Cytel

Shaping the Future of
Drug Development

# Novel designs in early phase Oncology studies

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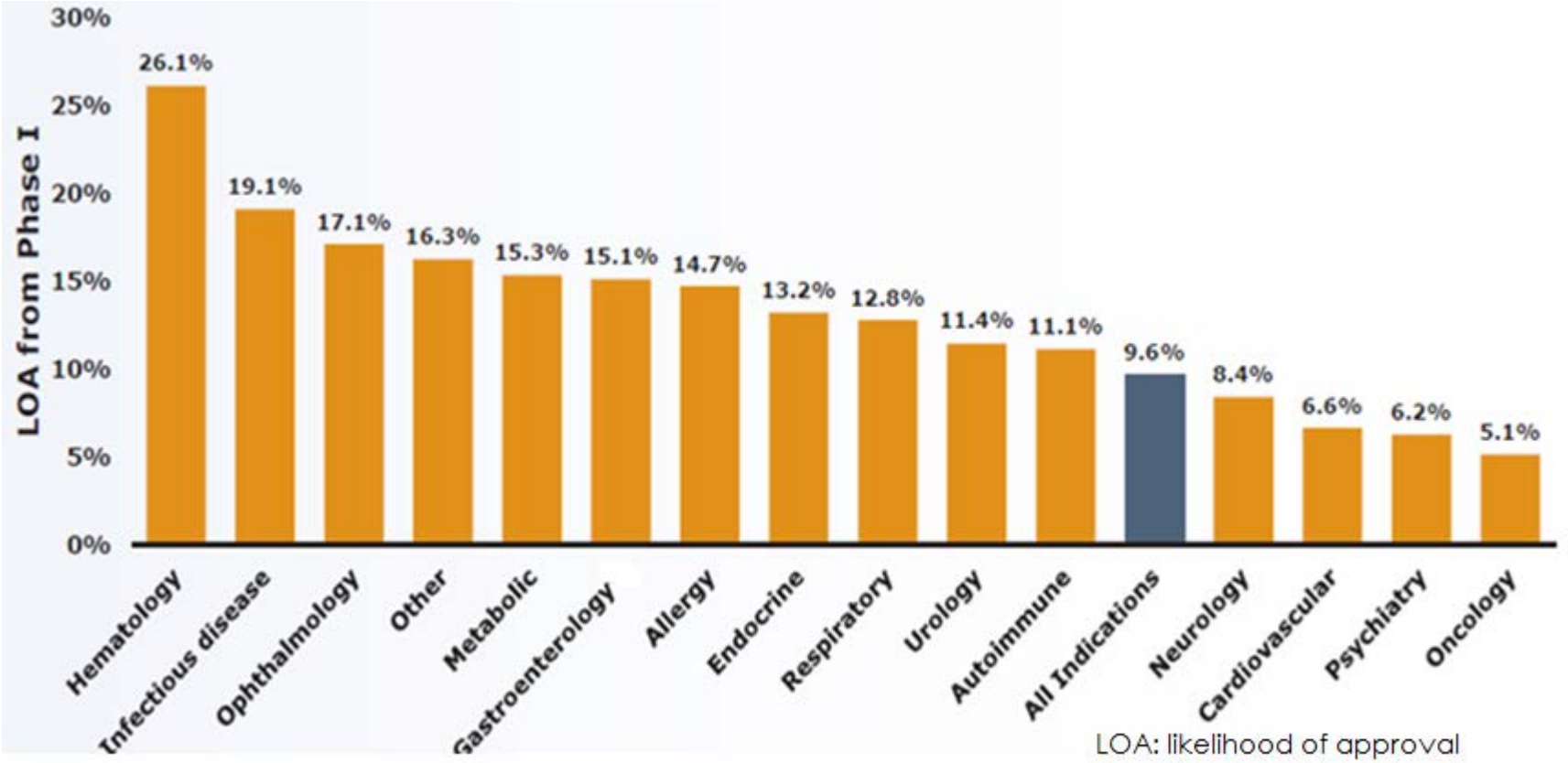
# Agenda

- Background - Dose escalation studies
- Challenges
- Dose escalation study designs
  - Rule based
  - Model based
- Bayesian Logistic Regression (BLR) design
  - Case study
  - Interpretation of results
- Highlights

# Dose Escalation Studies

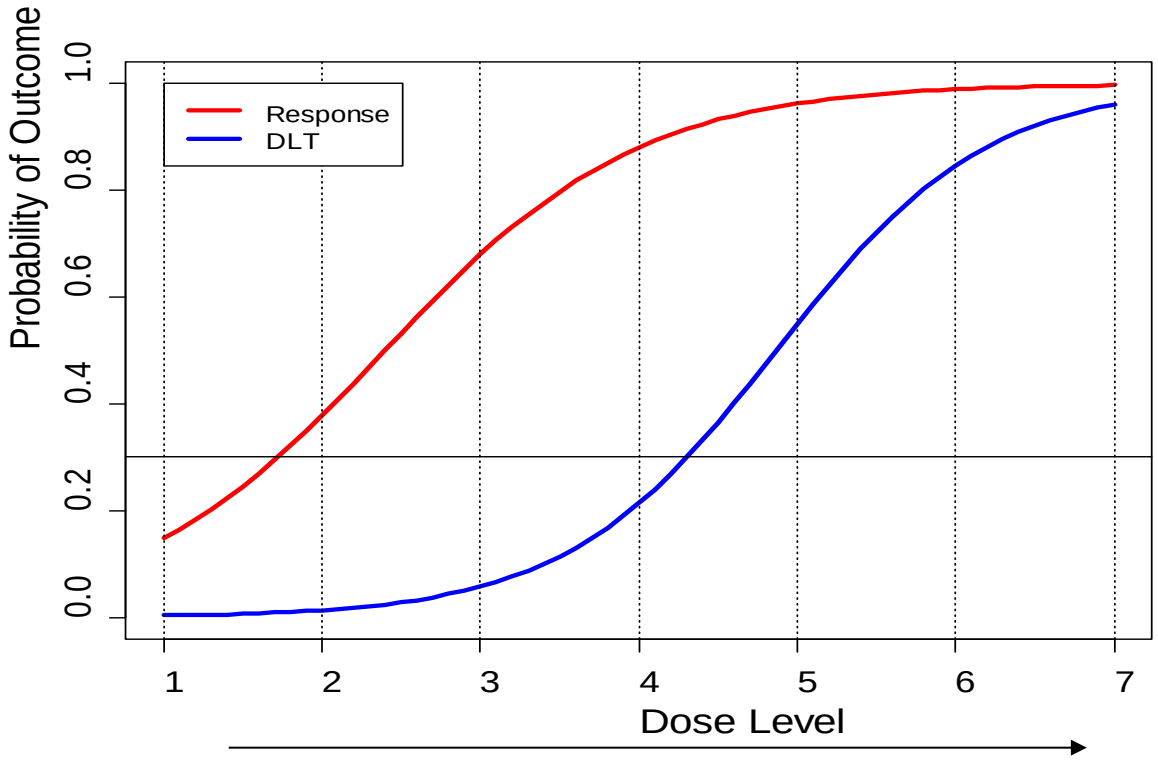
- Success rate of journey from phase I to FDA approval for Oncology drug molecule is the lowest (5.1% over timeframe 2006-2015)*






** Biotechnology Innovation Organization Report, June 2016*

# Dose Escalation Study- Oncology




Based on Presumption:
Efficacy and toxicity both increase with dose

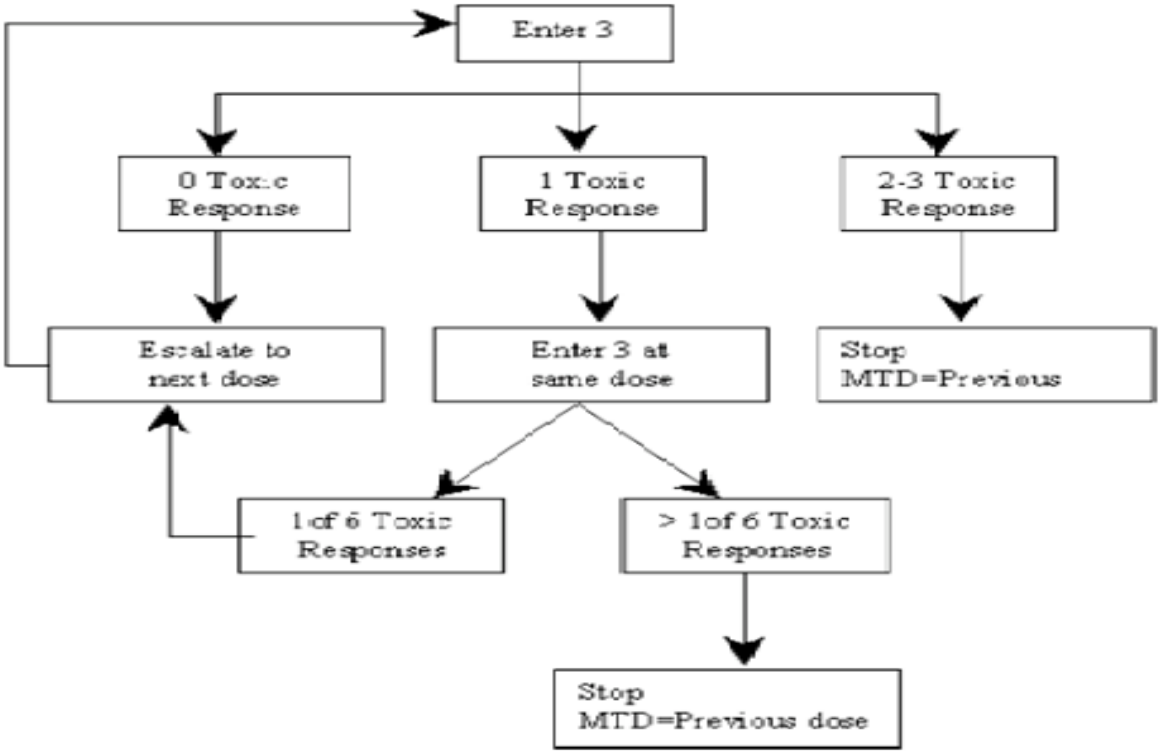
# Challenges: Dose Escalation Studies

- Investigational drug is examined in diseased patients; often suffering from advanced cancer
- Inability to distinguish between toxicity due to condition and toxicity due to drug
- Minimize the number of patients exposed to sub-therapeutic doses as well control severely toxic overdosing
- Use all available data efficiently
- Precisely estimating the MTD

# Dose Escalation Study Designs

- Multiple approaches are proposed using DLT as the primary endpoint.
  - Rule-based designs
    - Utilize dose-escalation/de-escalation rules
    - Based on actual observations of target events (DLT) to assign patients to dose level
    - E.g. 3+3 design, accelerated titration design
  - Model-based designs
    - Estimate the MTD by estimating the dose-toxicity relationship
    - E.g. continual Reassessment Method (CRM), Bayesian Logistic Regression Model (BLRM), Escalation with overdose control (EWOC), modified Toxicity Probability Interval (mTPI)

# Rule Based Design: 3+3 Study




- Pre specify a set of doses to consider, usually between 3 and 10 doses
  - MTD is defined as the maximum dose at which fewer than one-third (< 33%) of subjects experience a DLT

# Rule Based Design: 3+3 Study

- Most popular and widely used, costless implementation in practice
- Fixed cohort design
- Short memory, algorithm makes the decision
- Only recent cohort information and ignores data from earlier patients

# Model Based Design: Bayesian Logistic Regression Model

- Described by Neuenschwander et al. (2008)
- Inference: Bayesian
- Based on a dose- toxicity model ~ 2 parameter logistic regression
- Prior: Based on historical data
- Posterior Distribution: Gather DLT data (binary) for each patient. Update the dose-toxicity rate model
- Following are intervals for probability of toxicity (DLT)
  - Under dosing toxicity: (0, 0.2]
  - Targeted toxicity: (0.20, 0.35]
  - Excessive toxicity: (0.35, 0.60]
  - Unacceptable toxicity: (0.60, 1.00]

# Dose Recommendation Using BLRM

- Posterior probability is calculated for all candidate doses
- The recommended dose is the one which maximizes the probability of being in targeted toxicity, while controlling the probability of excessive or unacceptable toxicity at 25%
  - Priority No. 1: target toxicity window
    Dose should maximize chance that DLT rate $\in (20\%, 35\%)$
  - Priority No. 2: overdose control
    Dose must have < 25% risk that DLT rate is > 35%
- BLRM implements the concept of escalation with overdose control

# Case Study

# First-in-human – Phase I Dose Escalation Study

**Primary Objectives**

- Evaluate the safety and tolerability of investigational drug in adult subjects with relapsed adenocarcinoma

- Determine the maximum tolerated dose (MTD) and/or biologically active dose (e.g. recommended phase 2 dose)

# Study Design

- Multi-center, open-label, dose-escalation study

Study has 2 parts

**Dose-escalation:**

- The dose-escalation will define the MTD, safety, tolerability, pharmacokinetic (PK) and pharmacodynamics (PD) of study drug

**Dose-expansion:**

- Dose-expansion will enroll additional subjects to gain further clinical experience with study drug

A final estimate of the recommended phase 2 dose will be based on BLRM using all subjects from dose escalation and expansion cohorts

# Dose Escalation Phase

- Dose levels : 200, 400, 800, 1600, 3200, and 6400, 12800 µg/day
- 3-6 subjects per cohort
- Dose decision analyses performed after every cohort
  - Recommendation for subsequent doses is based on Bayesian model, the next dose is the one with

- The highest probability of being in target interval (0.20, 0.35)
- With a less than 0.25 probability of an excessive or unacceptable target interval

- Can incorporate intermediate dose levels
- The Dose Level Escalation Meeting is planned for dose level decisions

# Data for Ongoing Escalation Study

| | Doses | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 200 | 400 | 800 | 1600 | 1600 | 3200 | 6400 | 12800 |
| No. of patients | 3 | 3 | 3 | 3 | 3 | 4 | 3 | 3 |
| No. of DLTs | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |

# Inputs for Running BLRM

- Planned doses : 200, 400, 800,1600, 3200, 6400 and 12800
- Intermediate doses : 4800, 9600
- Input data : subj dose response
- BLRM_Int : (0.2 0.35 0.60)
- BLRM_cut : (0 0.25 0.25)

| Modeling after 1600 µg cohort | | |
|---|---|---|
| No of Subject | Dose | Response (DLT) |
| 3 | 200 | 0 |
| 3 | 400 | 0 |
| 3 | 800 | 0 |
| 6 | 1600 | 1 |

# Results

| Dose | Prob (Target Toxicity) | Prob (Over dosing) | Centiles of probability of target toxicity | | |
|---|---|---|---|---|---|
| | 0.20-0.35 | 0.35-1 | 2.5% | 50% | 97.5% |
| 200 | 0.0024 | 0 | 0.000084 | 0.0112 | 0.1121 |
| 300 | 0.0047 | 0 | 0.000216 | 0.0168 | 0.1307 |
| 400 | 0.0072 | 0.001 | 0.000411 | 0.0225 | 0.1473 |
| 600 | 0.0151 | 0.0006 | 0.000981 | 0.0337 | 0.1790 |
| 800 | 0.0269 | 0.0012 | 0.00169 | 0.0445 | 0.2051 |
| 1600 | 0.1143 | 0.0131 | 0.00694 | 0.0870 | 0.3103 |
| 3200 | 0.2711 | 0.1247 | 0.0221 | 0.1644 | 0.5093 |
| 4800 | 0.2998 | 0.27 | 0.0354 | 0.2305 | 0.6570 |
| 6400 | 0.2850 | 0.389 | 0.0459 | 0.2876 | 0.7613 |
| 9600 | 0.2344 | 0.5446 | 0.0611 | 0.3781 | 0.8709 |
| 12800 | 0.1944 | 0.6372 | 0.0736 | 0.4508 | 0.9247 |

# Recommendation & Dose Level Review Meet

- Next recommended dose is 3200 µg/day
  - with probability of target toxicity interval as 0.2711
  - with overdosing control as 0. 1247 (<0.25%)

- Statistician informs the highest dose level one may escalate to as per statistical analysis

- Participants of Dose level escalation meet decide if synthesis of relevant clinical data justifies a dose escalation and to which dose (highest supported by the Bayesian analysis and protocol)

# Highlights

- Next recommended dose is determined based on toxicity responses of all patients previously treated in the trial
- Evaluate intermediate doses in the trial
- Model tries to limit chances of overdosing
- Patient safety is the primary objective
  - Model quantifies knowledge about toxicity (DLT) data
  - Statistical inference serves as one component of a decision-making framework

# Reference


- Cancer Phase I Clinical Trials: Efficient Dose Escalation With Overdose Control. *James Babb1 et al. Statist. Med. 17, 1103Ð1120 (1998)*

- Critical aspects of the Bayesian approach to phase I cancer trials. Neuenschwander, Beat, Michael Branson, and Thomas Gsponer. *Statistics in medicine 27.13 (2008)*

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- Phase 1 Trial Design: Is 3+3 the Best? *A Hansen et.al. cancer control. Vol 21 (2014)*

# Thank-You

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