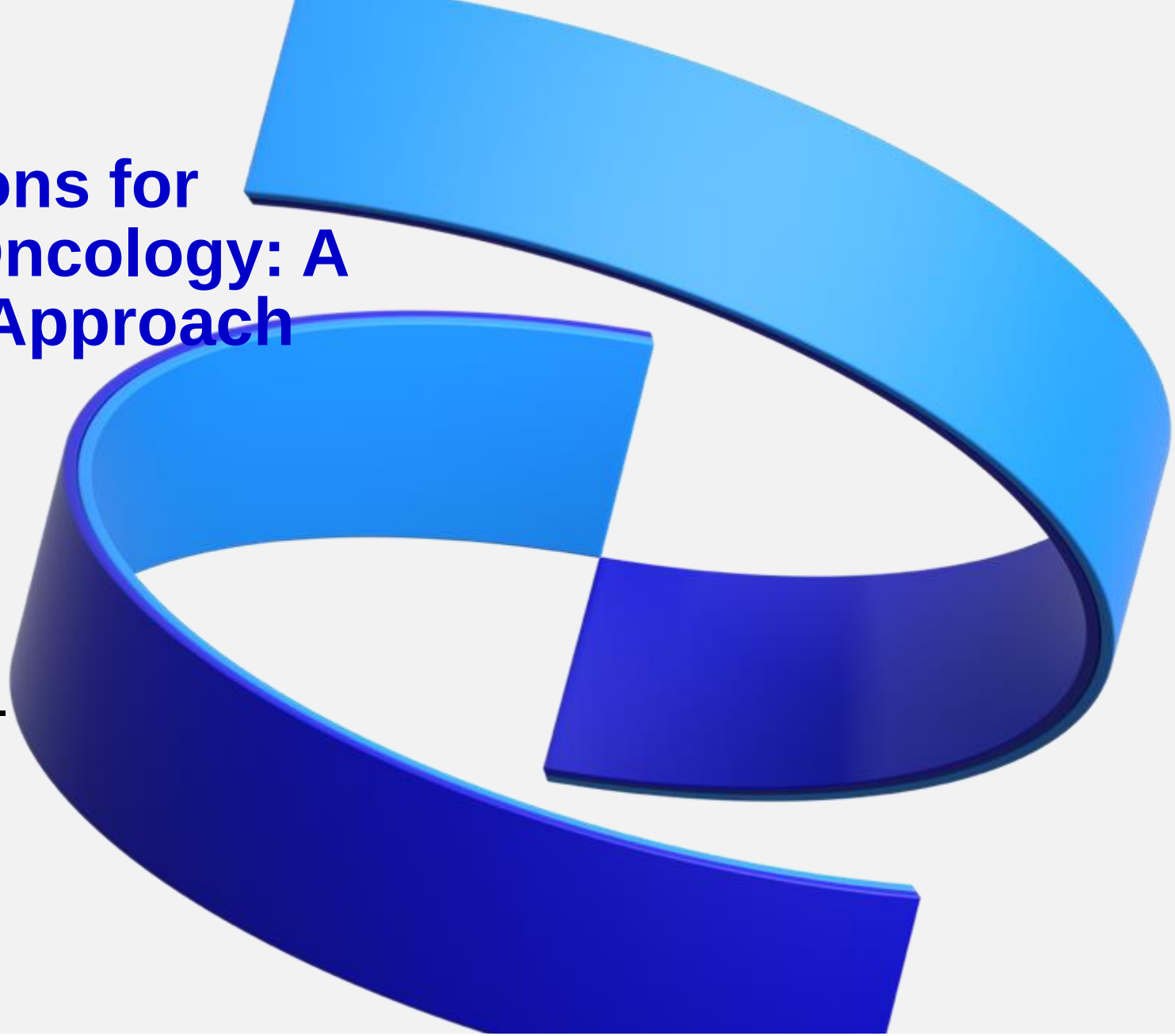
Statistical Considerations for Dose Optimization in Oncology: A Practical and Holistic Approach



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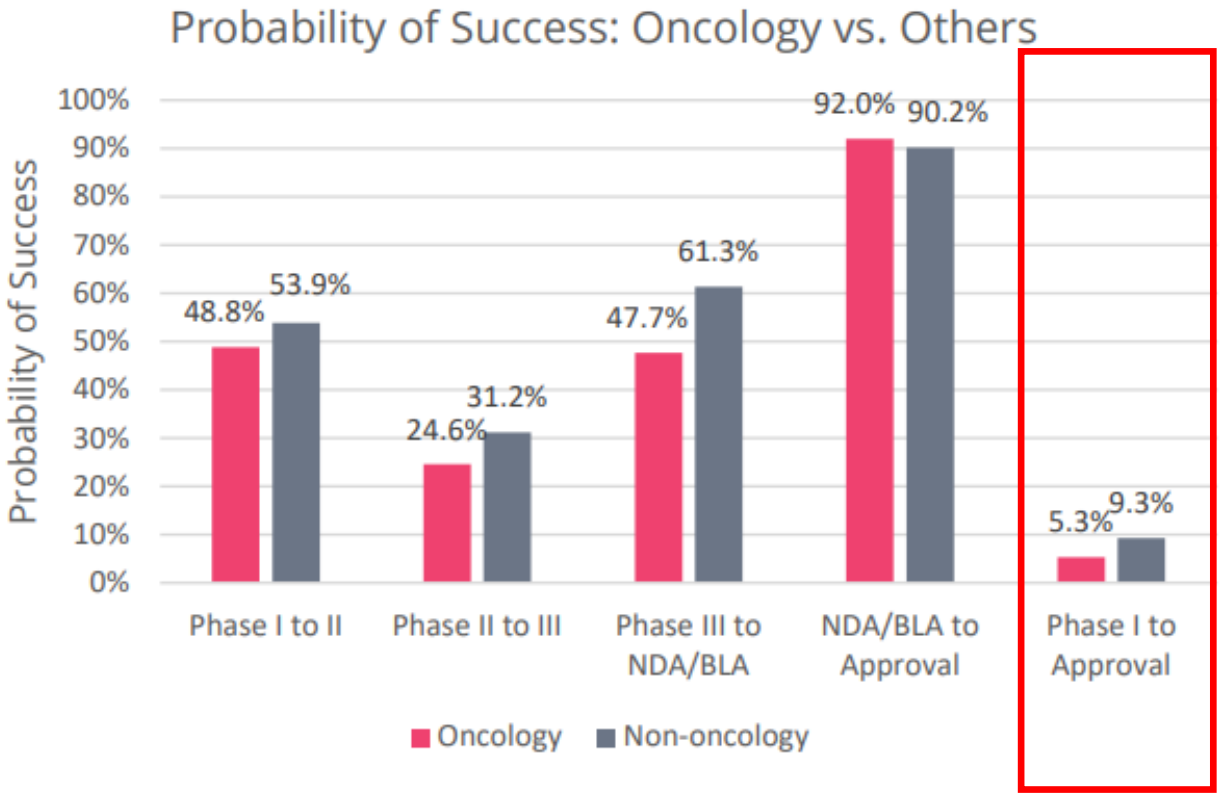
Overall likelihood of approval (LOA) from Phase I is low for Oncology candidates

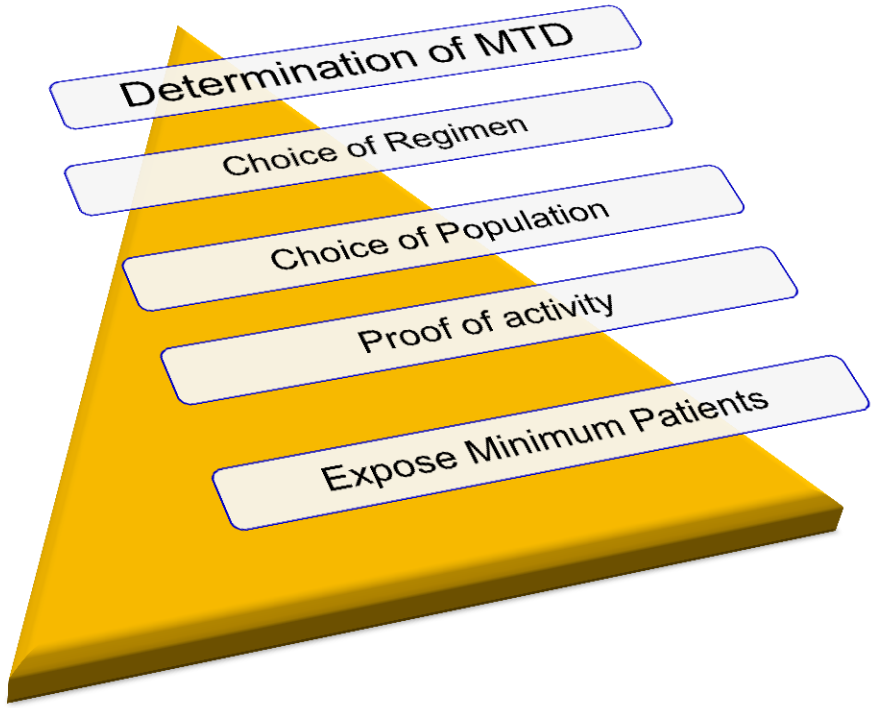


- LOA is defined as the probability of successfully passing all the stages from phase I till regulatory approval
- Most Oncology drugs fail because:
  - Early development focus on limited safety information (e.g., dose limiting toxicity (DLT))
  - Moving to go/no-go decision without essential components
    - Dose optimization
    - Appropriate regimen selection
    - Clear idea about regulatory path
    - Choice of potential combination partners
- Need better evidence synthesis framework in early phase Oncology trials

Data source: https://pharmaintelligence.informa.com/~/media/informa-shop-window/pharma/2021/files/reports/2021-clinical-development-success-rates-2011-2020-v17.pdf

The wish list for Oncology phase I trials is "Long"

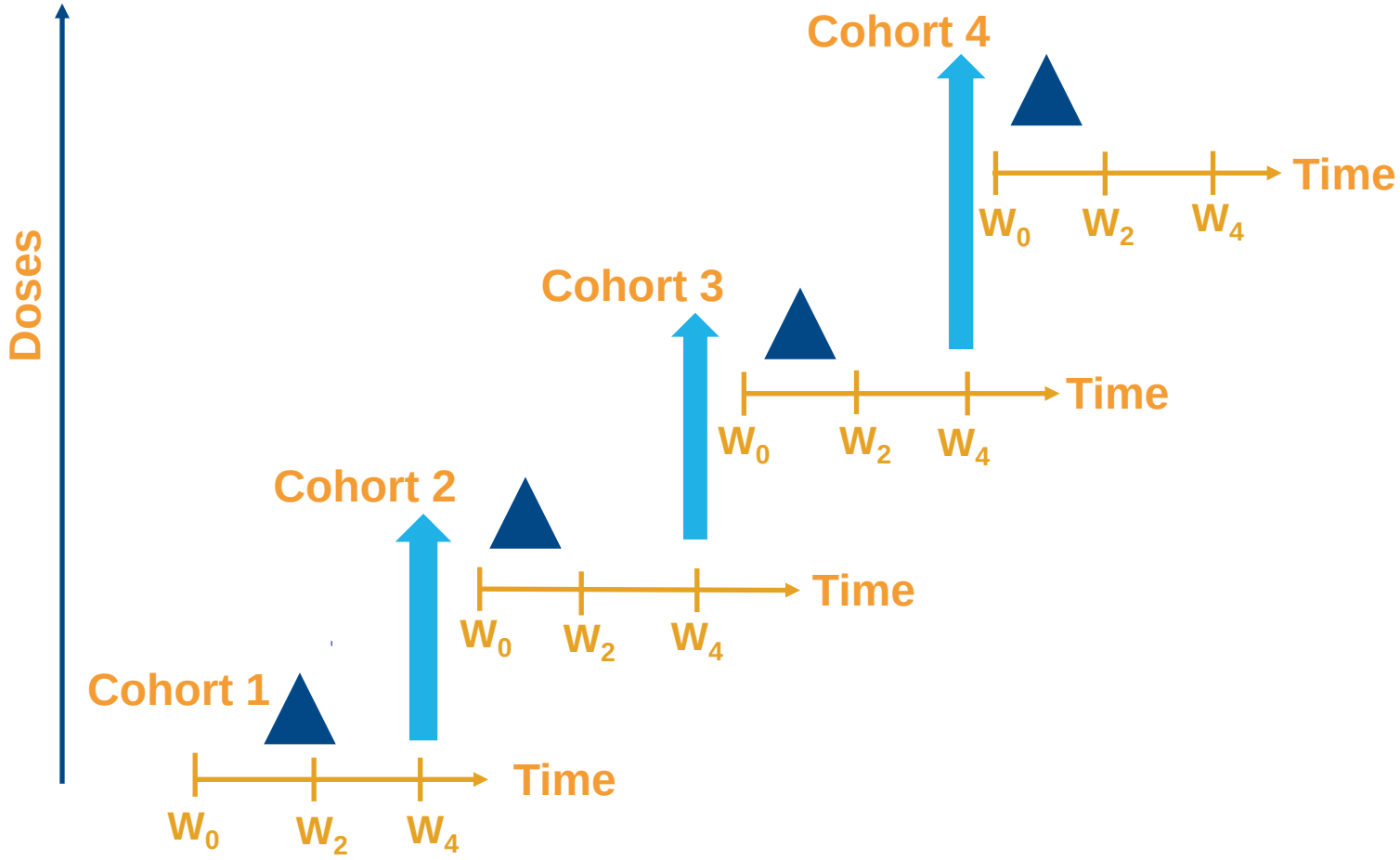
- Phase I/II trials need better preparation (or design) to collect the necessary data for "good" decision-making for late phase:
  - ➢ Data that provides confidence whether the drug is safe and has sufficient activity in the selected indication
    - DLT, tolerability, long-term AE'S, other safety information, receptor occupancy, evidence of clinical efficacy (e.g., tumor response, overall response)
    - Early look into some of the data: requires planning
  - ➢ Model based framework to integrate information from different sources
  - ➢ Inclusion of the comparators data: directly or indirectly
  - ➢ A good quantitative framework for robust go/no-go decision-making



Success in the development program requires good understanding of five key factors

Right Target	Right PK/PD	Right Safety	Right Patients	Right Market
• Strong link between target and disease • Differentiated efficacy • Predictive biomarkers	• Definition of PD biomarker • Understanding of preclinical and clinical PK/PD • Identification of drug-drug interaction	• Differentiated and clear safety margin • Understanding of risk • Proper Mitigation plans	• Identification of most responsive patient population • CDX development plan • Benefit-risk assessment	• Differentiated value proposition • Market access, payers, and providers • Personalize health-care strategy

Doses are escalating gradually to determine the maximum tolerated dose (MTD) in current practice



- Selects a safe starting dose based on pre-clinical data
- Toxicity is measured as a binary endpoint referred to as **dose-limiting toxicity (DLT)**
- Dose is increased incrementally if the current dose is safe (no DLT)
- Decisions are made at a dose escalation teleconference
- **Target:** highest safe dose, or maximum tolerated dose (MTD)

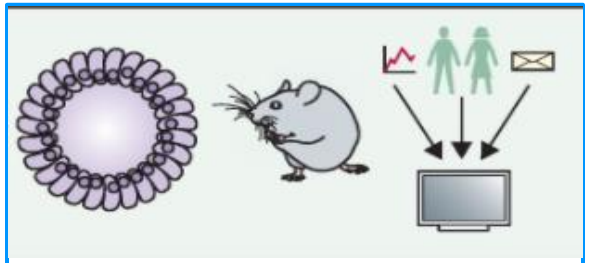
The current dose expansion studies use single dose-level for further exploration

- Escalation phase is followed by an expansion cohort with MTD or R2PD selected at the escalation phase
- **Objective:** evaluating safety, tolerability, and preliminary efficacy
- Typically, the population is different for the escalation phase
- May include more than one indications: basket trials
- Additional dose groups or potential control arms are rarely included
  - Challenges the statistical validity of the results of the dose expansion phase
  - No opportunity for dose-optimization

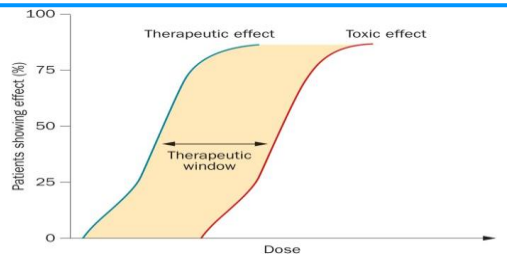
There is an emerging paradigm shift in Oncology phase I study Design

- **Project Optimus**
  - Oncology Center of Excellence (OCE)
  - **Mission**: “To ensure that doses of cancer drugs are optimized to maximize efficacy as well as safety and tolerability”
- Targeted agents are administered longer,so long-term tolerability is very important
  - MTD is no longer optimal dose
- Multi-disciplinary discussions are ongoing to best achieve dose optimization goals in oncology are ongoing

Innovative statistical design and analysis methods



Translate knowledge from predictive non-clinical models



Collection an appropriate use of PK-PD and pharmacogenetics data

Holistic decision-making based on totality of evidence

There are several challenges in Phase I Oncology trials

Untested drug in resistant patients

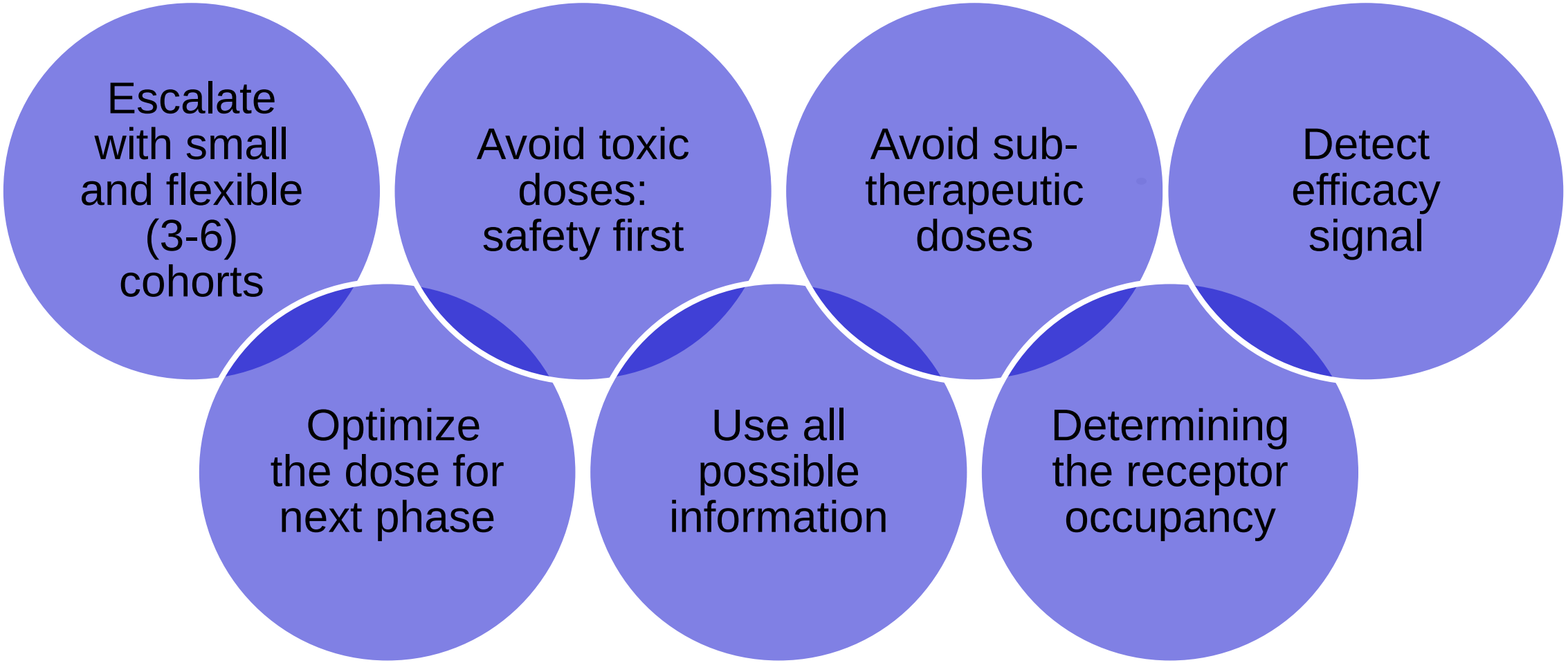
Determination of right dose

Number of patient and budget constraints

High toxicity potential

Completing trial in timely fashion

A good early phase Oncology design needs to cope with these challenges



- Provides sensible dosing decisions which take patient safety into account

Several design strategy for dose optimization in expansion phase are possible

- **Strategy 1**: Randomized expansion phase
  - ➢Randomized to two or more potential dose groups in the expansion phase
  - ➢Head-to-head comparison to choose the best dose group
  - ➢Direct or indirect comparison with control group
  - ➢Requires larger sample size, appropriate multiplicity adjustment
  - ➢ Operational challenges
- **Strategy 2:** Expanding multiple dose groups in the escalation phase
  - ➢ Enrolling more patient in the multiple dose groups at certain point
  - ➢Seamless expansion
  - ➢ More involved statistical inference: model-based approaches

There are several steps for quantitative decision-making

- Early phase trials require stepwise decision-making process as information is available at different times during the trial
- Experts make the decision: not statisticians
- A framework is required to perform multi-criteria decision analysis
- Structuring and recomposing expert knowledge in a framework helps to
  - ➢Understand the problem
  - ➢ Assess the main drivers of a decision
  - ➢ Communicate issues in a transparent, rational and consistent way
  - ➢Appropriately handle uncertainty and perform sensitivity analysis

Data accrues graduation at different timepoints

During dose escalation	• DLT data, Limited PK data, grade 3/4 AE
End of dose escalation	• DLT data, PK data, Receptor occupancy data
During dose expansion	• DLT data (if collected), PK data , Limited long-term safety data, limited efficacy data
End of dose expansion	• DLT data (if collected), PK data , long-term safety data, efficacy data, other PD marker data (if collected)

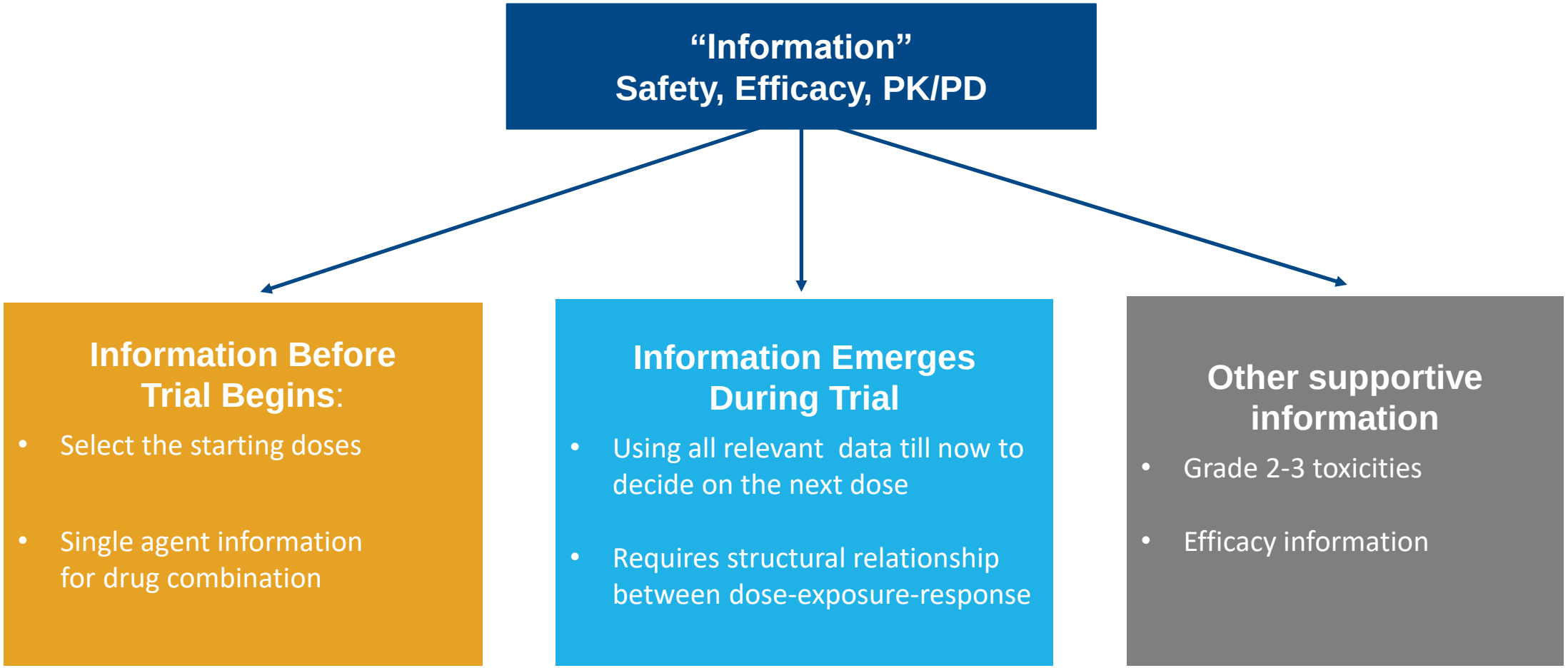
Outcomes are appropriately weighted using utility function approach

- Outcomes are divided into different broad categories
  - Safety, efficacy, activity…..
- Each category can have multiple subcategories
  - Safety: DLT, grade 3/4 toxicity, long-term toxicity..
  - Efficacy: tumor response, pd marker response, direct comparison with control
- We used a “bottom-up swing weights” method to elicit within category weights
  - Rank-order the criteria by the relative value of bringing each from its worst to its best plausible outcome
  - Assign the top-ranked criterion a weight of 100 and assign the other weights corresponding to their (subjective) relative values
- Cumulative weight for each sub-category is calculated using within and between category weights

Here is an example

Category	Between Category weight	Sub-category	Within category weight	Normalized weight (w)	Value (V)	Score
Safety	a	DLT	a1	(a1/a1+a2)*(a/a+b+c)	P(DLT rate > 33%| data)	∑w*V
		Long term AE	a2			
Efficacy	b	OR	b1			
		PFS	b2			
Activity	c	RO	c			

A good decision must use all relevant information



Good dose escalation (DE) design should make formal use of all relevant information available

There are different design approaches for Phase I Oncology Trials

- Simplistic «non-statistical» approaches (still) prevail in Phase I Oncology trials
- This includes:
  - 3+3 design, a simple algorithm
  - More sophisticated algorithmic designs
- No proper statistical inference for these approaches
  - No uncertainty quantification associated with the sparse data

Proper statistical inference helps robust decision-making

- Adaptive design based on the available data
  - Frequent looks at the data with decisions about next dose-level
- Inference and decisions: knowing vs acting
  - Statistical inference quantifies uncertainties (e.g. MSE, p-value, probability)
  - Good inference precedes informed decision-making
- Inference must be probabilistic
  - Properly quantify risks: must be presented in intuitive ways
- Majority of decision-makers are not statisticians

Model based approaches allow you to quantify your knowledge and assess risk to future patients

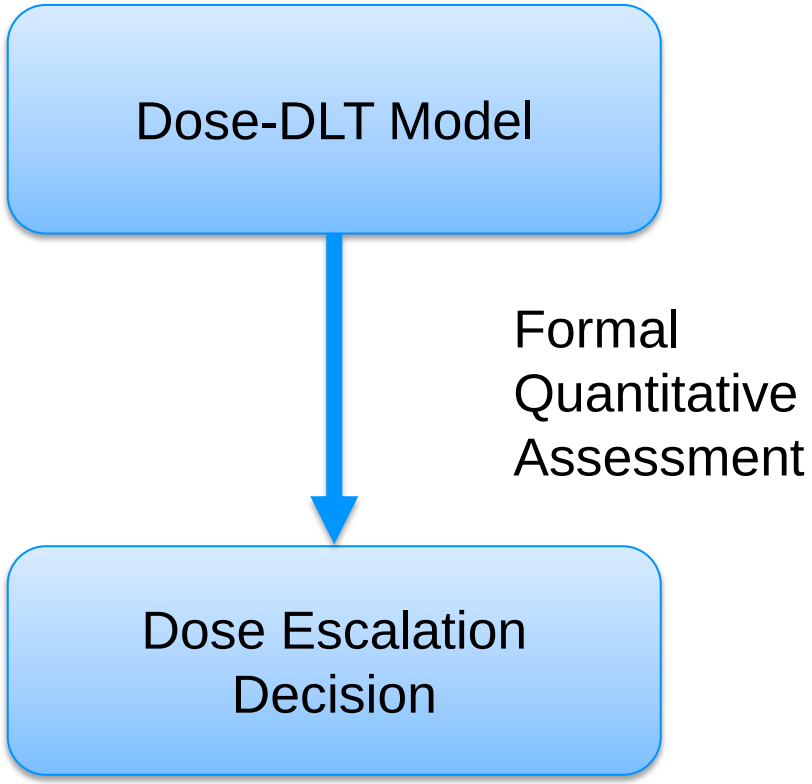
- Requires simplistic model for easy practical interpretations
- Allows flexibility and adaptiveness: additional dose levels, shift regimen, flexile cohort size, parallel exploration of multiple dose level, re-test doses
- Natural use of available historical data (e.g. pre-clinical)

The statistical literature for model-based dose escalation design is massive

- Huge amount of statistical research since 1990
  - Still the real-life application is relatively sparse
- What is missing?
- There are many model-based approaches available
  - Continual reassessment method (CRM)
  - Bayesian logistic regression model (BLRM)
  - Many others…

"*All models are wrong, but some are useful*"—George Box[11]

Current BLRM models the dose toxicity relationship with binary endpoints – DLT or no DLT

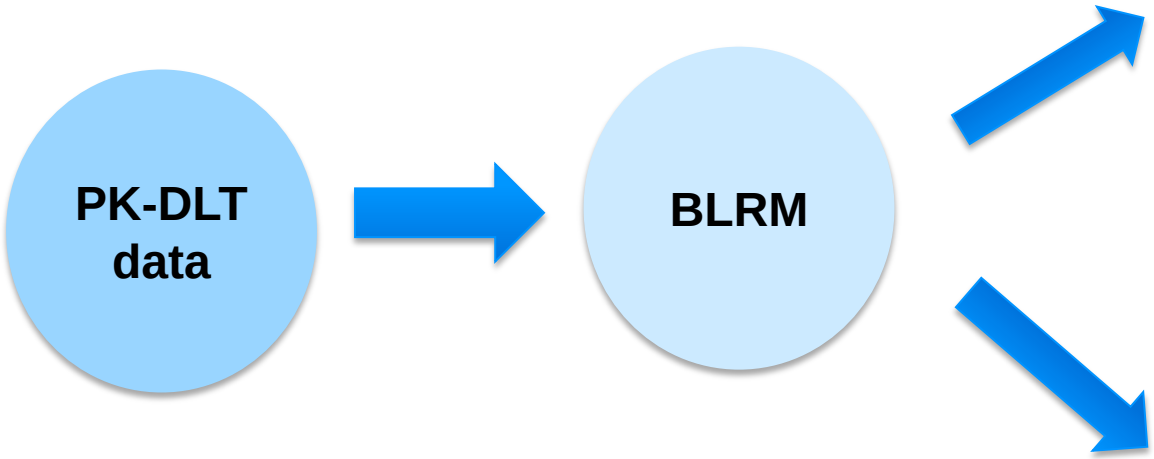


Qualitative Assessment

Final dose recommendation depends on

- Pharmacokinetic (PK) Data
- Other Grade 3 or 4 Adverse Events (AE)
- Pharmacodynamics (PD) and Biomarker Data
- Efficacy

Probabilistic metrics allow comprehensive decision making



Not available analytically for BLRM: can be obtained using MCMC

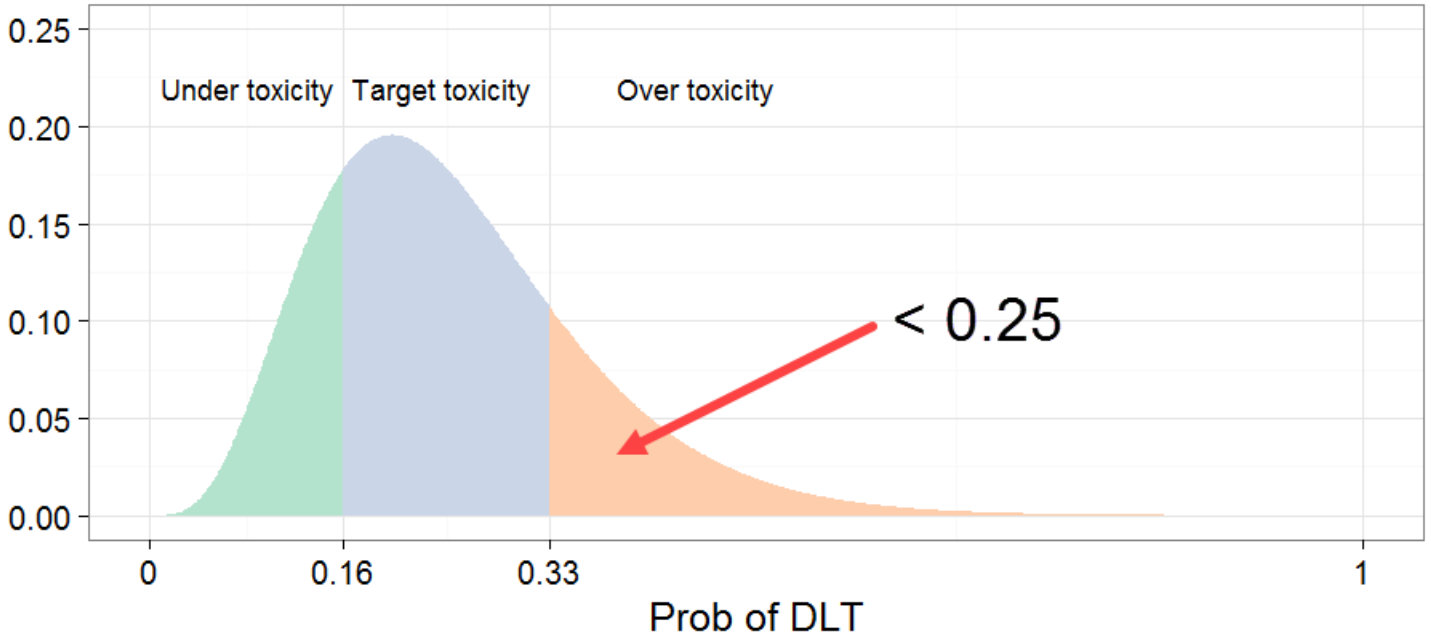
Posterior distribution

- Inference of true DLT rate of all dose level given data
- Summary includes: (for all doses)
  - Mean, standard deviation and 95% interval
  - Probabilities of underdosing, target toxicity and overdosing intervals

Predictive distribution

- Predict the toxicity of future patients given current data
- Useful for discussion with non-statisticians

Dose escalation with Overdose Control (EWOC) is used to ensure patient's safety



Possible candidate for next dose level: Doses satisfy EWOC criteria

- Pr(True prob of DLT > 33% | data) < 25%

Pharmacokinetic (PK) data

- Pharmacology is the study of the interactions between drugs and the body. The two broad divisions of pharmacology are pharmacokinetics and pharmacodynamics. Pharmacokinetics (PK) refers to the movement of drugs through the body, whereas pharmacodynamics (PD) refers to the body's biological response to drugs
- PK data is summarized by dose, cycle, day, and time
- The common summaries are
  - Maximum plasma concentration (Cmax)
  - Time to maximum plasma concentration (Tmax)
  - Area under the plasma concentration versus time curve (AUC)

Modeling of PK data in dose finding has the potential to allow better estimation of the dose-toxicity curve

- In most phase I studies, dose-finding and PK analysis are done separately and no attempt is made to combine them during dose allocation (Ursino et al, 2016)
- Currently PK data are only used by clinical teams in a subjective manner to aid decision making
- If exposure is dramatically low then we expect that we could be more aggressive in dose escalation
- Formal incorporation of PK data in dose-escalation model can lead to an increase precision and hence can make the decision process more efficient

There are different approaches to consider PK-data

Simple Model

- Replace the dose levels with the PK data in the current Dose-DLT model.
- The formal assessment of Dose-PK relationship is not considered.
- The dose escalation decision will have no or very little impact from information of doses and thus will face difficulty in determining next safe dose

Covariate Model

- Add the PK data as covariates in the current model.
- Statistically, it will provide more information in predicting the safe doses, however, scientifically, again, the relationship is not captured.

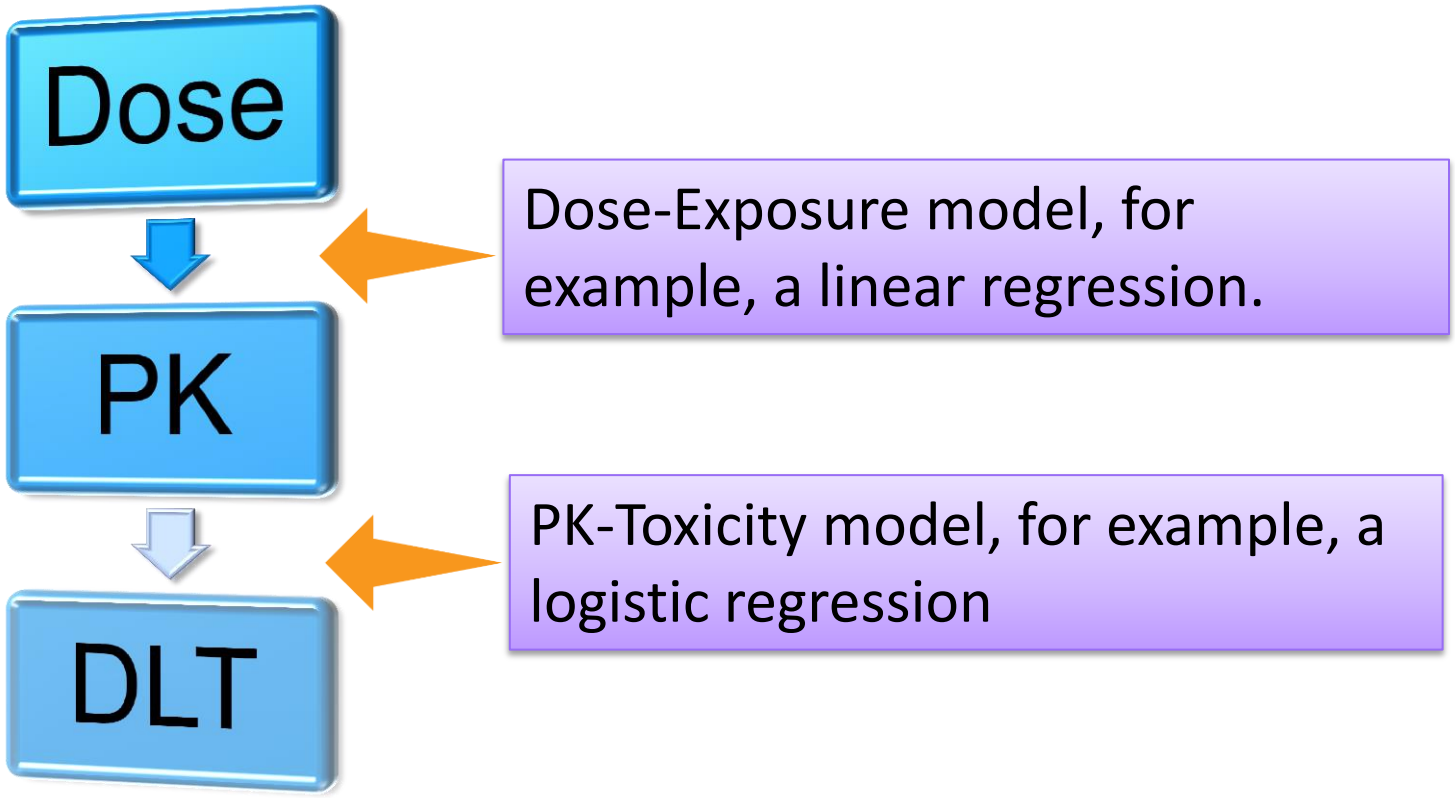
Separate Models

- Two models
  - Dose-DLT model
  - PK-DLT model
- It will be difficult to integrate the conclusions provided by two separate models.

Joint Model

- A joint PK-DLT shared parameter model
- The interpretation is simple and can retain the current dose recommendation process

Joint PK-DLT Model

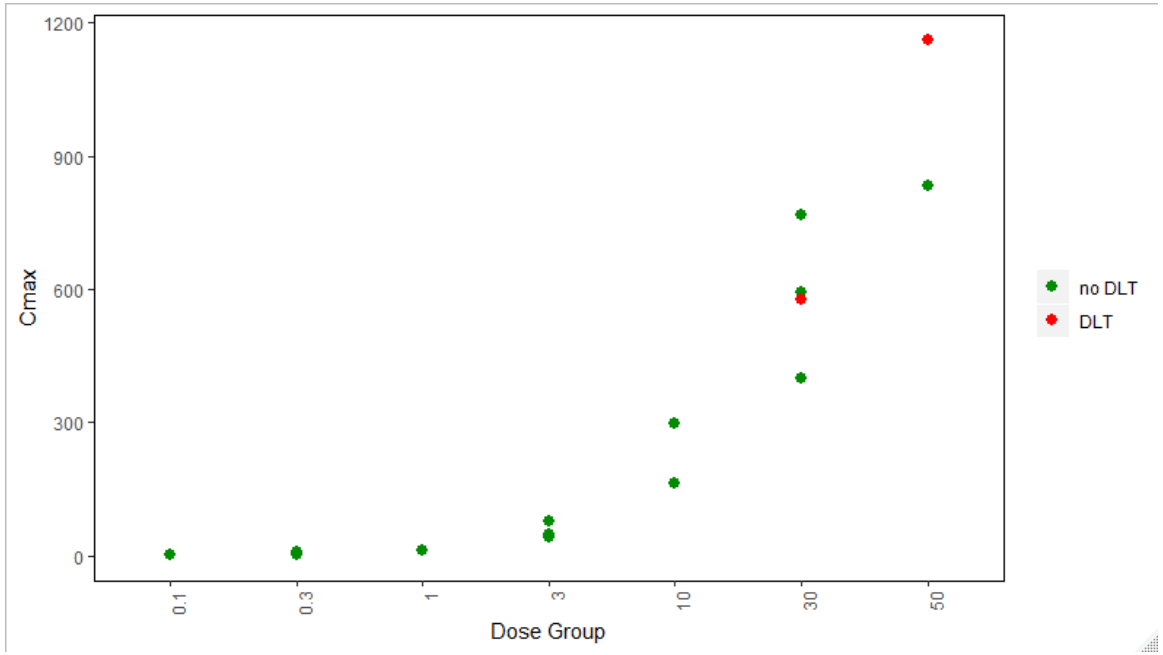


Model based approach is used for other “estimand” of interest

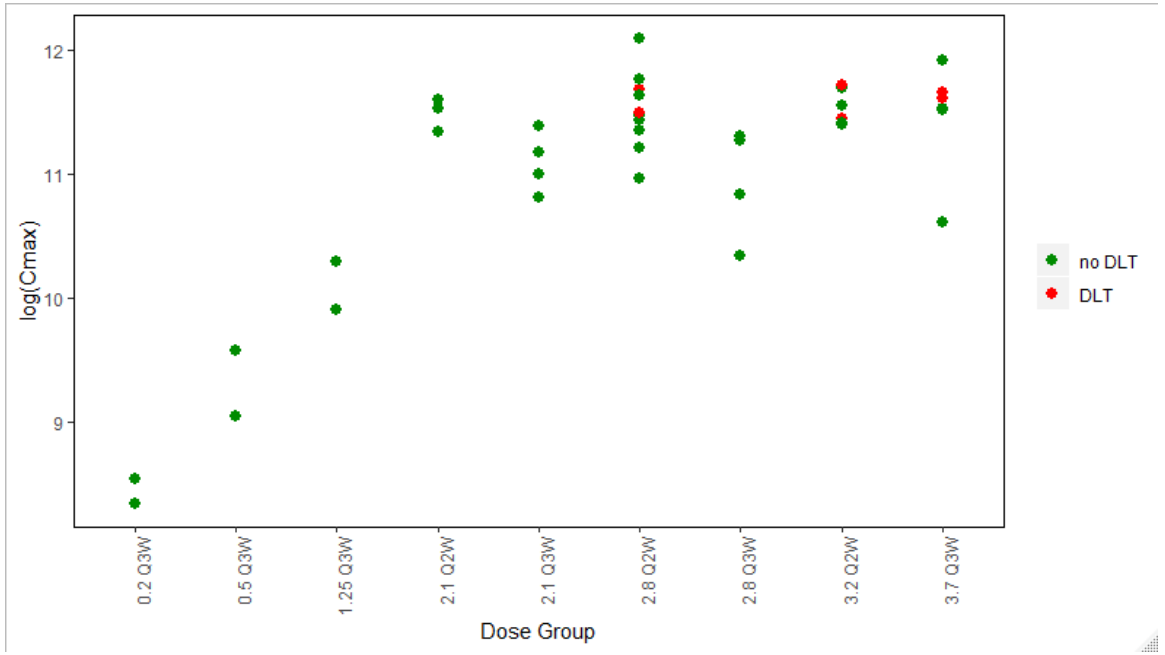
- Receptor Occupancy vs exposure: Emax model
- Efficacy vs exposure: Emax model
- Long term AE vs exposure/dose: Poisson regression model
- Appropriate probability metrics are used to define “good” and “not so good” zones for each estimand

Below are the two dose-exposure relationship

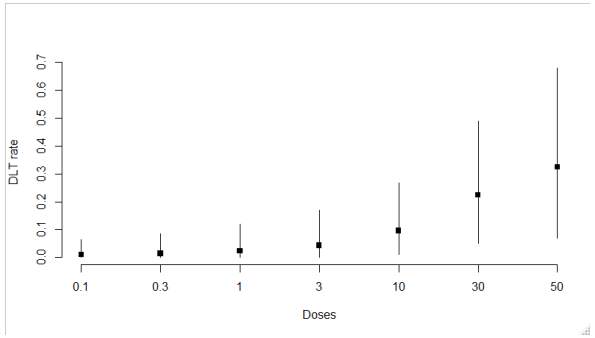
Example 1



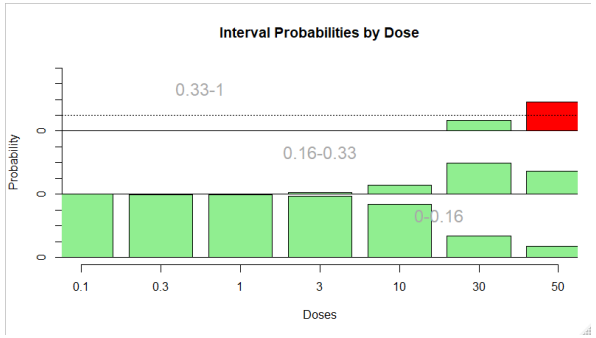
Example 2



Dose-DLT and PK-DLT models provide consistent results for example 1

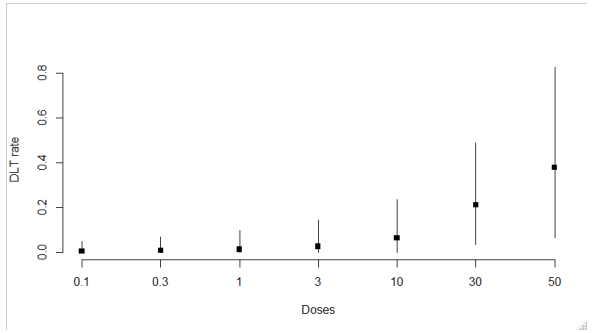


Dose 50 ug/kg is not safe dose



Posterior probabilities of the DLT rates

Interval probabilities by dose



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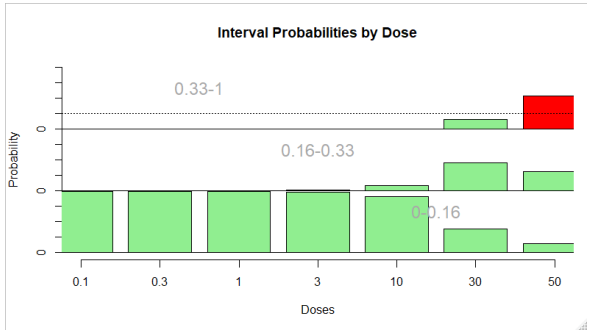
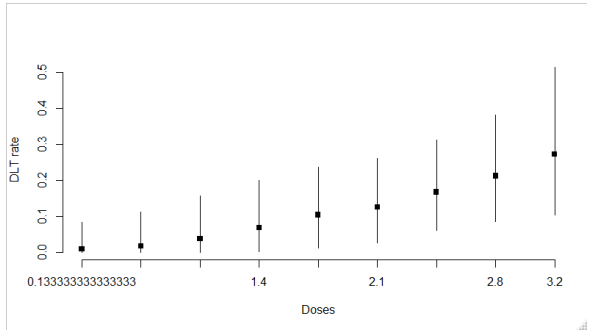
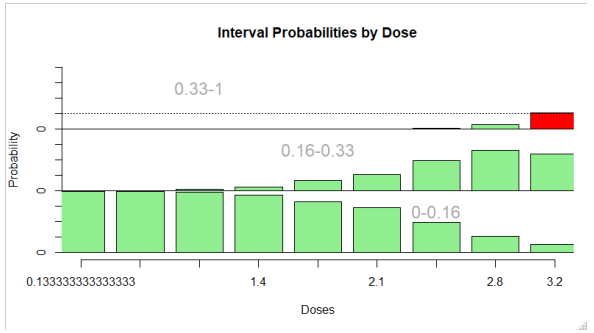


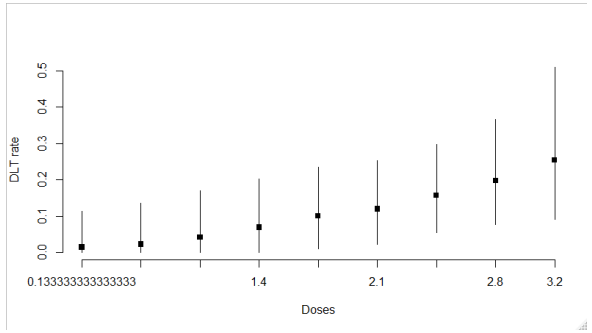
Top Panel: Dose-DLT Model and Bottom Panel: Joint Model

PK-DLT models result reasonable result for example 2

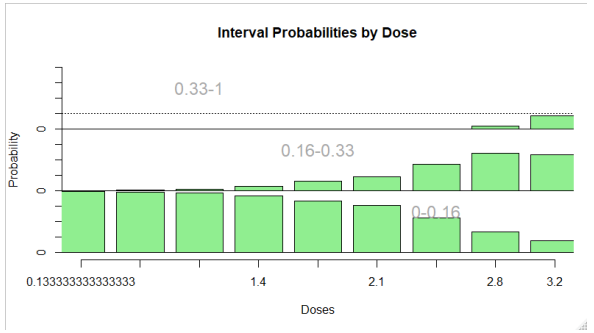


Dose 3.2 is not safe dose





Dose 3.2 is a safe dose



Top Panel: Dose-DLT Model and Bottom Panel: Joint Model

Extensive simulations showed PK-DLT model performed well

- Extensive simulation study is performed with
  - Different dose-exposure-DLT relationship
  - Violation of model assumption
- PK-DLT model performs better than the dose-DLT model or PK covariate model in terms of
  - Probability of determining right MTD
  - Percentage of patients allotted to safe doses
- Currently we are testing this model in some ongoing studies as
  - Supportive analysis of dose-DLT
  - PK data is not always current for the dose escalation meeting

Work in progress with other components

- Work is ongoing with
  - ➢Efficacy model
  - ➢Receptor occupancy model
  - ➢Long term safety model
- A few internal pilots are detected
  - ➢Results will be shared in the near future conference

Conclusion

- Dose-exposure-DLT model often provides a estimates of risk and benefit
  - However, it is difficult to have quality PK data in the ongoing basis
  - Current approach is still using dose-DLT model for escalation and dose-PK for sensitivity
  - More rigorous modeling is done at the decision points (end of escalation or expansion phase)
  - This is operationally possible hurdle for clinical team
- Dose optimization should be addressed early to better understand benefit-risk of different doses
- Multi-criteria decision analysis (MCDA) is a potential tool for dose-optimization
  - Assess main value drivers of decision
- Needs to be a mix of different analysis/data on both safety and efficacy from statistics, PK, clinical and non-clinical that contribute to the final decision

Thank You