FDA-AACR Public Workshop On

OPTIMIZING DOSAGES FOR ONCOLOGY DRUG PRODUCTS: QUANTITATIVE APPROACHES TO SELECT DOSAGES FOR CLINICAL TRIALS

February 15 and 16, 2024 I Washington, DC

Session 1B: Alternative Designs for Dose-Finding Trials: Ending Reliance on Short-Term Safety

Patricia Mucci LoRusso, D.O., Ph.D. FASCO, FAACR
Yale University, Yale Cancer Center
New Haven, CT

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Disclosure Information

Speaker Name

I have the following relevant financial relationships to disclose:

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SESSION 1B: ALTERNATIVE DESIGNS FOR DOSE-FINDING TRIALS: ENDING RELIANCE ON SHORT-TERM SAFETY

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MODERATOR

Patricia M. LoRusso, DO, PhD (hc), FAACR
Yale Cancer Center

INTRODUCTORY SPEAKER

Ying Yuan, PhD
MD Anderson

ADDITIONAL PANELISTS

Jonathon Vallejo, PhD
U.S. Food and Drug Administration

Jamie Brewer, MD
U.S. Food and Drug Administration

Amit Roy, PhD
PumasAI

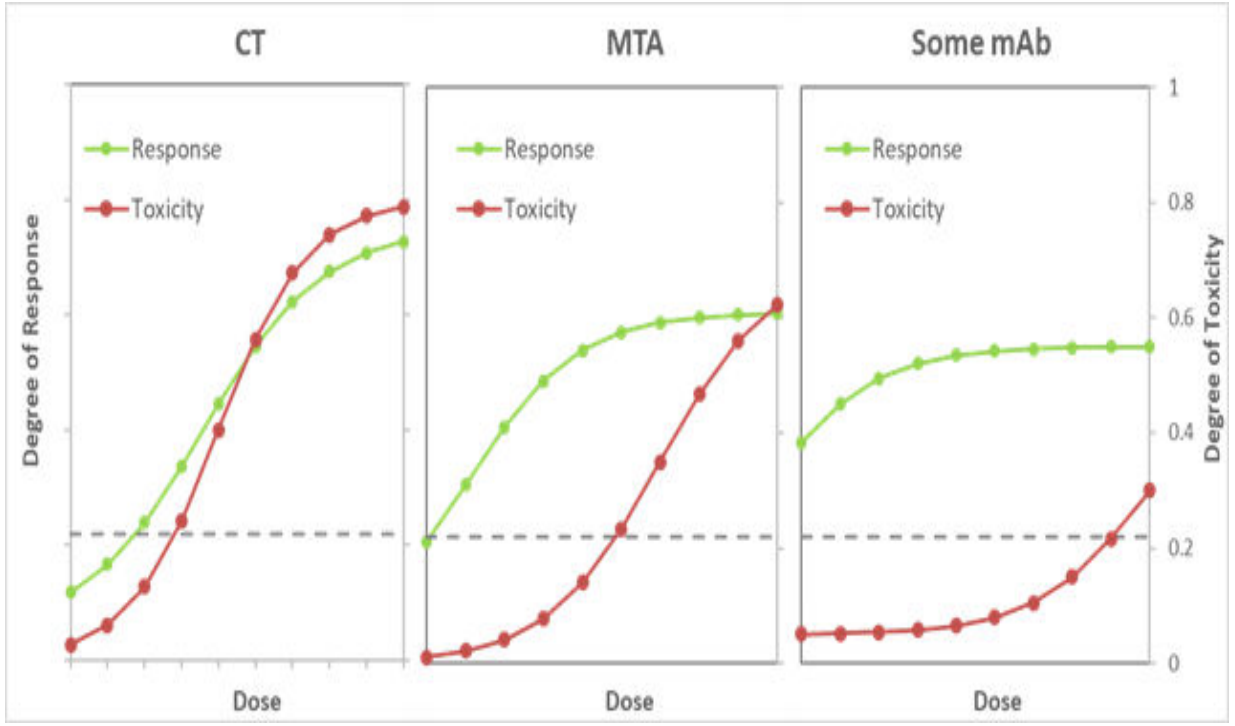
Bruno Gomes DVM, PhD
Roche

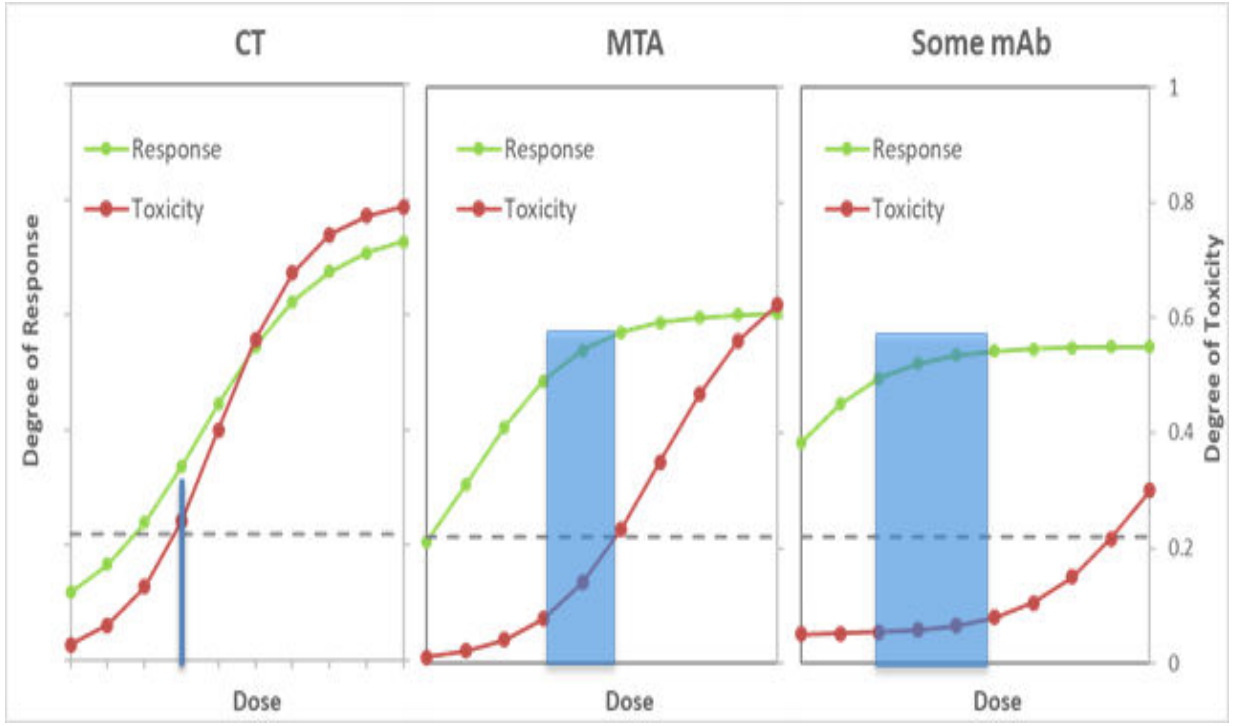
Brian Koffman, MDCM (retired), MSEd
CLL Society

1st Cycle MTD Identification no Longer Sufficient

- Phase I trials becoming more complex
  - Primary Objective(s): identification of RP2D & schedule – components going into making the right dose selection more complex
  - Historically 1st cycle – defined MTD (RP2D)
  - "Next Generation Agents:" Determining MTD with C1 is becoming obsolete
    - Reason behind using 1st cycle DLTs was time
    - Ideal Scenario: assessing totality of data to justify RP2D

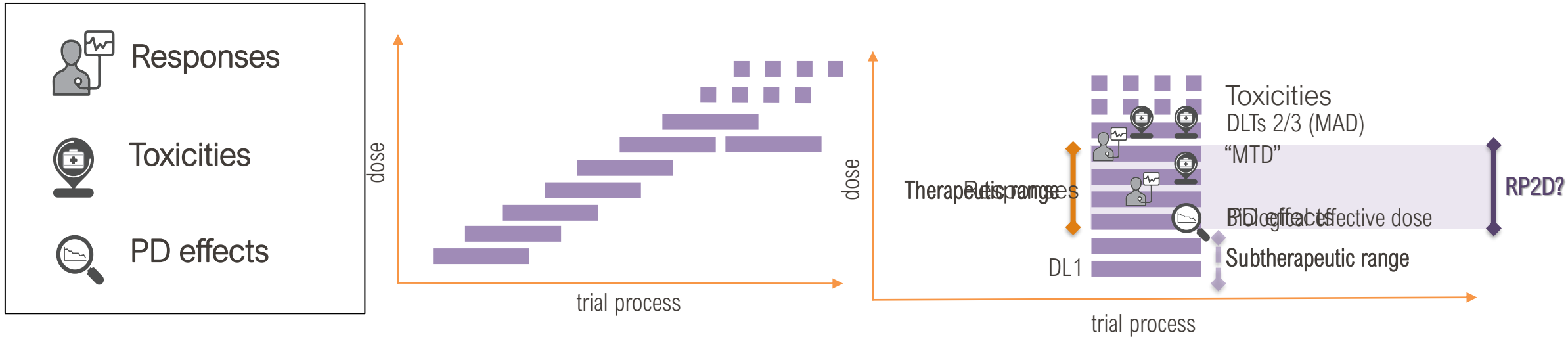
Therapeutic Window





With wider therapeutic window – "more" not necessarily be better

Basic Dose Escalation Concepts

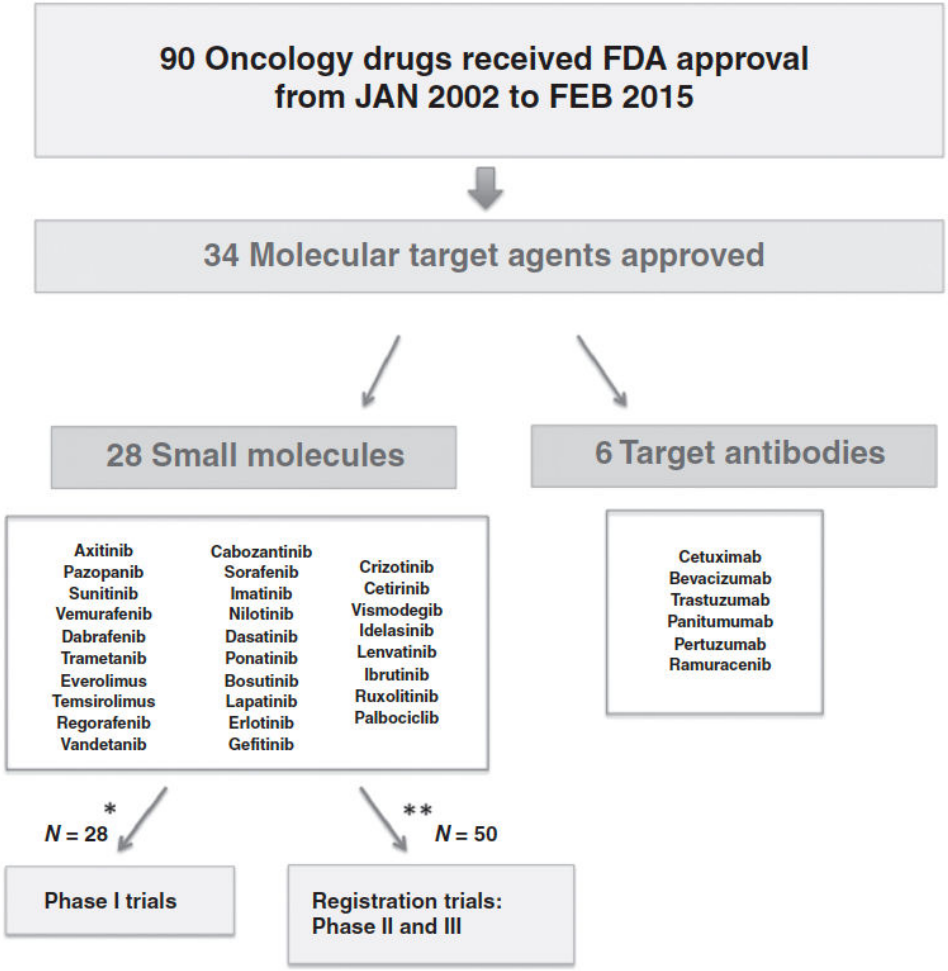


Phase I (early Phase) Clinical Trials

With many novel agents, additional data beyond safety are becoming important:

- Preclinical Data
- Efficacy Data
- Pharmacokinetics
- Pharmacodynamics
- Patient Reported Outcomes

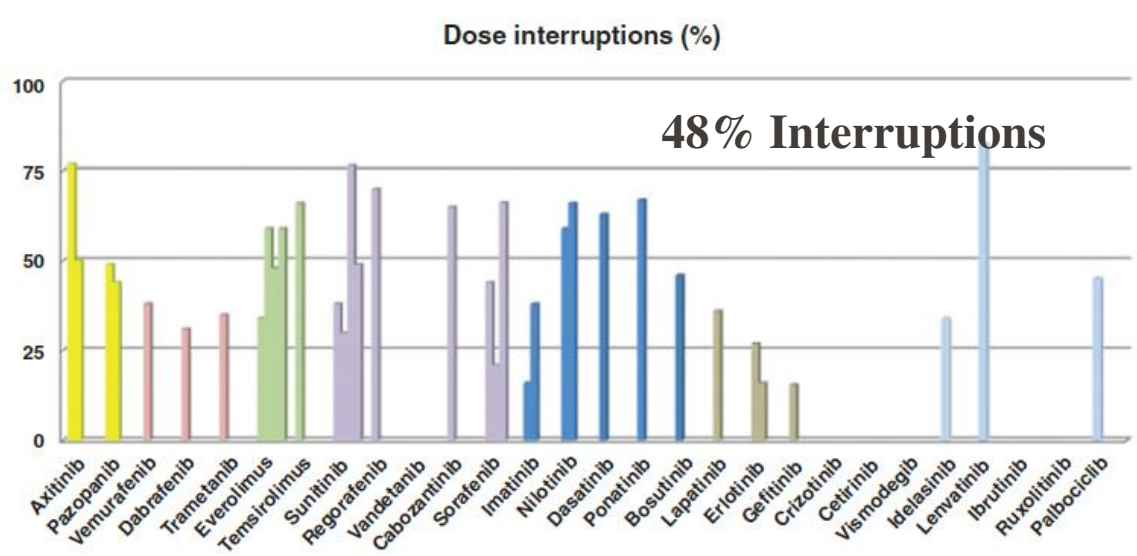
Are we even getting the dose right in phase I?

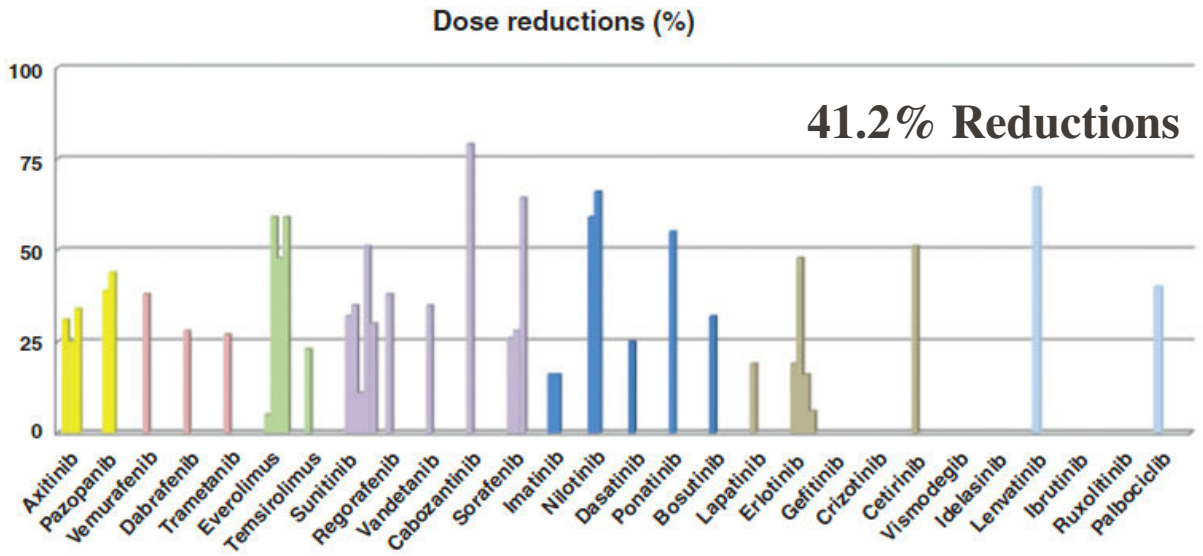


- Significantly increased G3-4 adverse events with small molecules vs monoclonal antibodies [40% vs. 27%; p=0.038] in phase III studies.
- 9% discontinuation rate

Roda et al, Clin. Cancer Res. 2016

45% of patients on small molecules required dose modifications due to drug-related toxicity in phase III trials





Important as combinations will be required for most small molecules to optimize efficacy

Higher incidence of G3–4 toxicity in phase III trials in combos versus single-agent small molecules (64% vs. 37%; p=0.001).

25% SM-MTA Phase I trials recommended Phase II dose below the MTD based on PK/PD data and had fewer dose modifications in subsequent Phase III registration trials (32% vs 50%; RR 0.64; 95% CI 0.43-0.88).

Roda et al, Clin. Cancer Res. 2016

European Journal of Cancer 107 (2019) 1–7

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Available online at www.sciencedirect.com

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Original Research

Delayed immune-related adverse events in assessment for dose-limiting toxicity in early phase immunotherapy trials

Y. Kanjanapan [a,b,c], D. Day [a,b,c], M.O. Butler [a,b,c], L. Wang [d], A.M. Joshua [a,b,c], D. Hogg [a,b,c], N.B. Leighl [a,b,c], A.R. Abdul Razak [a,b,c], A.R. Hansen [a,b,c], S. Boujos [c], M. Chappell [a], K. Chow [c], B. Sherwin [a], L.-A. Stayner [c], L. Soultani [c], A. Zambrana [a], L.L. Siu [a,b,c], P.L. Bedard [a,c], A. Spreafico [a,b,c,*]

[a] *Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada*
[b] *Department of Medicine, University of Toronto, Toronto, Canada*
[c] *Drug Development Program, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada*
[d] *Biostatistics Department, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada*

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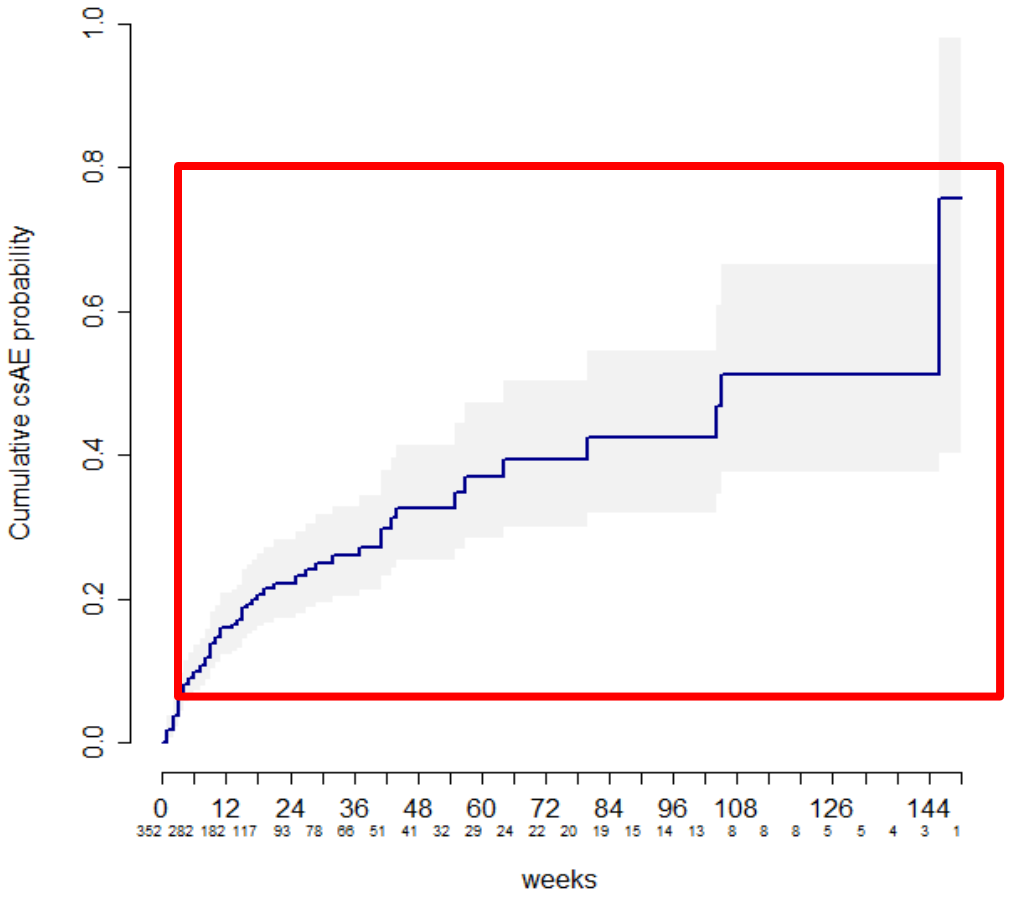
Available online 7 December 2018

Risks of Clinically Significant Adverse Events Over Time on IO Therapy

352 trial enrollments:

- Odds Ratio of csAE within first 4 weeks vs after 4 weeks = 3.13 (95% CI 1.95-5.02)
- The median time to first onset csAE was significantly shorter amongst patients receiving combination compared with single-agent IO (32 vs 146 days, P < 0.0001)
- 5.7% of trial enrollments experienced delayed csAE (24 events) that qualify for DLT outside of DLT window

csAE = treatment-related adverse event requiring corticosteroids, hormone replacement, IO delay or discontinuation.



Kanjanapan et al, Eur J Cancer 2019

Conclusions

- Although many csAEs were delayed well beyond the DLT period (11-14w), it is important to collect and report delayed csAEs, as these may provide further refinement

- As most IO agents do not report a linear relationship between dose and toxicity, the RP2D for most IO agents relies on PK/PD and not DLTs

Phase I (Early Phase) Clinical Trials

- What we want:
  - minimize both under- and overdosing patients
  - maximize Patient Risk:Benefit

- Novel trial designs are overcoming some of the known deficiencies of Early Phase Clinical Trials

From Hypothesis to Statistical Analysis

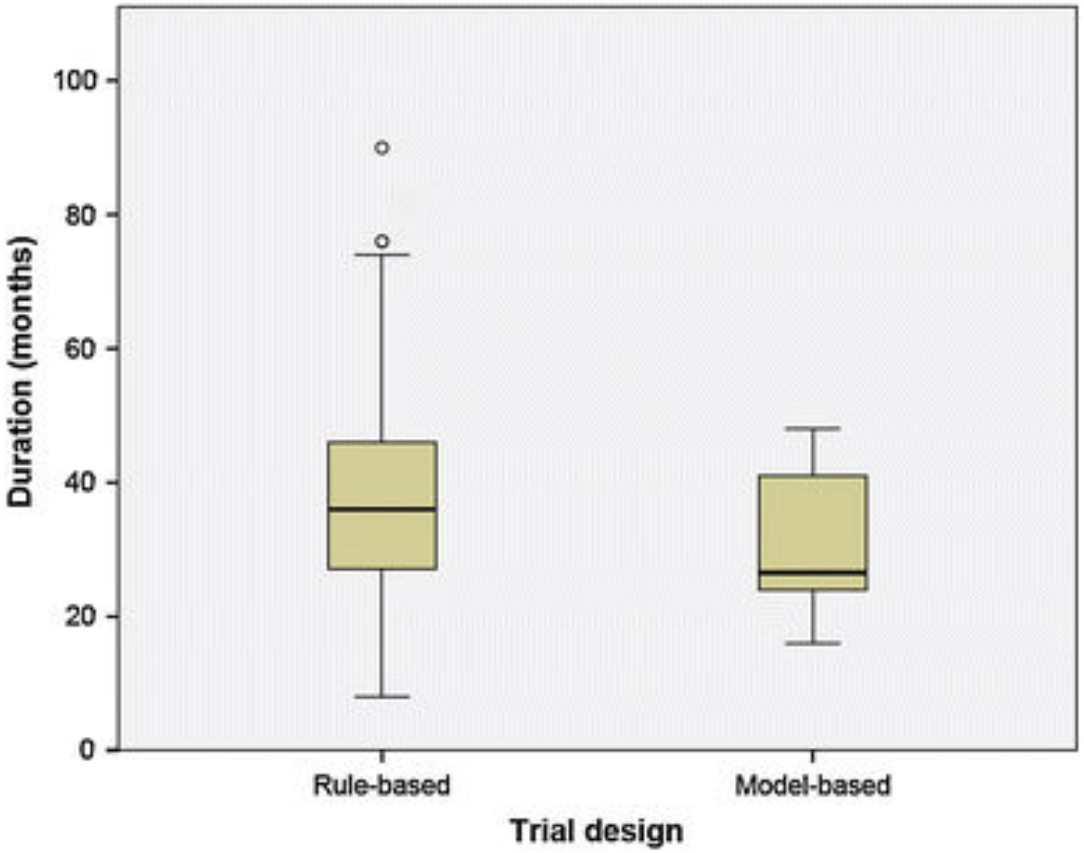
- Phase I trials typically not hypothesis-driven, e.g., the primary objective is to evaluate safety and establish MTD/RP2D
- Statistical analysis typically descriptive, e.g., tabulate toxicity by grade and type
- Challenging and critical part lies in gathering additional data to justify RP2D
- The data collected must be “fit for purpose”

Phase I Trial Designs

- **Algorithm-based designs**
  - Example: 3+3 design
  - **Transparent, easy to implement, but poor performance**
- **Model-based designs**
  - Examples: Continual Reassessment Method (CRM), Escalation With Overdose Control (EWOC), Bayesian Logistic Regression Method (BLRM)
  - **Superior performance, but function as a "blackbox" and difficult to implement**
- **Model-Assisted Designs**
  - Examples: Bayesian Optimal Interval (BOIN), and keyboard design
  - **Transparent and easy to implement with superior performance**

References: O'Quigley et al. 1990; Babb et al., 1998; Neuenschwander et al., 2008; Liu and Yuan, 2015; Yan, Mandrekar and Yuan, 2017

Model-based/Model-Assisted vs. Rule-Based Phase I Oncology Trials: Duration



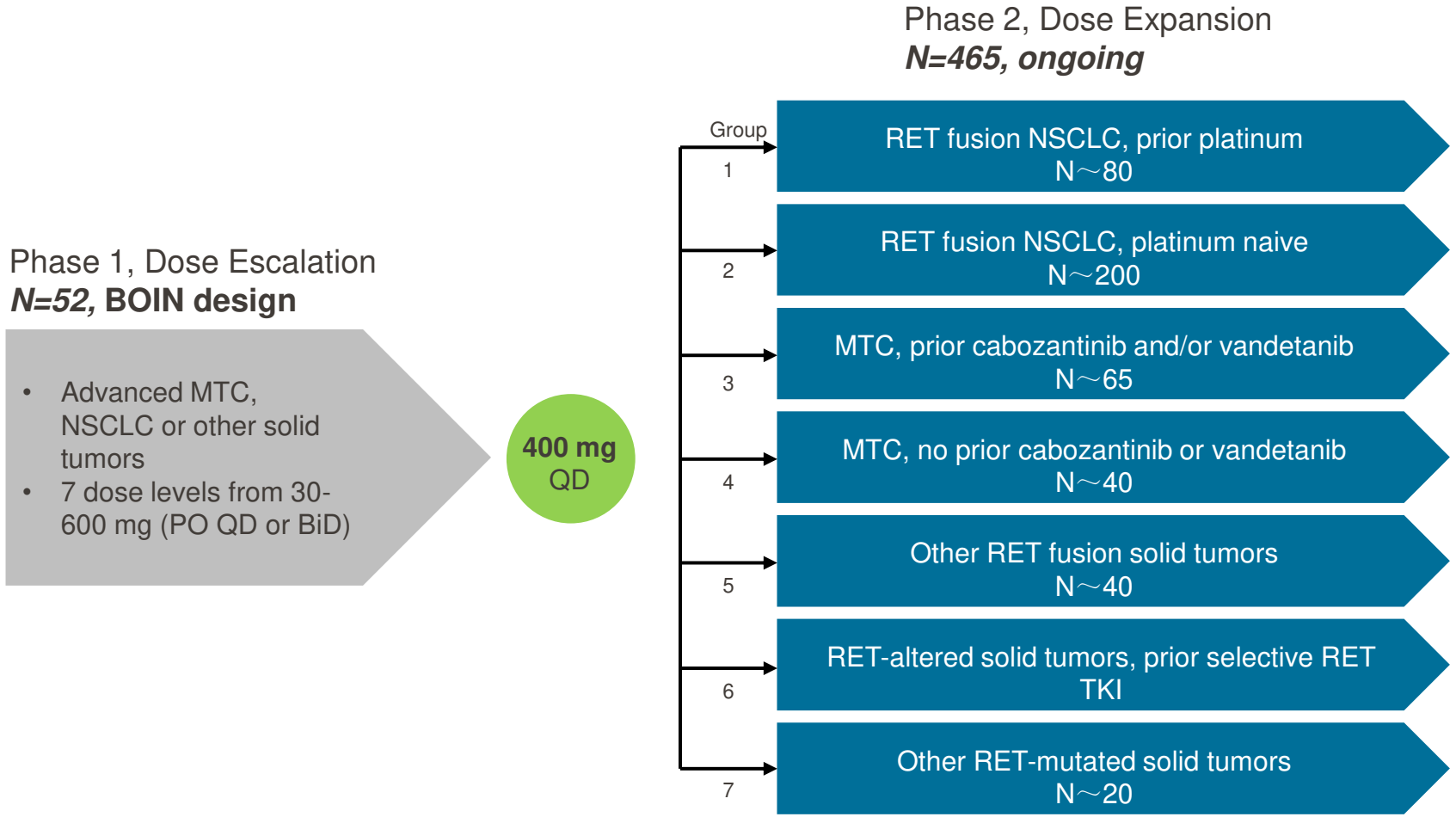
172 articles published over 2 years

Model-based trials:

- needed 10 months less than rule-based trials (26 vs. 36 months; p = 0.25)
- Fewer patients treated at dose-levels below the RP2D (31 % versus 40 %; p = 0.73)
- Safety preserved (13 % DLTs versus 14 % DLTs)

van Brummelen. *et al. J Pharmacokinet Pharmacodyn* **43**, 235–242 (2016)

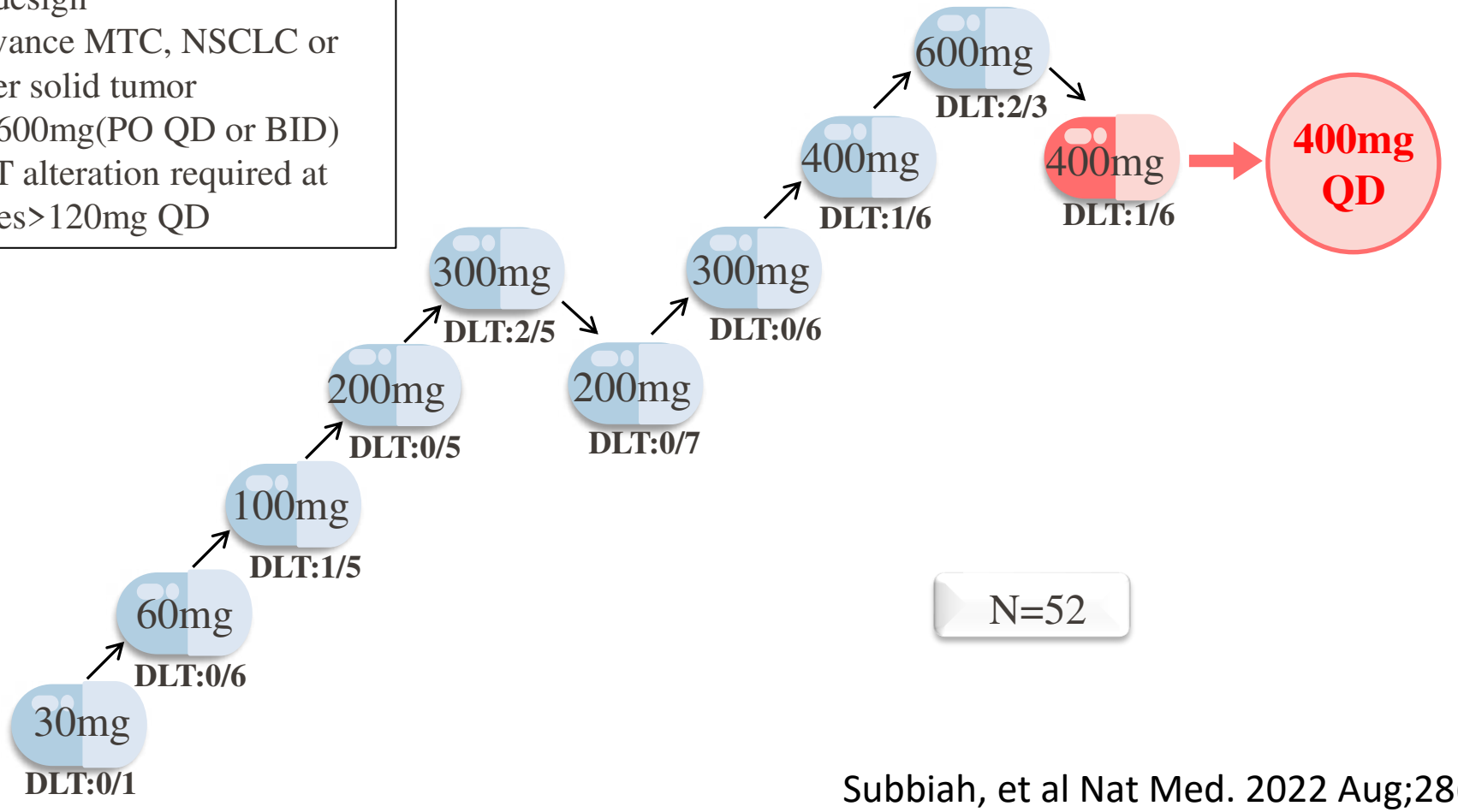
ARROW Trial: Design



Abbreviations: BOIN = Bayesian optimal interval; MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; RET = rearranged during transfection; TKI = tyrosine kinase inhibitor; PO, orally; QD, once daily; BID, twice daily.

ARROW Trial: using BOIN

BOIN design
- Advance MTC, NSCLC or other solid tumor
- 30-600mg(PO QD or BID)
- RET alteration required at doses>120mg QD



Subbiah, et al Nat Med. 2022 Aug;28(8):1640-1645.

Phase II Dose Expansion Cohorts

Table 2. Efficacy results in ARROW.

***RET* fusion–positive NSCLC**	**Previously treated w/platinum chemotherapy (*N* = 87)**	**Treatment naïve (*N* = 27)**
Overall response rate[a] (95% CI)	57 (46–68)	70 (50–86)
Complete response, %	5.7	11
Partial response, %	52	59
Duration of response	*N* = 50	*N* = 19
Median in months (95% CI)	NE (15.2–NE)	9.0 (6.3–NE)
% with ≥ 6 months[b]	80	58
***RET*-mutant MTC**	**Prior cabozantinib or vandetanib (*N* = 55)**	**Cabozantinib and vandetanib naïve (*N* = 29)**
Overall response rate[a] (95% CI)	60 (46–73)	66 (46–82)
Complete response, %	1.8	10
Partial response, %	58	55
Duration of response	*N* = 33	*N* = 19
Median in months (95% CI)	NR (15.1–NE)	NR (NE–NE)
% with ≥ 6 months[b]	79	84
***RET* fusion–positive thyroid cancer**	***N* = 9**	
Overall response rate[a] (95% CI)	89 (52–100)	
Complete response, %	0	
Partial response, %	89	
Duration of response	*N* = 8	
Median in months (95% CI)	NR (NE–NE)	
% with ≥ 6 months[b]	100	

Accelerated Approval of Pralsetinib

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FDA approves pralsetinib for lung cancer with RET gene fusions

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On September 4, 2020, the Food and Drug Administration granted accelerated approval to pralsetinib (GAVRETO, Blueprint Medicines Corporation) for adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

Today, FDA also approved the Oncomine Dx Target (ODxT) Test (Life Technologies Corporation) as a companion diagnostic for pralsetinib.

Efficacy was investigated in a multicenter, open-label, multi-cohort clinical trial (ARROW, NCT03037385) in patients whose tumors had RET alterations.

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FDA approves pralsetinib for RET-altered thyroid cancers

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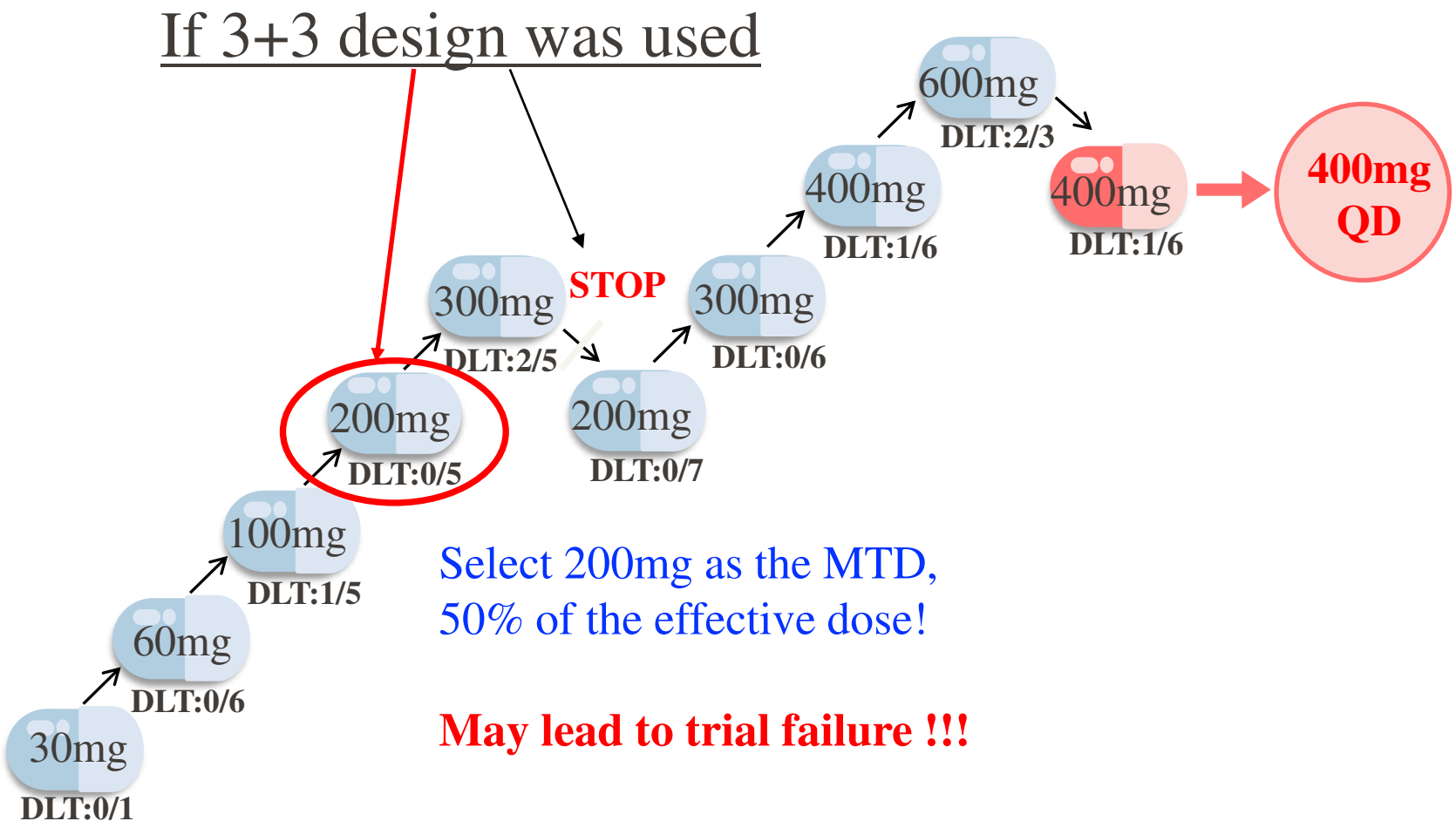
On December 1, 2020, the Food and Drug Administration approved pralsetinib (GAVRETO, Blueprint Medicines Corporation) for adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy or *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

Efficacy was investigated in a multicenter, open label, multi-cohort clinical trial (ARROW, NCT03037385) in patients whose tumors had *RET* gene alterations. Identification of *RET* gene alterations was prospectively determined in local laboratories using either next generation sequencing, fluorescence *in situ* hybridization, or other tests.

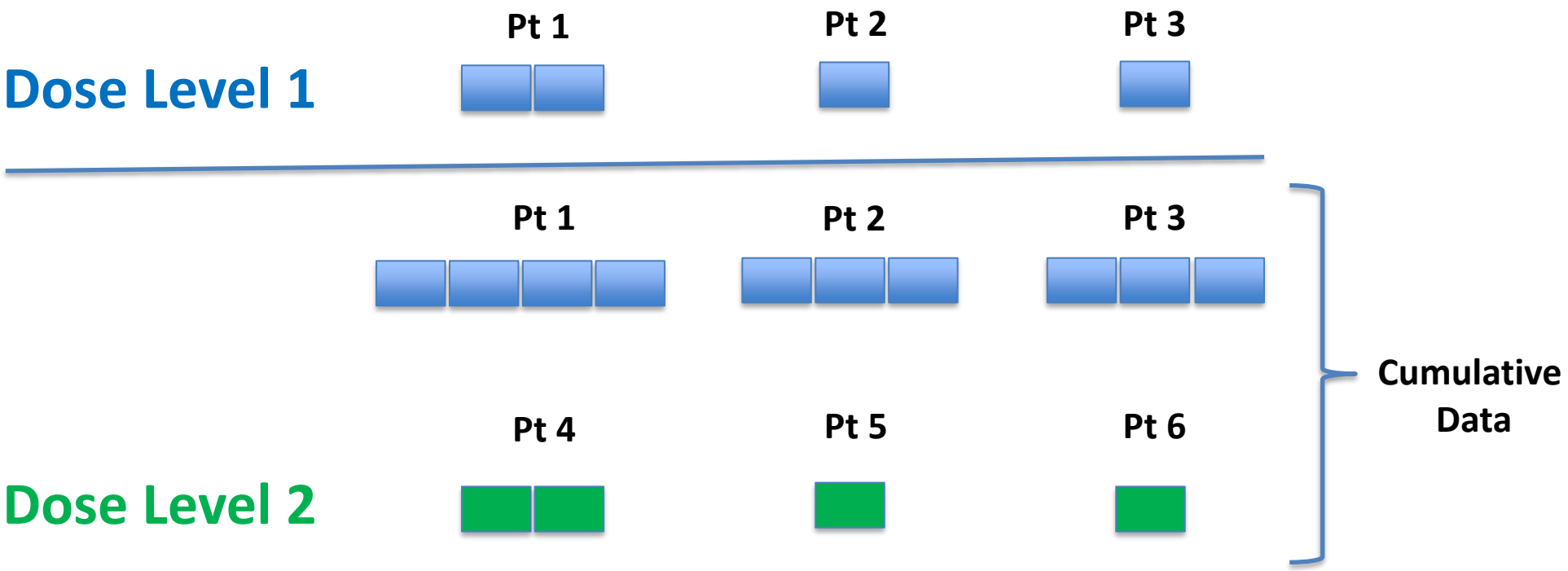
What if 3+3 design was used?



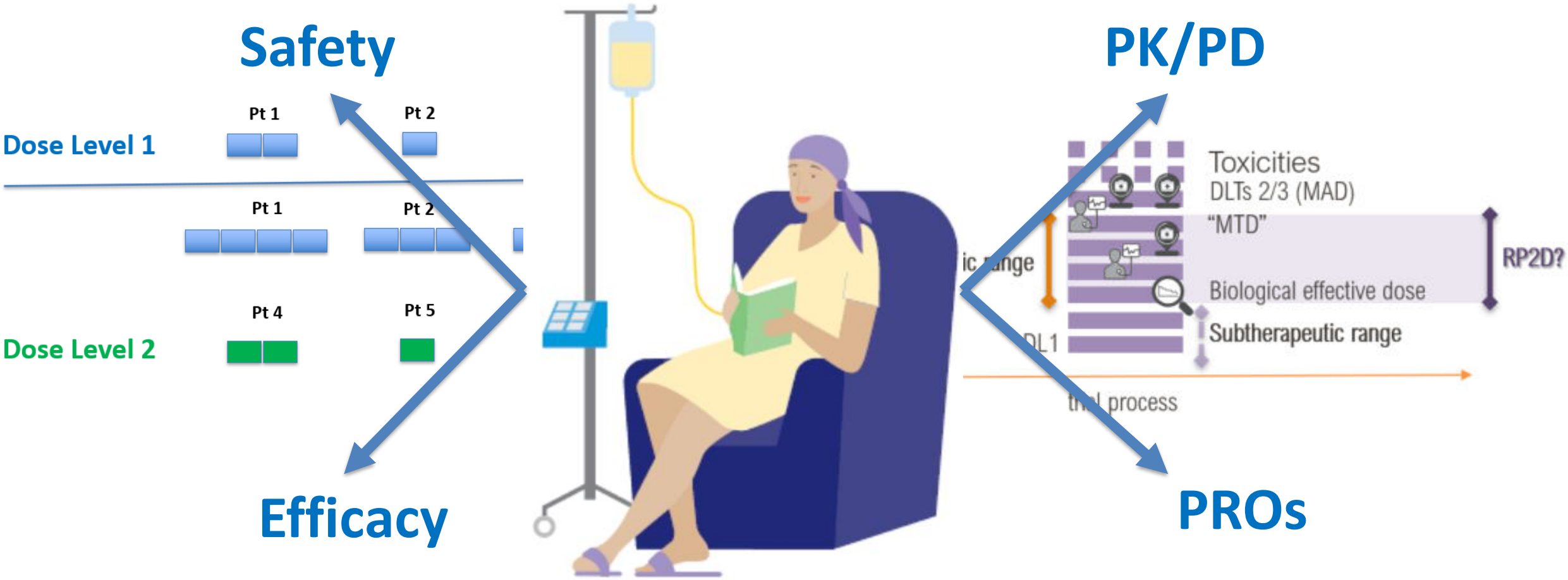
Phase I (Early Phase) Clinical Trials – Opportunities & Challenges

- **Model Assisted/Based Designs**: more flexible, nimble and accurate in identifying the RP2D
- **Challenges**:
  - More patients may be needed
  - Most model designs still utilizing toxicity data from C1
  - Collecting and incorporating PD and efficacy data
  - **Investigator mindset:** rule-based →model-based designs

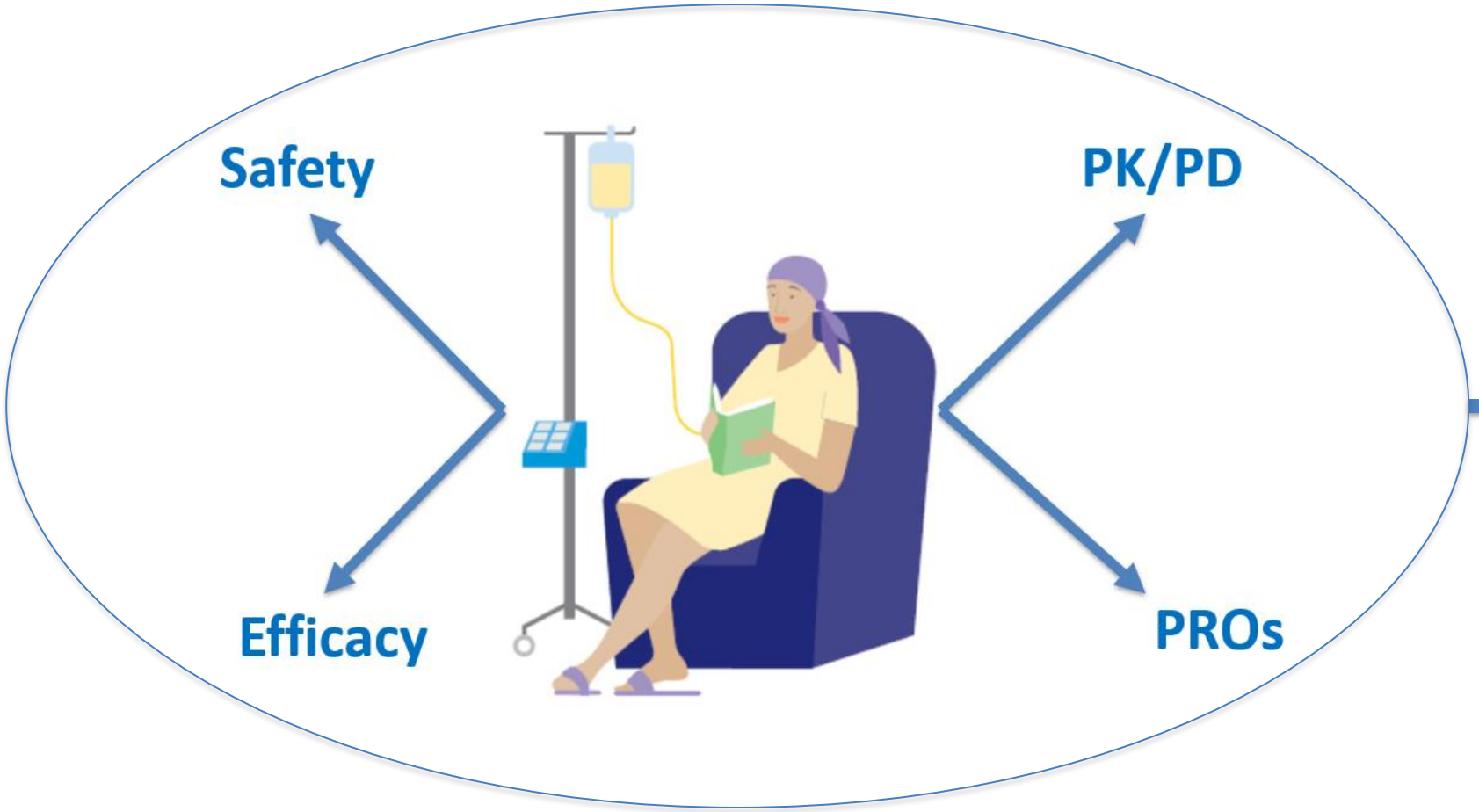
Flexible Smart Model



Flexible Smart Model



Flexible Smart Model



Collect Cumulative Data for RP2D Decision Making

Conclusions

- Primary Phase I Trial Objective(s): efficiently and accurately evaluate the safety profile of the drug at potentially therapeutic doses
- Model Based Designs: more flexible and accurate at identifying RP2D and can be as easy to implement as the 3+3 design
- Don't always aim to cut the sample size. A reasonable sample size will save on patient numbers, cost, and time by substantially improving the trial's success rate.
- Challenge: incorporation of later cycle safety data, efficacy, pre-clinical, PD and “class effects” in identification of the RP2D


ThankYou!

FDA-AACR Public Workshop On
OPTIMIZING DOSAGES FOR ONCOLOGY DRUG PRODUCTS: QUANTITATIVE APPROACHES TO SELECT DOSAGES FOR CLINICAL TRIALS
February 15 and 16, 2024 I Washington, DC

How to Pivot Beyond Rule-Based and Model-Based Determinations to Support Dosage Selection

Ying Yuan, Ph.D.
The University of Texas MD Anderson Cancer Center

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Disclosure Information

Ying Yuan

I have the following relevant financial relationships to disclose:

Founder of Polaris Consulting LLC

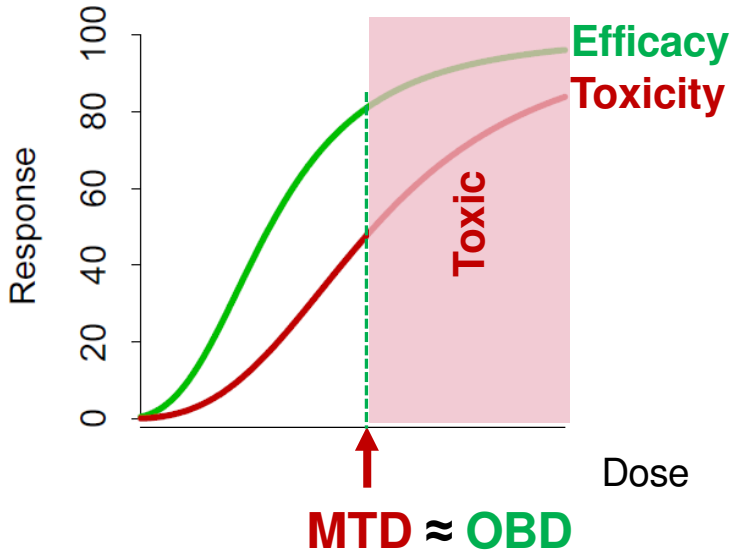
Challenges of dose optimization

- Dose optimization presents a high-dimensional challenge, encompassing diverse data and considerations.
  - "Relevant nonclinical and clinical data, as well as the dose- and exposure-response relationships for safety and efficacy should be evaluated to select a dosage(s) for clinical trial(s)." (FDA Guidance)
- I will focus on two key areas for trial design and decision-making:
  - **Risk-benefit tradeoff**
  - **Tolerability** (e.g., late-onset toxicity and low-grade toxicity)

Target therapies demonstrate different dose-response relationships

Cytotoxic Chemotherapy

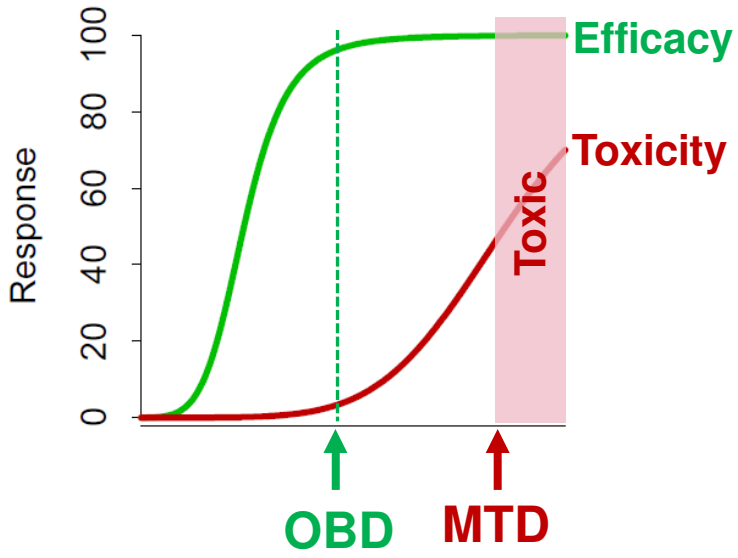
Narrow Therapeutic Index



- MTD-based dose finding is often appropriate

Targeted Therapies

Wide Therapeutic Index



- **Safety alone is not sufficient to inform optimal RP2D** (recommended phase 2 dose)

MTD: maximum tolerated dose. **OBD**: optimal biological dose

Consider both toxicity and efficacy

- To determine the optimal dose, it is imperative to consider both toxicity and efficacy

MTD

	d1	d2	d3	d4	d5
Pr(toxicity)	0.08	0.12	0.3	0.45	0.55
Pr(efficacy)	0.30	0.50	0.51	0.51	0.52

Optimal biological dose (OBD)

Measuring risk-benefit tradeoff

- Toxicity and efficacy endpoints should be carefully chosen to reflect the risk and benefit
- Utility provides an intuitive approach to evaluating risk-benefit tradeoff (aka., desirability)
  - Example:

Toxicity	Response	
	No	Yes
No	40	100
Yes	0	60

Desirability of a dose

- Example (cont.)

Toxicity	Response	
	No	Yes
No	40 Prob (occurrence) = 0.1	100 Prob (occurrence) = 0.4
Yes	0 Prob (occurrence) = 0.3	60 Prob (occurrence) = 0.2

Desirability = $100\times0.4 + 40\times0.1 + 60\times0.2 + 0\times0.3 = 56$

Use the utility to identify the OBD

- Revise the example:

MTD

Pr(toxicity) = (0.08, 0.12, 0.30, 0.45, 0.55)

Pr(efficacy) = (0.30, 0.50, 0.51, 0.51, 0.52)

Desirability = (54.8, **65.2**, 58.6, 52.6, 49.2)

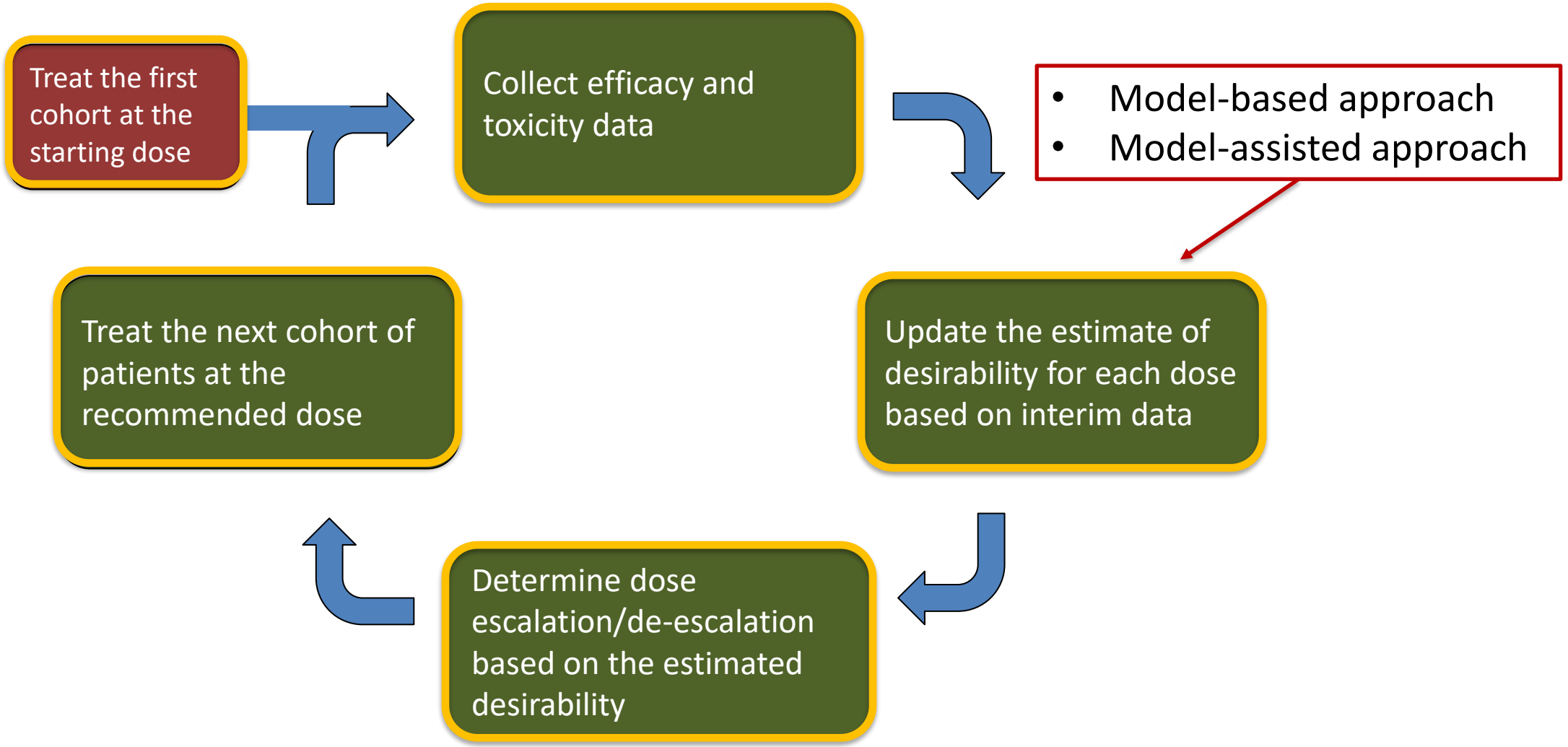
Dose $d = 2$ is the **OBD**

Advantages of utility approach

- **Easy to understand:** clinicians and patients understand clinical outcomes better than probabilities
- **Scalable**: straightforward to account for low-grade toxicity and more endpoints (Liu et al., 2018).

Toxicity	Response	
	No	**Yes**
No	40	**100**
Low grade	20	70
DLT	**0**	50

Efficacy-integrated dose finding



Model-based approach

- Assume a statistical model describing dose-toxicity and dose-efficacy relationships
  - Often complicated
- Examples: EffTox (Thall and Cook, 2004), Late-onset EffTox (Lo-EffTox, Jin et al., 2014)
- Pros: accounts for risk-benefit trade
- Cons: complicated to implement, re estimation, subject to the influence

Example: Gumbel model (e.g., EffTox design)

- Dose-toxicity model: $logit(\pi_T|d_j) = \alpha_T + \beta_T d_j$, where d_j is the dose of level j
- Dose-efficacy model: $logit(\pi_E|d_j) = \alpha_E + \beta_{E,1} d_j + \beta_{E,2} d_j^2$
- Joint model: $\pi_{a,b} = (\pi_E)^a(1-\pi_E)^{1-a}(\pi_T)^b(1-\pi_T)^{1-b} + (-1)^{a+b}\pi_E(1-\pi_E)\,\pi_T(1-\pi_T)\left(\frac{e^{\psi}-1}{e^{\psi}+1}\right)$, $a, b = 0 \text{ or } 1$,

where $\pi_T|d_j = \Pr(y_T = 1|d_j)$ and $\pi_E|d_j = \Pr(y_E = 1|d_j)$

Trial examples

- Dose optimization trials based on the Lo-EffTox design (Jin et al., 2014)

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

A phase 1-2 trial of sitravatinib and nivolumab in clear cell renal cell carcinoma following progression on antiangiogenic therapy

Pavlos Msaouel[1,2,3]†‡, Sangeeta Goswami[1,4]†, Peter F. Thall[5], Xuemei Wang[5], Ying Yuan[5], Eric Jonasch[1], Jianjun Gao[1,2], Matthew T. Campbell[1], Amishi Yogesh Shah[1], Paul Gettys Corn[1], Alda L. Tam[6], Kamran Ahrar[6], Priya Rao[7], Kanishka Sircar[3,7], Lorenzo Cohen[8], Sreyashi Basu[9], Fei Duan[9], Sonali Jindal[9], Yuwei Zhang[9], Hong Chen[9], Shalini S. Yadav[9], Ronald Shazer[10], Hirak Der-Torossian[10], James P. Allison[4,9], Padmanee Sharma[1,4,9]*‡, Nizar M. Tannir[1]*‡

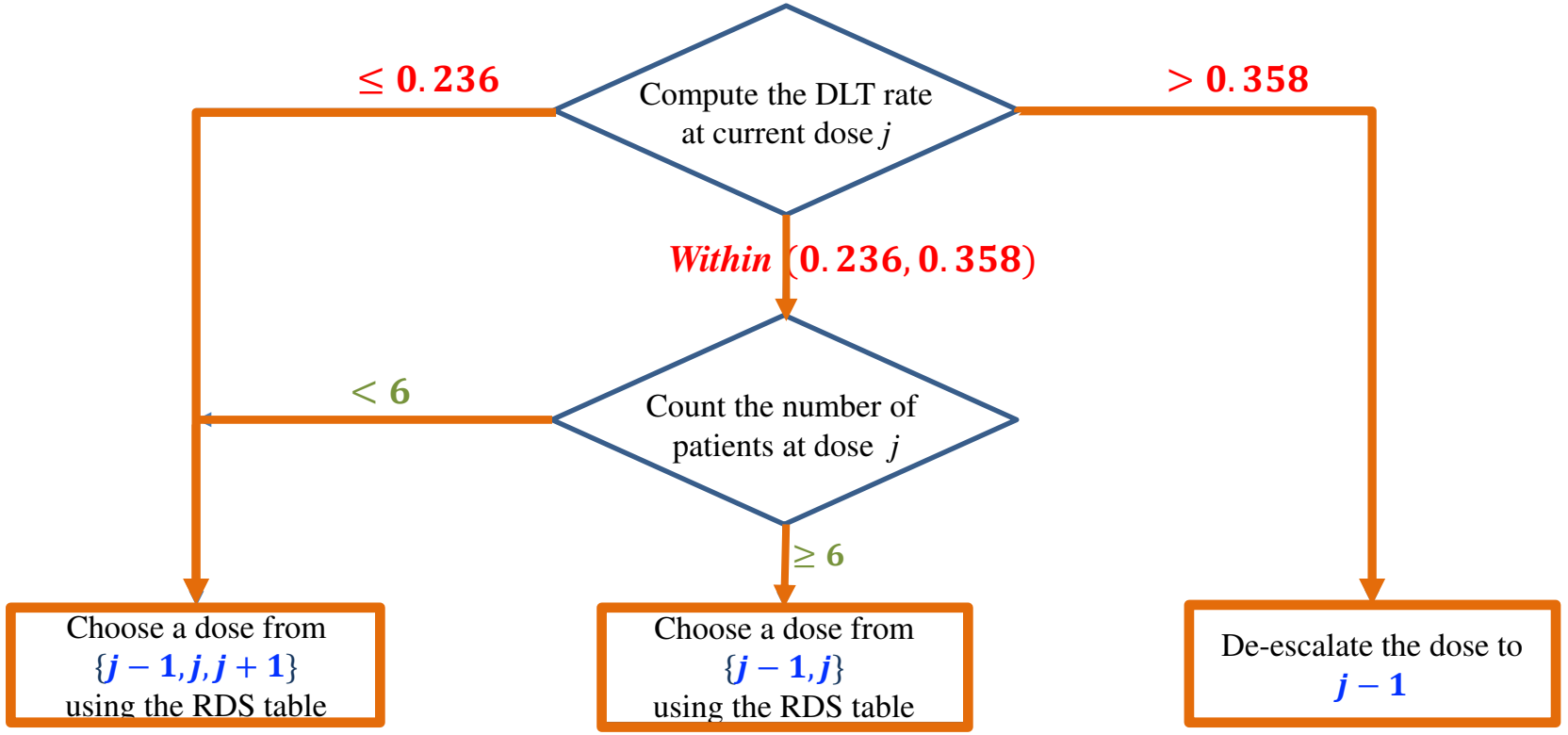
Lancet Oncol 2023; 24: 1387–98

Stereotactic body radiotherapy with or without selective dismutase mimetic in pancreatic adenocarcinoma: an adaptive, randomised, double-blind, placebo-controlled, phase 1b/2 trial

Cullen M Taniguchi, Jessica M Frakes, Todd A Aguilera, Manisha Palta, Brian Czito, Manoop S Bhutani, Lauren E Colbert, Joseph Abi Jaoude, Vincent Bernard, Shubham Pant, Ching-Wei D Tzeng, Dae Won Kim, Mokenge Malafa, James Costello, Geena Mathew, Neal Rebueno, Eugene J Koay, Prajnan Das, Ethan B Ludmir, Matthew H G Katz, Robert A Wolff, Sam Beddar, Gabriel O Sawakuchi, Shalini Moningi, Rebecca S Slack Tidwell, Ying Yuan, Peter F Thall, Robert A Beardsley, Jon Holmlund, Joseph M Herman, Sarah E Hoffe

Model-assisted approach

- An example: Decision tree of BOIN12 (Lin et al., 2020)



* RDS: rank-based desirability score, see next page

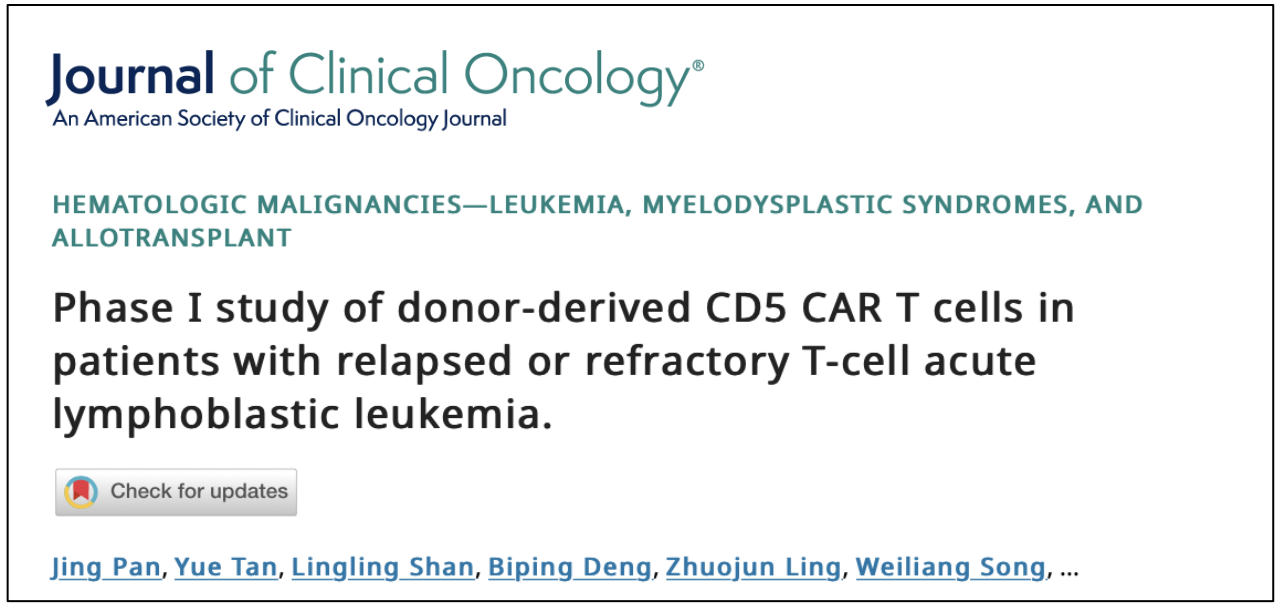
Desirability table

No. Pts.	No. Tox.	No. Eff.	Desirability Score
0	0	0	60
3	0	0	35
3	0	1	55
3	0	2	76
3	0	3	91
3	1	0	24
3	1	1	44
3	1	2	63
3	1	3	80
3	2	0	13
3	2	1	31
3	2	2	48
3	2	3	69
3	3	*Any*	E
6	0	0	22
6	0	1	38
6	0	2	51
6	0	3	67

No. Pts.	No. Tox.	No. Eff.	Desirability Score
6	0	5	93
6	0	6	100
6	1	0	15
6	1	1	27
6	1	2	42
6	1	3	56
6	1	4	72
6	1	5	87
6	1	6	96
6	2	0	8
6	2	1	19
6	2	2	34
6	2	3	47
6	2	4	64
6	2	5	77
6	2	6	90
6	3	0	4
6	3	1	12

Trial examples

- BOIN12 (NCT04835519, NCT05032599)
  - Phase I/II Study of Enhanced CD33 CAR T Cells in Subjects With Relapsed or Refractory Acute Myeloid Leukemia
  - Donor-Derived CD5 CAR T Cells in Subjects With Relapsed or Refractory T-Cell Acute Lymphoblastic Leukemia



Account for late-onset toxicity

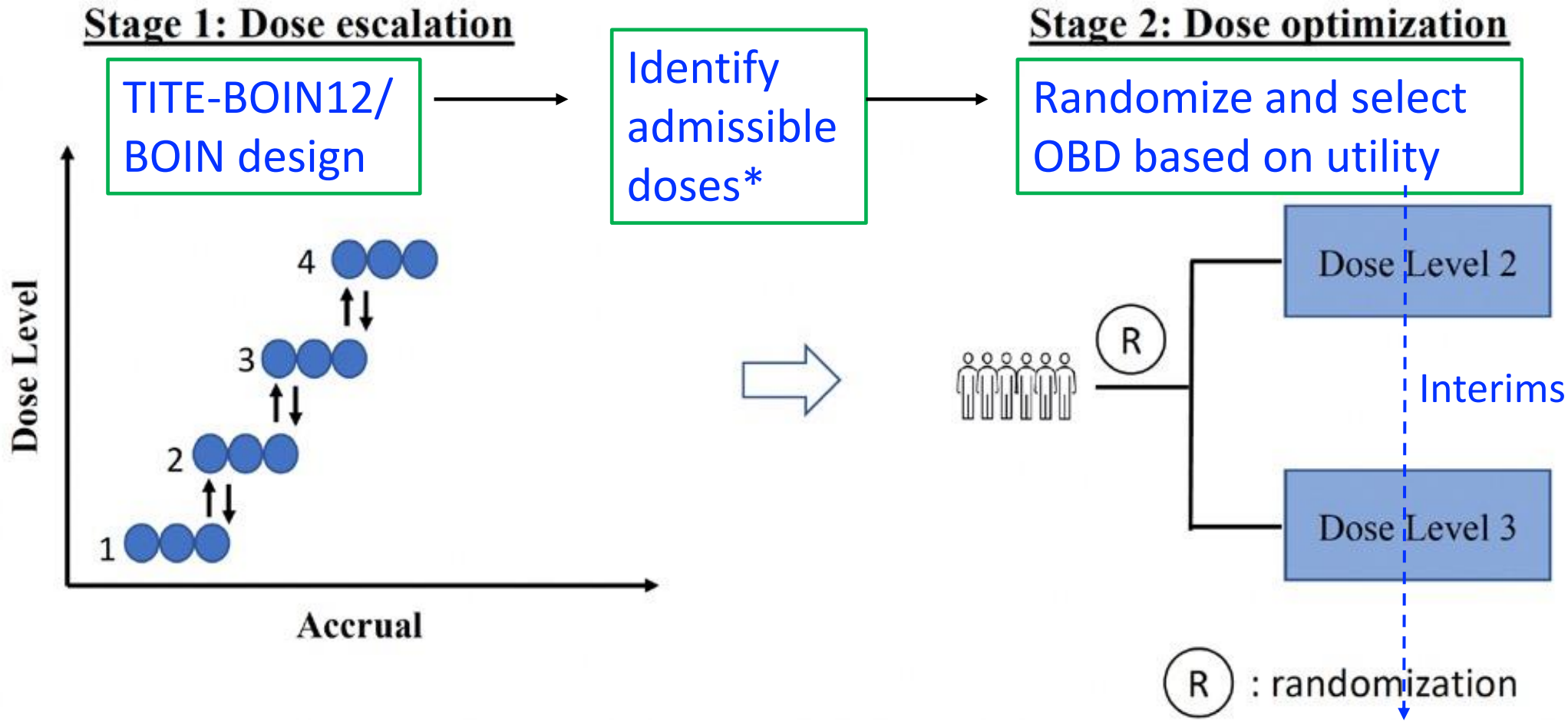
- Targeted therapies are often administered for long periods, leading to late-onset toxicities and persistent low-grade toxicities

- **Key challenge**: these toxicity events require long observation windows over multiple cycles, thus very limited data are available during the trial

Some solutions for late-onset toxicity

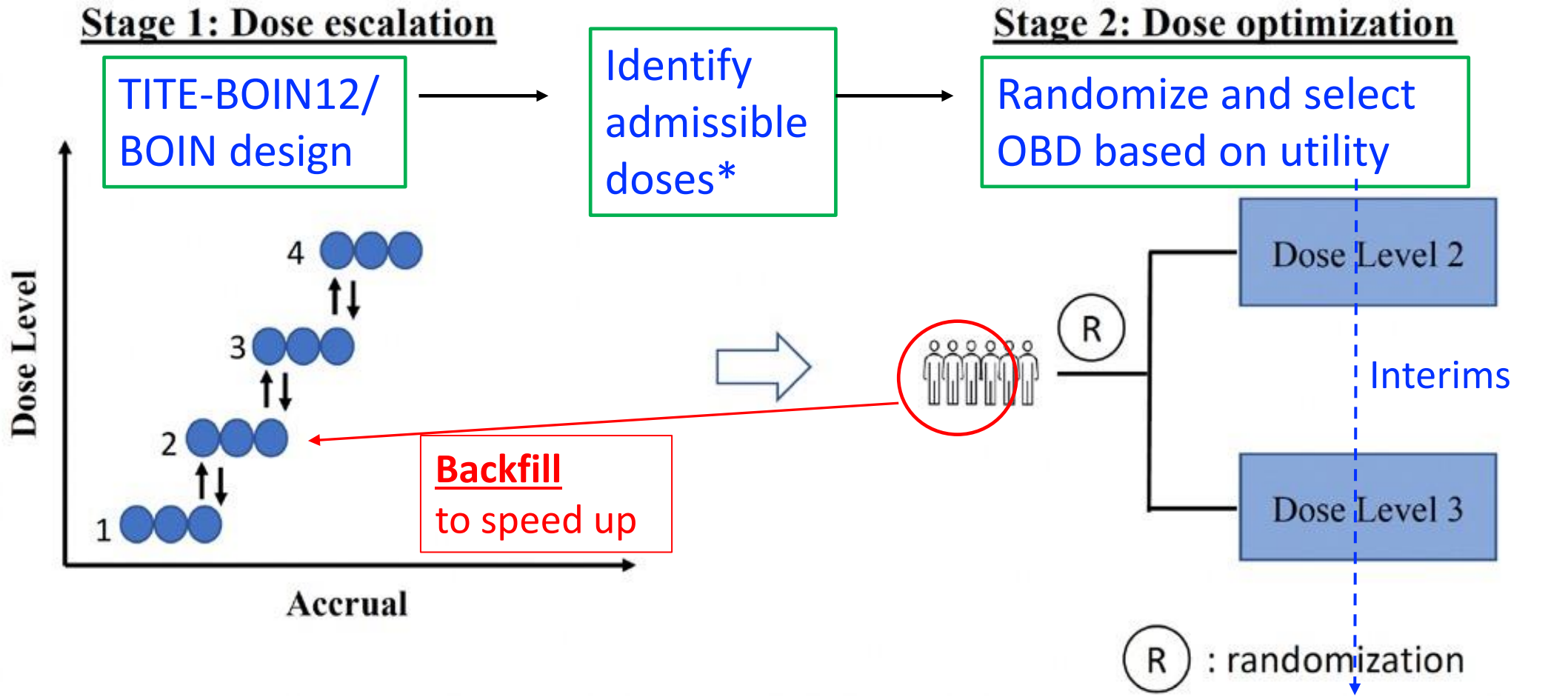
- Time-to-event (TITE) designs (e.g., TITE-BOIN12, Lo-EffTox)
  - Predict late-onset toxicity using a statistical method
- Two-stage approach
  - After the dose escalation, add a second stage of assigning more patients to two candidate RP2D. This buys some time and enables the collection of more long-term safety data
- Seamless phase 1-2-3 designs
  - Continue optimizing dose in phases 2 and 3

Two-stage dose finding



*doses are safe with promising antitumor activities
BOP2: Bayesian optimal phase 2 design (Zhou et al., 2017)

Two-stage dose finding



*doses are safe with promising antitumor activities
BOP2: Bayesian optimal phase 2 design (Zhou et al., 2017)

Backfill during dose escalation

CLINICAL CANCER RESEARCH | PERSPECTIVE

Backfilling Patients in Phase I Dose-Escalation Trials Using Bayesian Optimal Interval Design (BOIN)

Yixuan Zhao[1], Ying Yuan[2], Edward L. Korn[3], and Boris Freidlin[3]

ABSTRACT

In recent years, there has been increased interest in incorporation of backfilling into dose-escalation clinical trials, which involves concurrently assigning patients to doses that have been previously cleared for safety by the dose-escalation design. Backfilling generates additional information on safety, tolerability, and preliminary activity on a range of doses below the maximum tolerated dose (MTD), which is relevant for selection of the recommended phase II dose and dose optimization. However, in practice, backfilling may not be rigorously defined in trial protocols and implemented consistently. Furthermore, backfilling designs require careful planning to minimize the probability of treating additional patients with potentially inactive agents (and/or subtherapeutic doses). In this paper, we propose a simple and principled approach to incorporate backfilling into the Bayesian optimal interval design (BOIN). The design integrates data from the dose-escalation and backfilling components of the design and ensures that the additional patients are treated at doses where some activity has been seen. Simulation studies demonstrated that the proposed backfilling BOIN design (BF-BOIN) generates additional data for future dose optimization, maintains the accuracy of the MTD identification, and improves patient safety without prolonging the trial duration.

Reference

- Yuan Y., Zhou H., Liu S. (2024) Statistical and practical considerations in planning and conduct of dose-optimization trials, *Clinical Trials*, https://doi.org/10.1177/17407745231207085

Thank You!

SESSION 1B: ALTERNATIVE DESIGNS FOR DOSE-FINDING TRIALS: ENDING RELIANCE ON SHORT-TERM SAFETY

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AACR American Association for Cancer Research

MODERATOR

Patricia M. LoRusso, DO, PhD (hc), FAACR
Yale Cancer Center

INTRODUCTORY SPEAKER

Ying Yuan, PhD
MD Anderson

ADDITIONAL PANELISTS

Jonathon Vallejo, PhD
U.S. Food and Drug Administration

Jamie Brewer, MD
U.S. Food and Drug Administration

Amit Roy, PhD
PumasAI

Bruno Gomes DVM, PhD
Roche

Brian Koffman, MDCM (retired), MSEd
CLL Society