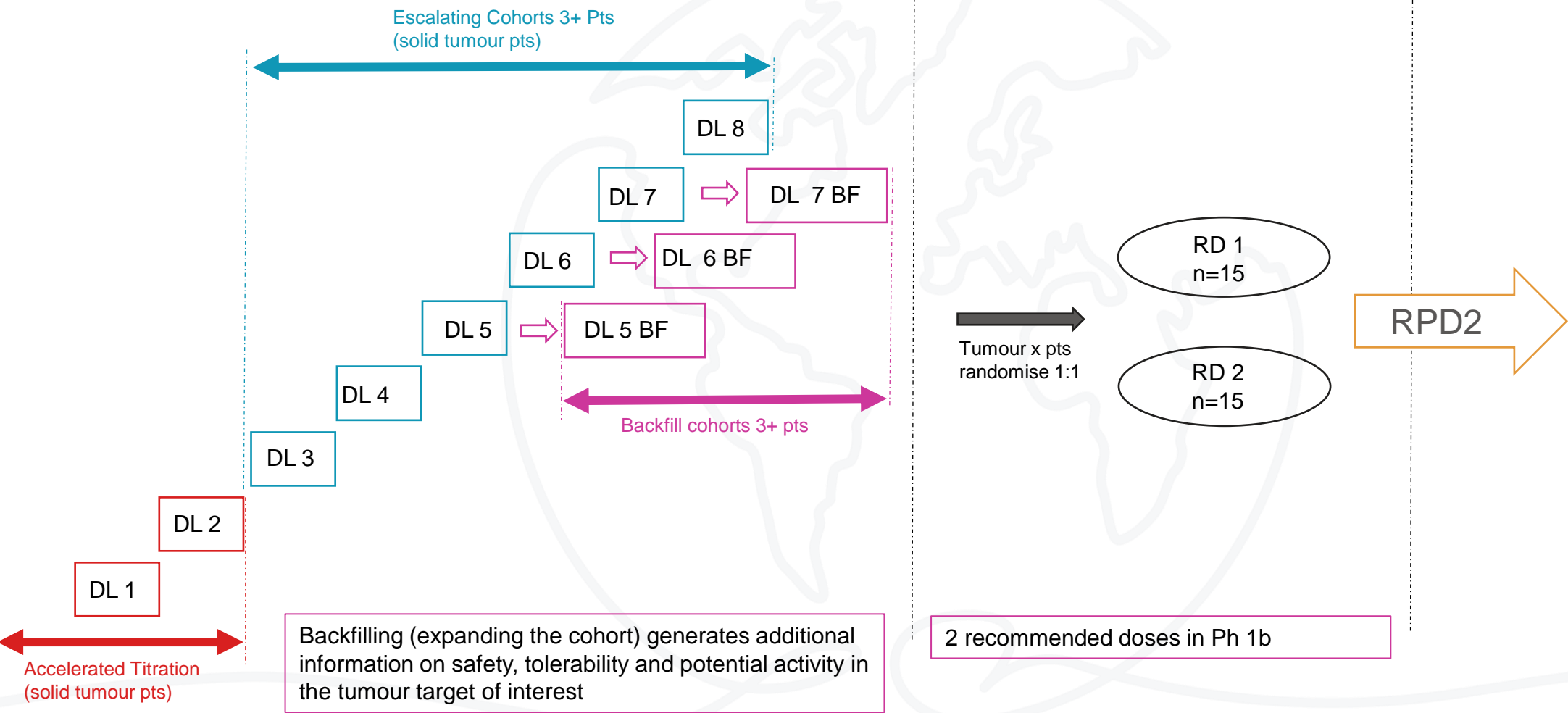
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- Bayesian Logistic Regression Model (BLRM) design - good for identifying MTD but also provide for good balance among studied dosage levels.
  - o Very useful for FIH studies that start off in the patient population of interest.

- Establishment of a therapeutic window based on activity and an acceptable level of toxicity, derived from a characterization of PK exposure and PD metrics is integral.

- Dose-finding studies are part of standard oncology drug development, pre-market, to allow efficacious and tolerable doses to be set for patients upon marketing approval.

Backfill BOIN

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Phase Ia Dose Escalation

Phase Ib Dose Expansion

Phase II

Escalating Cohorts 3+ Pts
(solid tumour pts)

DL 8

DL 7 → DL 7 BF

DL 6 → DL 6 BF

RD 1
n=15

DL 5 → DL 5 BF

Tumour x pts
randomise 1:1

RPD2

DL 4

Backfill cohorts 3+ pts

RD 2
n=15

DL 3

DL 2

DL 1

Accelerated Titration
(solid tumour pts)

Backfilling (expanding the cohort) generates additional information on safety, tolerability and potential activity in the tumour target of interest

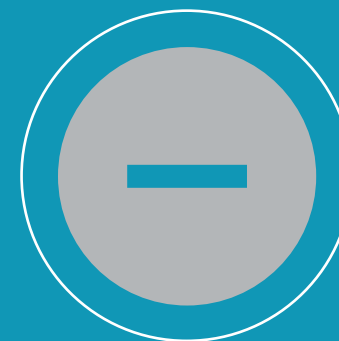2 recommended doses in Ph 1b

Adaptive

- Prospectively planned modification(s) to one or more aspects of the design based on accumulating data from subjects in that trial.

- Often include stopping rules to terminate arms that are not working (futility) which can prevent exposing more people to ineffective or suboptimal treatments.

- Changes are pre-planned (written into the study protocol) and have pre-defined rules, which allow these modifications to roll out during the trial without additional approvals, such as changes to sample size or the number of treatment arms or the allocation ratio of patients to different treatment arms.

- Examples - Platform studies or Seamless trial designs

Pro's And Con's Of Platform Designs

- Show efficacy in several tumor entities
- Adaptive elements for different tumor types
- Drop unsuccessful or unsafe cohorts earlier
- Synergies in protocol writing, regulatory submissions and contracts

- Overall more costly than simple trial
- Investment and effort spread across several cohorts so less power to demonstrate efficacy in the individual arm
- Regulatory and logistic drawbacks can affect and delay all arms
- Between stages, there is less time to fully interpret safety, efficacy and molecular data than between separate sequential trials.

Master Protocol Synergies & Efficiencies

Service Area	Efficiencies & Synergies of Master Protocol Studies

Site and Staff Assignments	• Consistency in operational team members across functional areas assigned to the program including:
	    ○ Focus on sites where multiple indications can enroll with appropriate physicians and study staff
	    ○ CRAs assigned to the same overlapping sites when possible
	    ○ Use of same countries to optimize efficiencies, regulatory filings and overall cost savings

Project Management	• Supply of SOC and combination drugs, cost assessments to identify opportunities to mitigate cost by central sourcing • Ensure project plan and processes consistency for expansions of protocol indications to maximize efficiency • Standardized and centralized metrics, KPIs and reporting • Not 100% site overlap, combine meetings and teleconferences with sites where possible to streamline attendance
Training	• Use consistent protocol specific resources (plans, manuals, templates) and training leveraged across the program • Subprotocol trainings can include all sites at once, with further training provided to individual sites as needed.
Clinical Monitoring	• Waive pre-study visits with abbreviated site participation calls during regular master protocol study site contacts • Conduct initial site initiation visits as sites become activated • Combine IMVs across tumor entities when possible reducing CRA travel time and related expenses • Reduced site management efforts by addressing/discussing program status and concerns in one site contact
Technology	• Reduce time and cost for management and setup of CTMS • Use consistency when building CRFs with EDC • Program level risk assessments study wide identifying trends and/or risk for mitigation

Master Protocol Risks and Limitations

Service Area	Risks and Limitations of Master Protocol Studies
Site and Staff Assignments	• Amount of overlap in sites/investigators to enroll selected indications • On-site staffing turnover rates
Study Execution	• Differential accrual complicates precise estimates of study metrics • Some sites may have great enrollment in one tumour type but poor enrollment in another
Project Management	• Supply of CPI's and combination treatment drugs vary by indication and treatment stage (induction vs. maintenance) • Project planning for expansions with varying patient enrollment • Coordination of overlapping and non-overlapping site meetings, each with unique agenda
Training	• Consistent protocol specific resources (plans, manuals, templates) and training not fungible across indications • Assessments vary by indication - different groups of central readers
Clinical Monitoring	• Other specialists vs. Oncologists at site and CRO • Differing clinical management of cancers
Study Design	• Complexity in creating one broad overarching Master Protocol e.g., current protocol not a master design • A common control arm not feasible, limits data sharing and interpretation across arms. • RP2D may not be justified across indications, notably for combination dose optimization • Hypothesis generation over hypothesis confirmation
Regulatory	• Enabling non-clinical data may differ by indication • Anticipated regulatory comments re: sample size (adjudication of multiple potentially conflicting opinions)

Biomarker Integration

Diagnostic (what type of cancer)

Prognostic (could you develop cancer)

Predictive (will drug *x* impact cancer *y*)

Pharmacodynamic (drug impact on cancer target)

Response (drug effect on cancer/ potential for recurrence)

- Circulating tumour DNA (ctDNA) can identify if a cancer is reacting favorably to a treatment much faster than traditional metrics such as progression-free survival.

Thank you.
Questions?

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