Bayesian Adaptive Designs for Dose Optimization

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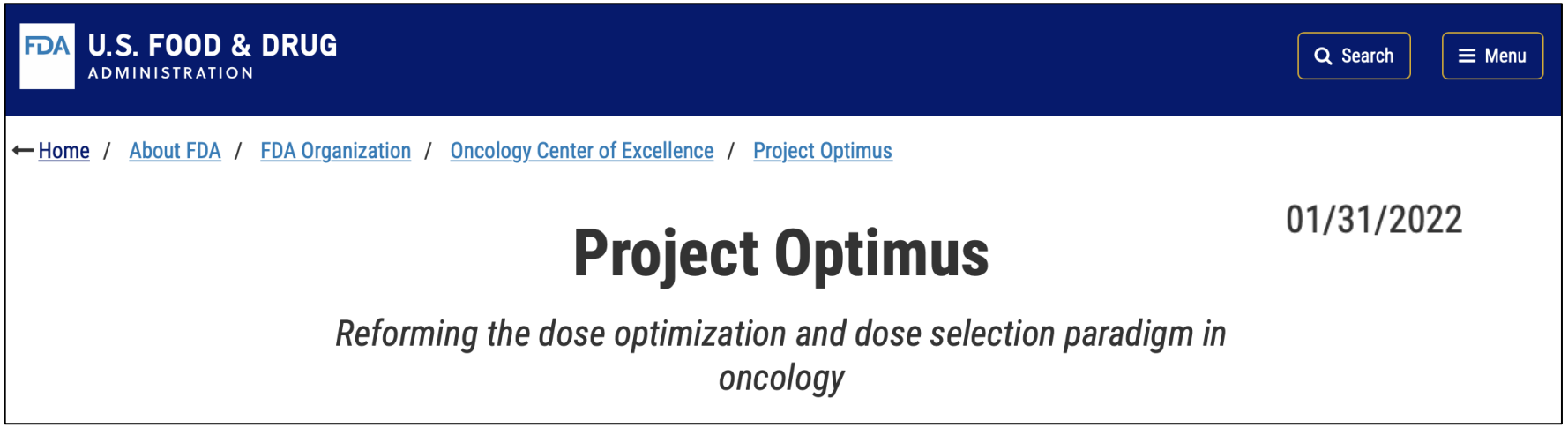
Project Optimus

- In 2022, FDA OCE initiated Project Optimus “ to reform the dose optimization and dose selection paradigm in oncology drug development.”



Sotorasib

- In May 2021, FDA approved sotorasib for metastatic non-small-cell lung cancers harboring the KRAS G12C mutation
- FDA has required that Amgen compared their approved 960mg dose with a 240mg dose, as one of their postmarketing requirements
- The FDA has required that Amgen submit a final study report by February 2023, also indicated that this study will inform possible future labeling updates
- This signals paradigm shifting with new scrutiny and more emphasis on optimizing the dose for targeted oncology drugs from the FDA

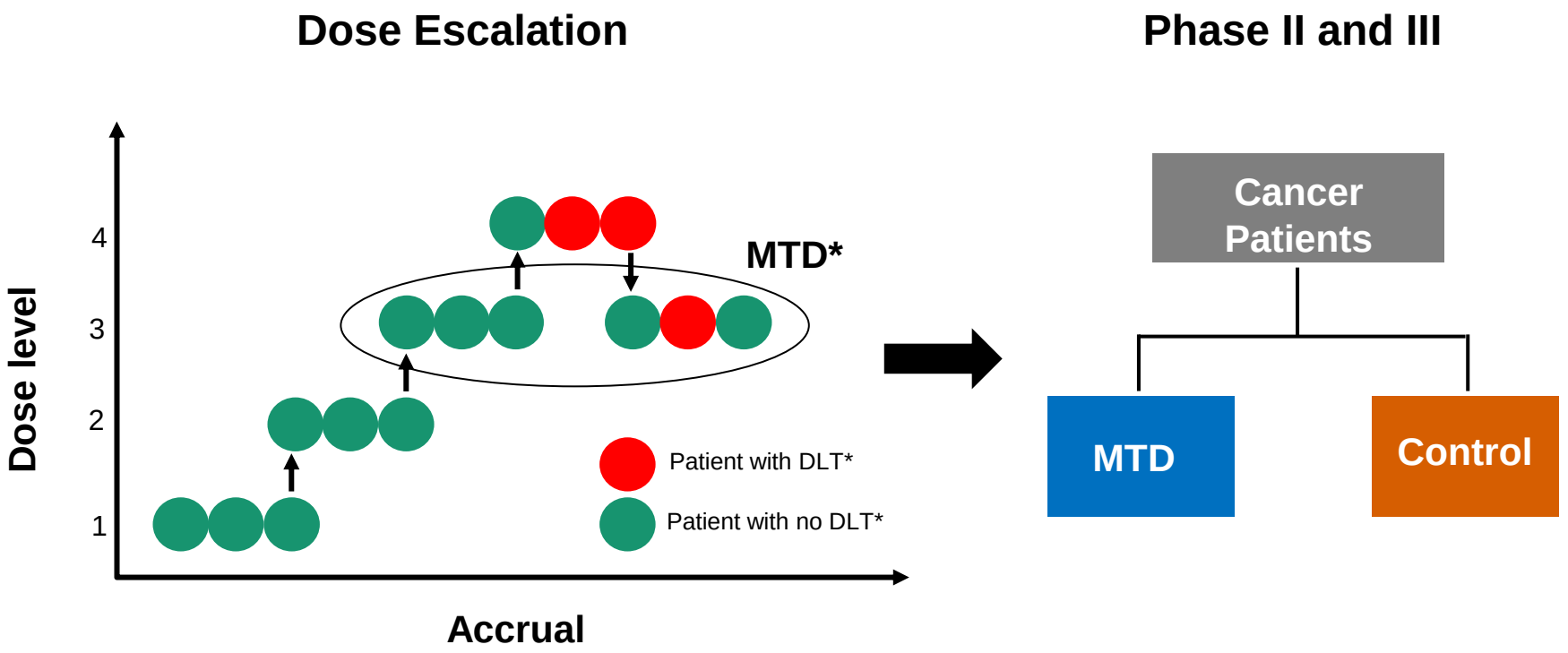
Benefit-Risk Assessment for New Drug and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)

September 2021
Clinical/Medical

Traditional Dose Selection Paradigm



*MTD = Maximum tolerated dose, DLT = Dose-limiting toxicity

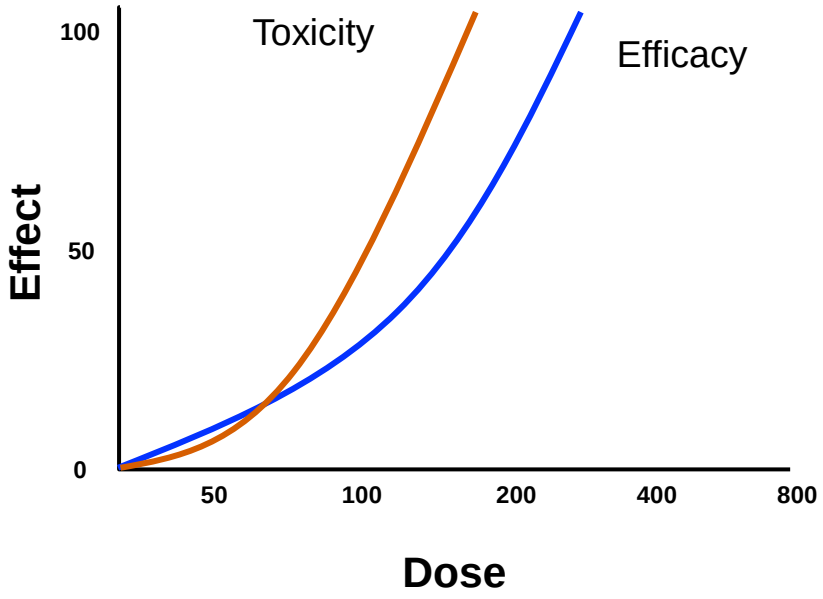
Targeted Drugs

- The traditional more-is-better paradigm is built upon the development of cytotoxic drugs
- It is not suitable for developing targeted drugs that have different mechanisms of action (Shah, et al., 2021)
  - Increasing doses beyond a certain level may not enhance antitumor activity
  - Dose-limiting toxic effects may not be observed at clinically active doses
  - Serious toxic effects may occur only after multiple cycles of experimental treatment

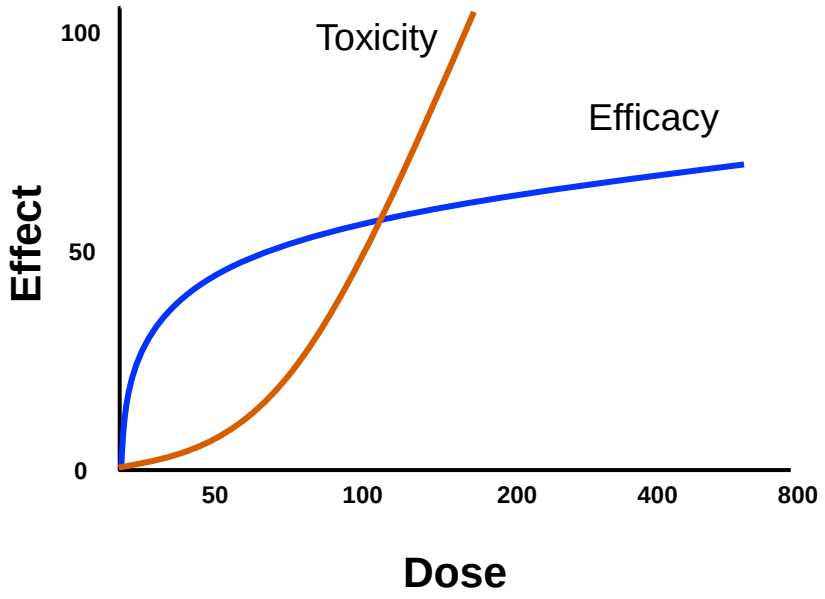
Shah, et al., NEJM, 2021, 385 (16), 1445-1447

Cytotoxic vs. Targeted Drugs

Cytotoxic Chemotherapy



Targeted Therapies



MTD vs. OBD

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)

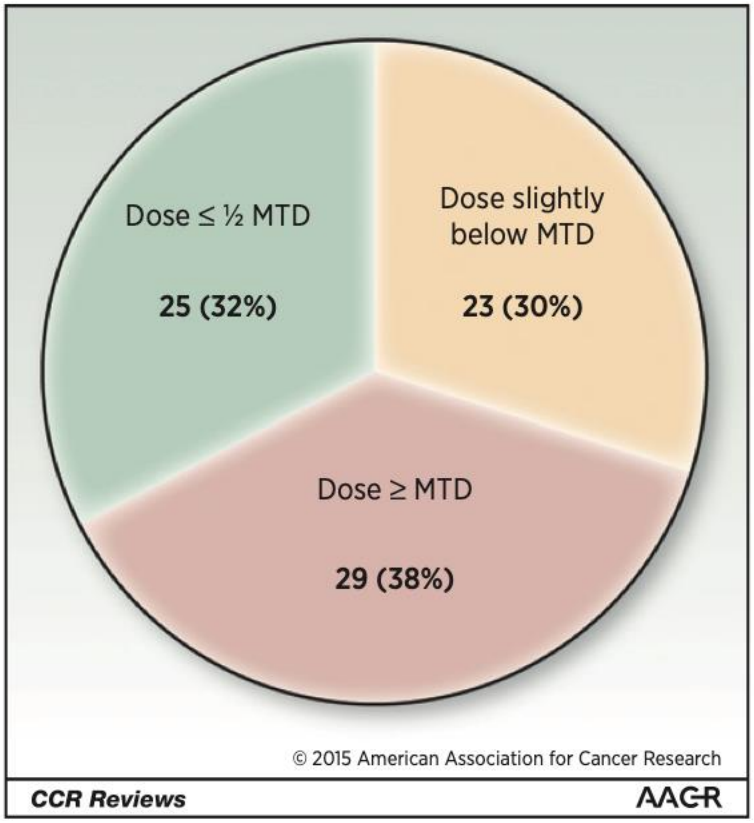


Figure 1.

Summary of results from the review of MTDs and approved doses. Roughly two thirds (48/77) of the compounds have approved doses less than MTD, with roughly one third of them being dosed at less than one half of MTD.

Sachs, et al., (2015) Clin Cancer Res; 22(6) 1-7

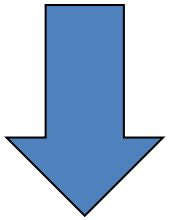
Compound	MTD	Clinical dose
Cetuximab	Not reached *	250 mg/m^2 q1w as maintenance dose (initial dose = 400 mg/m^2)
Pembrolizumab	Not reached up to 10 mg/kg q2w	2 mg/kg q3w
Idelalisib	Not reached up to 350 mg twice a day	150 mg twice a day
Decitabine	1,500–2,000/mg/m^2 over 1–3 days	20 mg/m^2/d over 5 days
Vismodegib	Not reached up to 540 mg/d	150 mg/d
Crizotinib	250 mg twice a day	250 mg twice a day (Alk-positive patients)
Galunisertib	Not able to determine MTD due to potential cardiovascular DLT	Not approved yet; pharmacokinetic–pharmacodynamic model–based intermittent dosing enabled clinical development

*Up to 500 mg/m^2

Sachs, et al., (2015) Clin Cancer Res; 22(6) 1-7

What does this entail?

- Dose transition and selection should be based on the benefit-risk tradeoff (i.e., consider efficacy and toxicity simultaneously), rather than only toxicity



Phase I-II design paradigm*

*Should be distinguished from the design that simply concatenates phase I and II (e.g., find the MTD, followed by cohort expansion)

Phase I-II designs

- Model-based designs
  - EffTox & LO-EffTox designs (Thall and Cook, 2004, Jin et al., 2014), bivariate CRM (Braun, 2002), time-to-event EffTox design (Yuan and Yin, 2009), immunotherapy trial design (Liu, et al., 2018)
  - Nonparametric phase I-II design (Liu and Johnson, 2016)
  - ……
- Model-assisted designs
  - U-BOIN (Zhou et al., 2019), BOIN12 (Lin et al., 2020), BOIN-ET (Takeda, et al., 2018), uTPI (Shi, et al., 2021)

Basic Elements of Phase I-II Design

- **Toxicity and efficacy endpoints** that characterize potential risks and benefits of the treatment being studied
- **Risk-benefit trade-off criterion** that characterizes and quantifies the trade-off between efficacy and toxicity for each dose
- **Statistical model** describing the dose-toxicity and dose-efficacy relationships
- **Adaptive decision rule** that determines the best dose for the next cohort, based on the (dose, toxicity, efficacy) data from all previous patients
- **Admissibility rules** that protect patients in the trial from unacceptably toxic or inefficacious doses
- **Stopping rule** that terminates the trial early if the all doses being considered are unacceptably toxic or inefficacious

Toxicity and Efficacy Endpoints

- Toxicity and efficacy endpoints should be carefully chosen and constructed to reflect the risk and benefit of the treatment, while accounting for logistics for trial implementation
- Toxicity endpoint: dose limiting toxicity, total toxicity burden (to account for low grade toxicity),…
- Efficacy endpoint: tumor response, surrogate efficacy endpoint (e.g., PD or other biomarkers),…
- Ideally, toxicity and efficacy endpoints should be quickly ascertainable to facilitate adaptive decisions

More on Endpoints

- What if the surrogate efficacy endpoint may be not reliable?
  - Typically not an issue as long as the surrogate endpoint is largely concordant with efficacy because we mainly use it to rank the benefit-risk tradeoff (desirability) of doses, not to estimate clinical benefit
  - Final dose selection decision can be based on the clinical efficacy endpoint
- What if efficacy or/and toxicity endpoints are late-onset?
  - Statistical methods are available, e.g., LO-EffTox (model-based),TITE-BOIN12 and U-BOIN (model-assisted)

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Risk-benefit Trade-off Criterion

- Risk-benefit trade-off should be tailored to the trial (e.g., drug and indication)
- Approaches

1) Marginal-probability-based approach

Let π_T and π_E denote toxicity and efficacy probabilities

a) (linear penalty) $U = \pi_E - w\pi_T$ or

$U = \pi_E - w_1\pi_T - w_2 I(\pi_T > \gamma)$,

where w_1 and w_2 are penalty, and γ is a threshold

(Liu and Johnson, 2016)

b) (nonlinear penalty) $U = g(\pi_E, \pi_T; \theta)$, where θ is prespecified parameters (Thall and Cook, 2004)

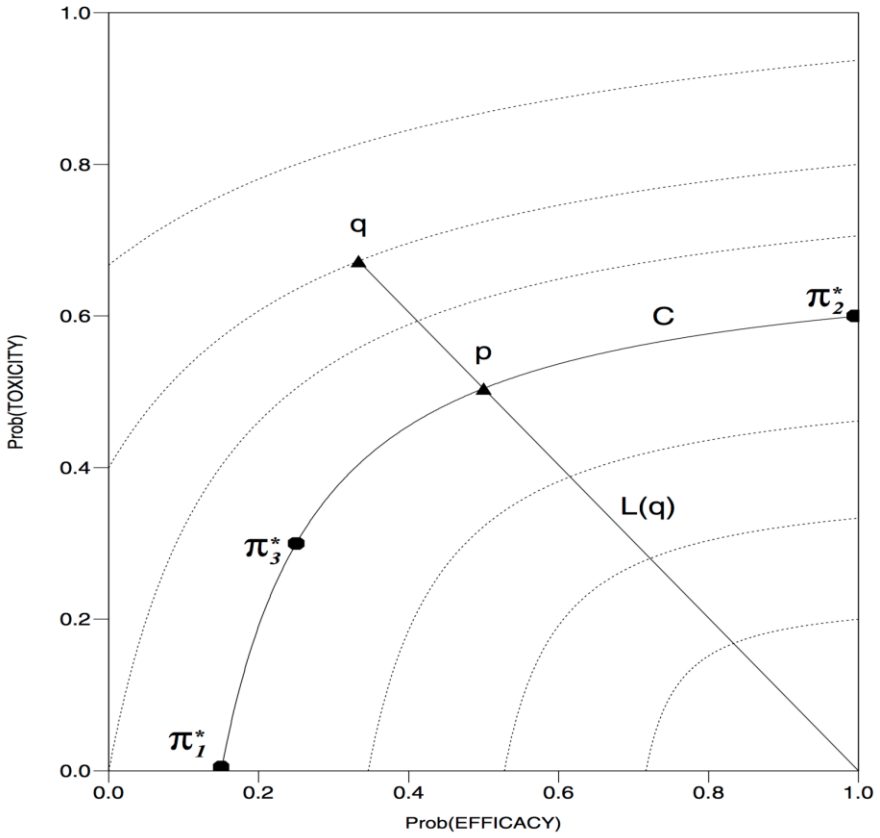


Figure 1. Efficacy–toxicity trade-off contours

$$U = 1 - \left(\left(\frac{1 - \pi_E}{1 - \pi_{1,E}^*} \right)^{\alpha} + \left(\frac{\pi_T}{\pi_{2,T}^*} \right)^{\alpha} \right)^{1/\alpha}$$

where α is estimated based on three elicited equally Desirable (efficacy, toxicity) pairs: $(\pi_{1,E}^*, 0)$, $(1, \pi_{2,T}^*)$ and $(\pi_{3,E}^*, \pi_{3,T}^*)$

Contour based on a nonlinear penalty function (Thall and Cook, 2004)

Risk-benefit Trade-off Criterion

2) Utility-based approach (defined at the outcome level)

Toxicity	Response	
	No ($Y_E = 0$)	Yes ($Y_E = 1$)
No ($Y_T = 0$)	$u_2 = 40$	$u_1 = 100$
Yes ($Y_T = 1$)	$u_4 = 0$	$u_3 = 60$

- Let $u_1, \ldots, u_4$ denote the score ascribed to, and $\pi_1, \ldots, \pi_4$ denote the probabilities of the four possible outcomes
- The desirability (or mean utility) of a dose is given by

$$U = u_1\pi_1 + u_2\pi_2 + u_3\pi_3 + u_4\pi_4$$

MTD vs. 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)

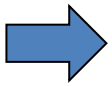
Desirability = (54.8, **65.2**, 58.6, 52.6, 49.2)

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

Advantages of Utility Approach

- **Easy to communicate:** clinicians understand outcomes better than probabilities
- **Very flexible**: contain marginal-probability-based approach as a specifical case when setting $u_2 + u_3 = 100$ (Zhou et al., 2019; Lin et al., 2020):

Toxicity	Response	
	No ($Y_E = 0$)	Yes ($Y_E = 1$)
No ($Y_T = 0$)	$u_2 = 40$	$u_1 = 100$
Yes ($Y_T = 1$)	$u_4 = 0$	$u_3 = 60$



Equivalent to $U = \pi_E - \frac{2}{3}\pi_T$

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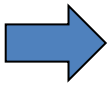

Equivalent to $U = \pi_E$ (select most effective dose)

Advantages of Utility Approach

- **Highly scalable**: more levels for each endpoint and more than two endpoints (Liu et al., 2018)

Toxicity	Response	
	No ($Y_E = 0$)	**Yes ($Y_E = 1$)**
Low ($Y_T = 0$)	$u_2 = 40$	$u_1 = 100$
Moderate ($Y_T = 1$)	$u_4 = 20$	$u_3 = 70$
Severe ($Y_T = 2$)	$u_6 = 0$	$u_5 = 50$

Basic Elements of Phase I-II Design

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Statistical Model

- Dose-toxicity and -efficacy model

  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:
    $\pi_{a,b} = (\pi_E)^a(1-\pi_E)^{1-a}(\pi_T)^b(1-\pi_T)^{1-b} + (-1)^{a+b}\pi_E(1-\pi_E)\,\pi_T(1-\pi_T)\left(\frac{e^{\psi}-1}{e^{\psi}+1}\right), \quad a,b = 0 \; or \; 1,$

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

Statistical Model

- Curve-free approach (used by model-assisted designs)
  - Multinomial model for (toxicity, efficacy) at each dose independently (e.g., U-BOIN)
    - Example: four-level multinomial model for binary toxicity and efficacy endpoints, i.e., (0, 0), (0, 1), (1, 0) and (1, 1)
  - Pseudo-binomial model for the utility at each dose (e.g., BOIN12)

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Admissibility rules

- A dose is admissible if it satisfies the following efficacy and toxicity criteria

  Efficacy: $\Pr(\pi_E > \phi_E | data) > C_E$

  Toxicity: $\Pr(\pi_T < \phi_T | data) > C_T$

  where ϕ_E is the efficacy lower limit, ϕ_T is the toxicity upper limit, C_E and C_T are probability cutoffs

- Stopping rule: stop the trial if none of the doses is admissible

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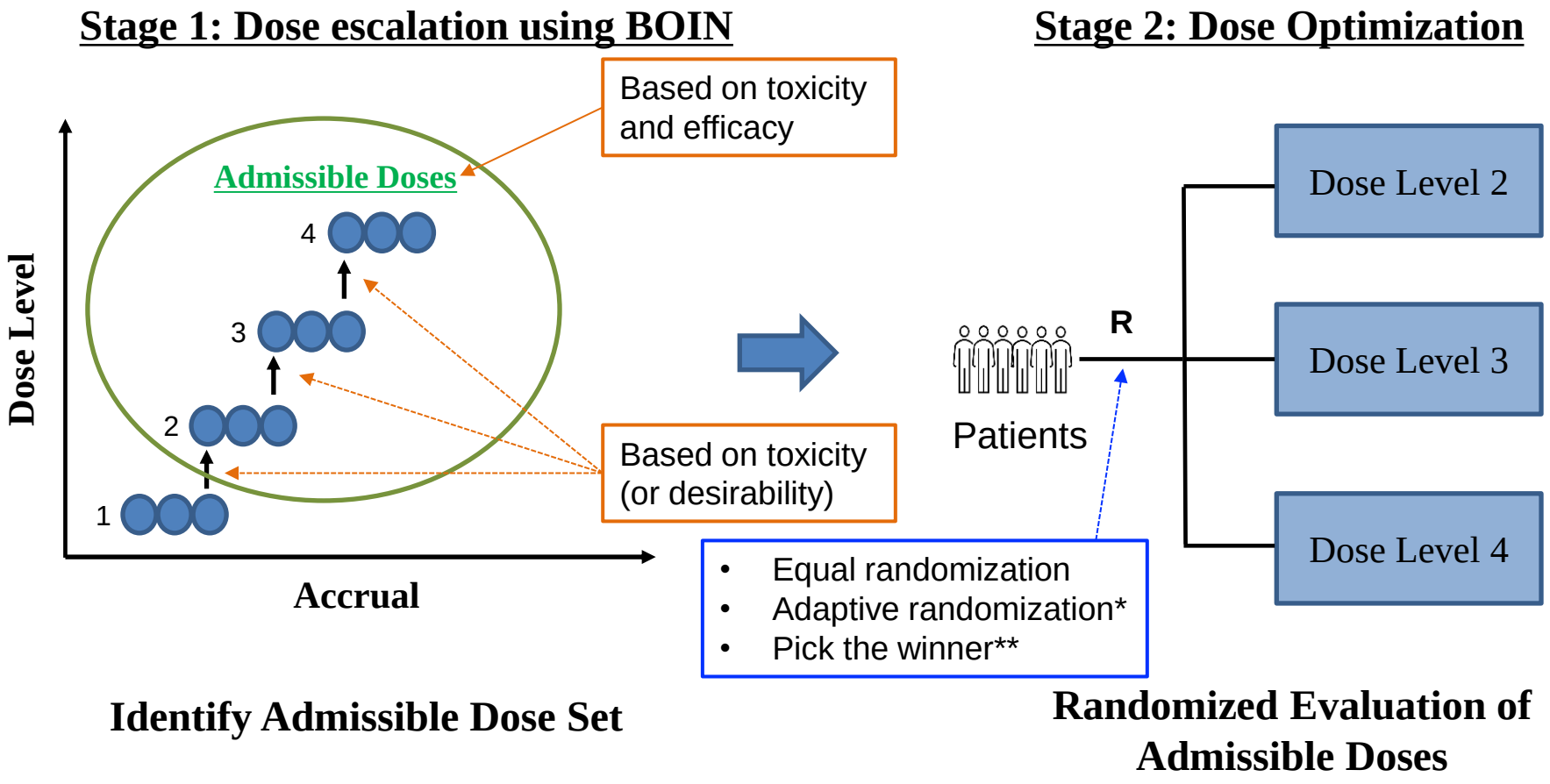
Adaptive Decision Rule

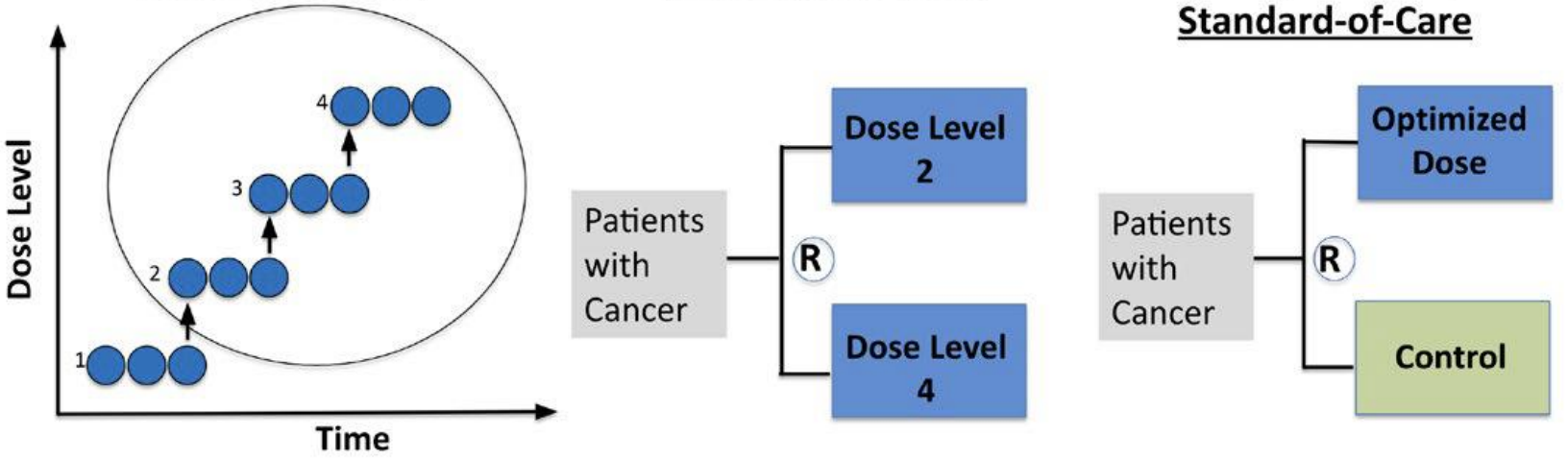
- Two-stage approach (e.g., U-BOIN)



*based on desirability

**approximation to adaptive randomization owing to high variability of small samples

Updated: Optimized Dose Selection Strategy



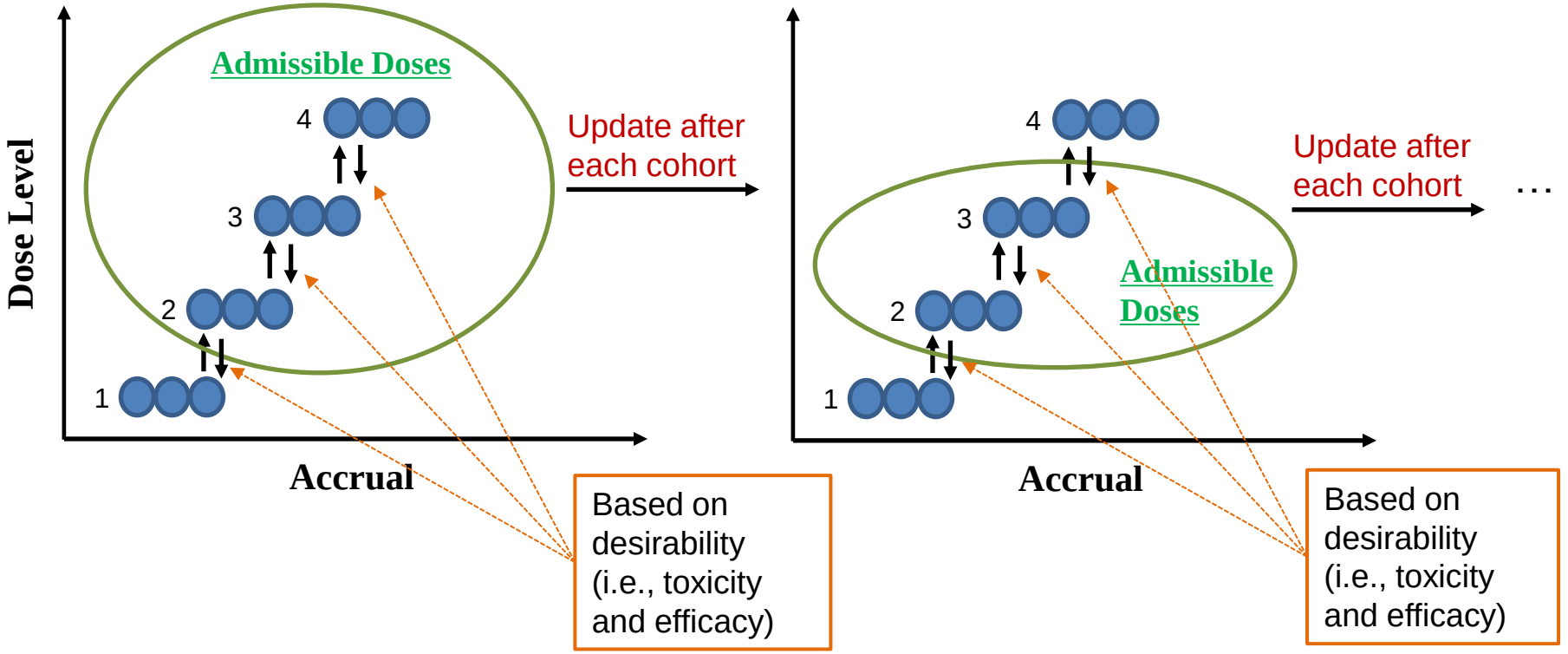
Select Dose Range

Randomized Evaluation of Several Dosages

Randomized Comparison to Standard-of-Care

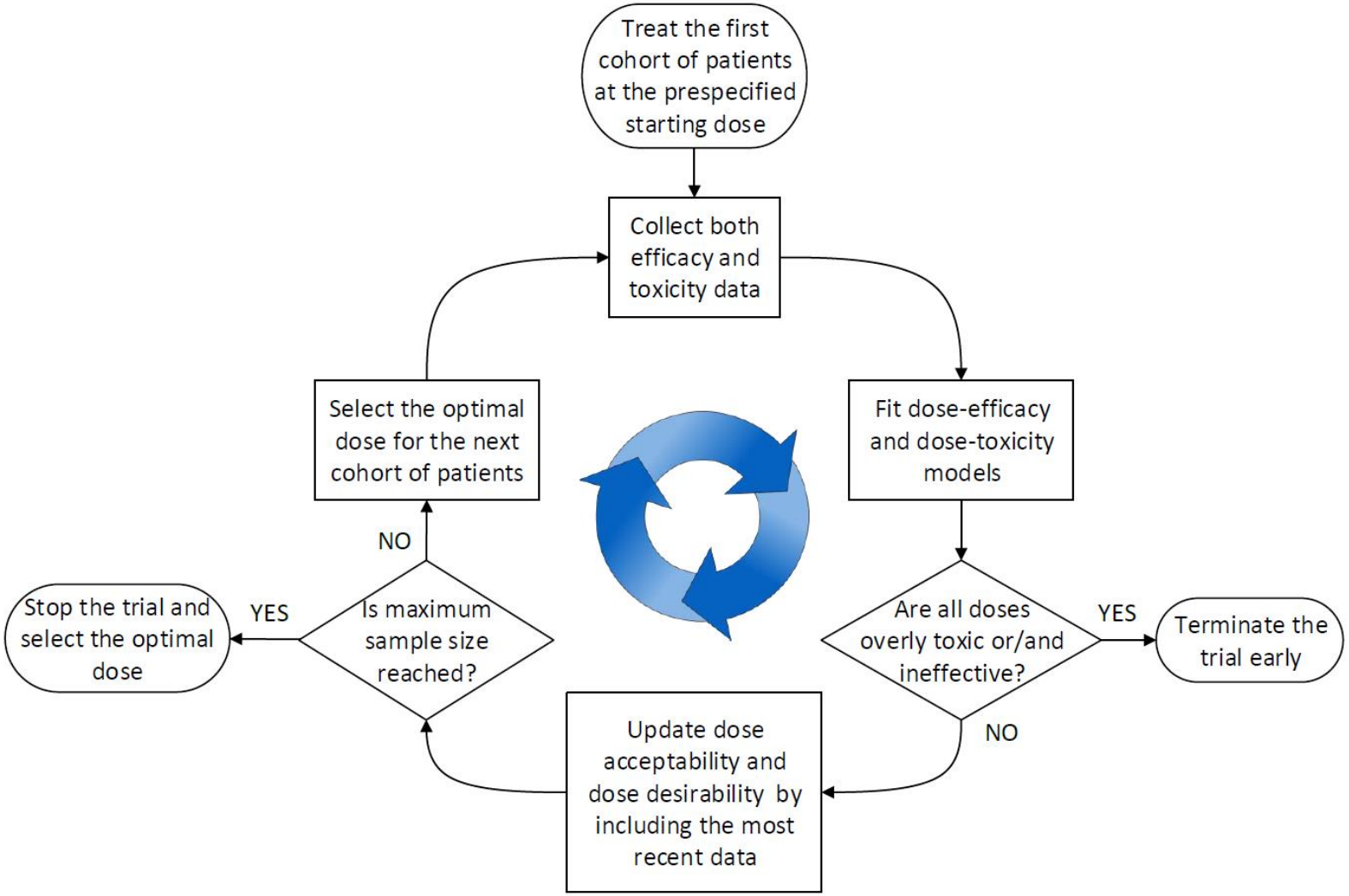
Adaptive Decision Rule

- Fully sequential approach (EffTox, BOIN12)
  - Often require a smaller sample size than two-stage design

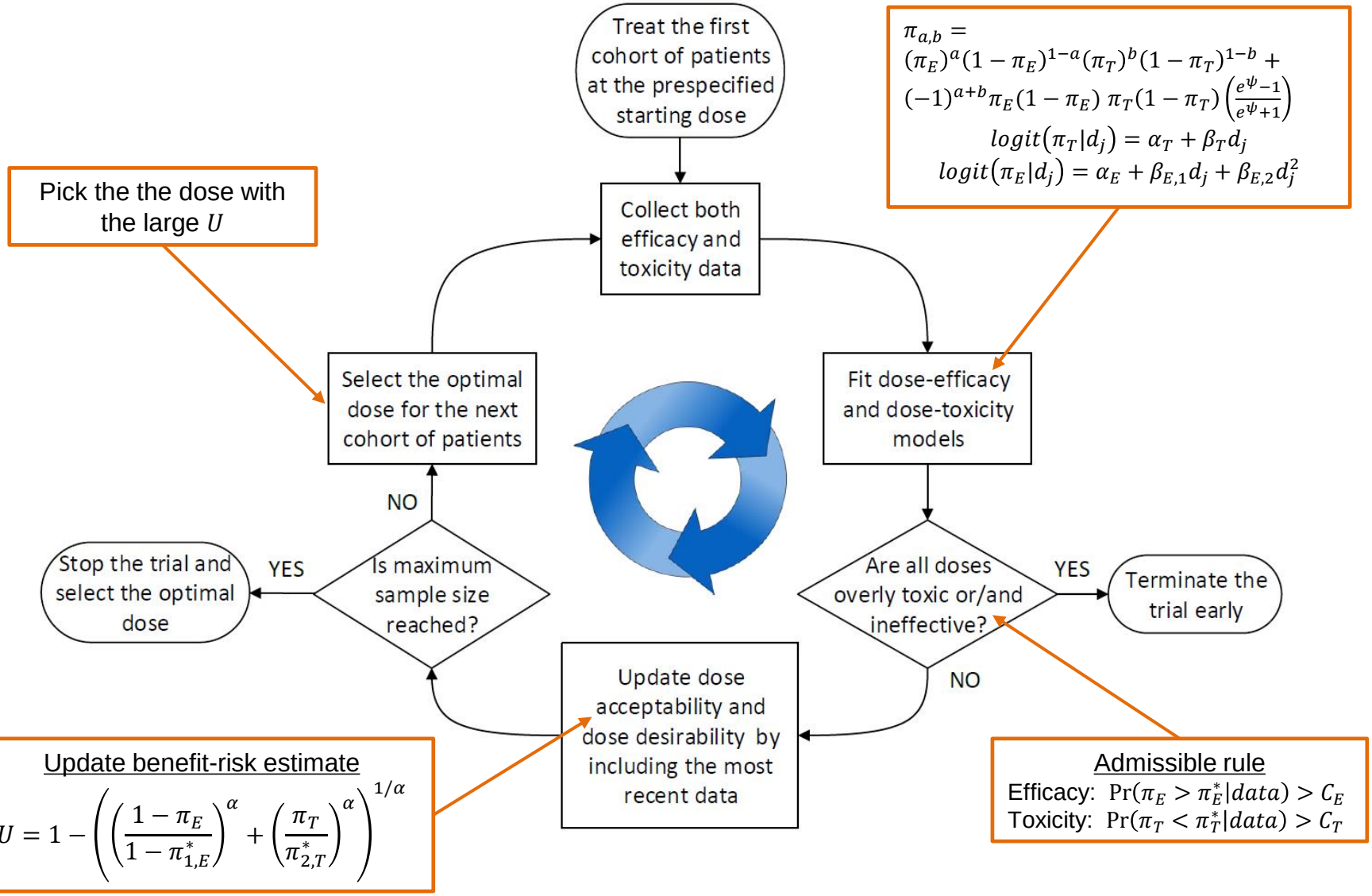


Put All Together

Phase I-II design paradigm



Model-based Approach: EffTox/Lo-EffTox

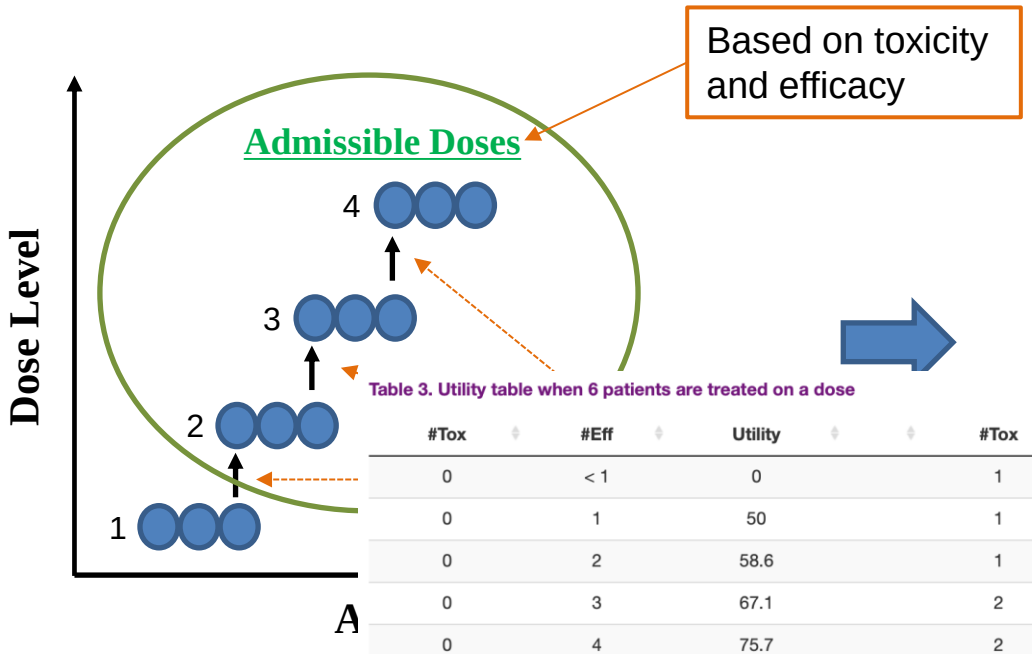


Model-Assisted Approach: U-BOIN

- Two-stage approach

Stage 1: Dose escalation using BOIN

Stage 2: Dose Optimization



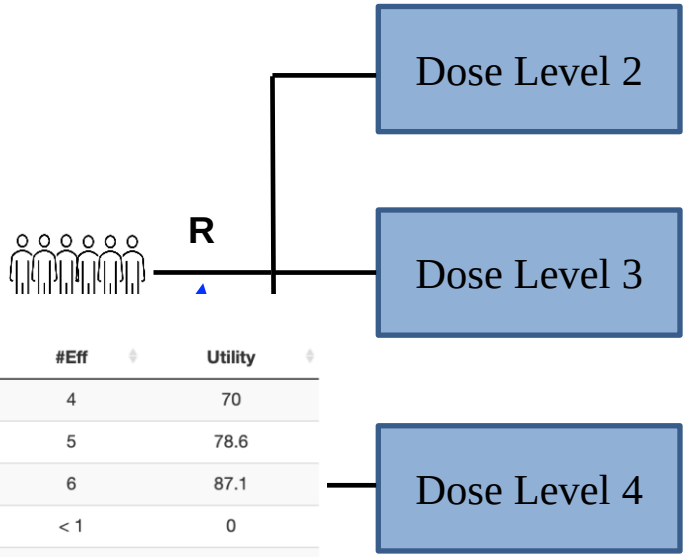


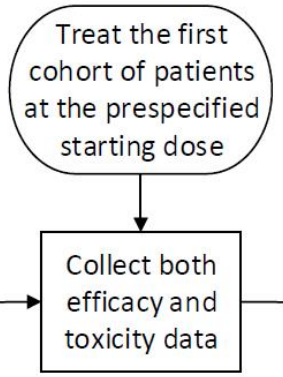
Table 3. Utility table when 6 patients are treated on a dose

#Tox	#Eff	Utility	#Tox	#Eff	Utility
0	< 1	0	1	4	70
0	1	50	1	5	78.6
0	2	58.6	1	6	87.1
0	3	67.1	2	< 1	0
0	4	75.7	2	1	38.6
0	5	84.3	2	2	47.1
0	6	92.9	2	3	55.7
1	< 1	0	2	4	64.3
1	1	44.3	2	5	72.9
1	2	52.9	2	6	81.4
1	3	61.4	> 2	Any	0

Identify Ad **ed Evaluation of issible Doses**

igh variability of small samples

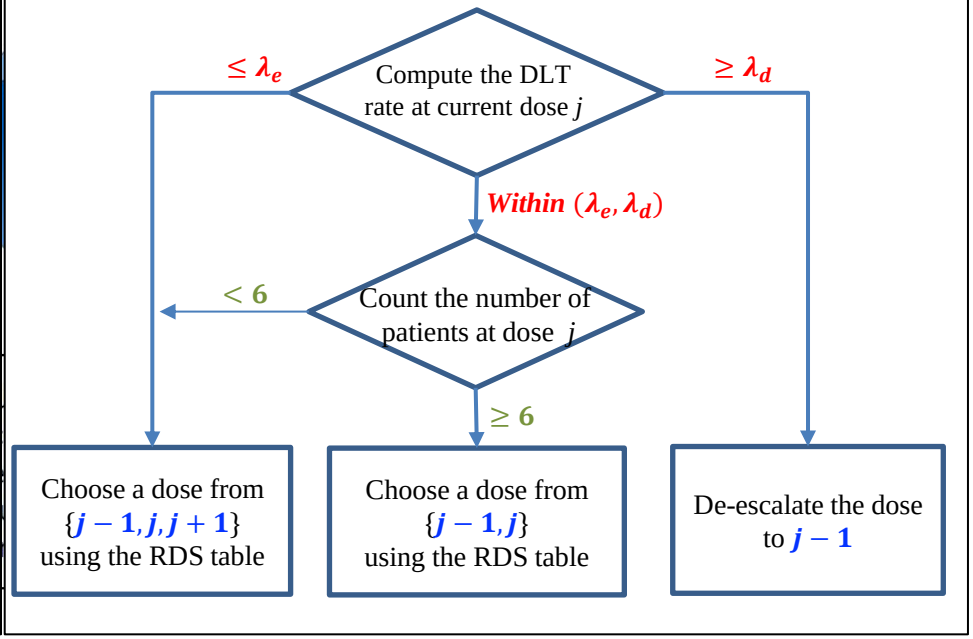
Model-Assisted Approach: BOIN12



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



BOIN12

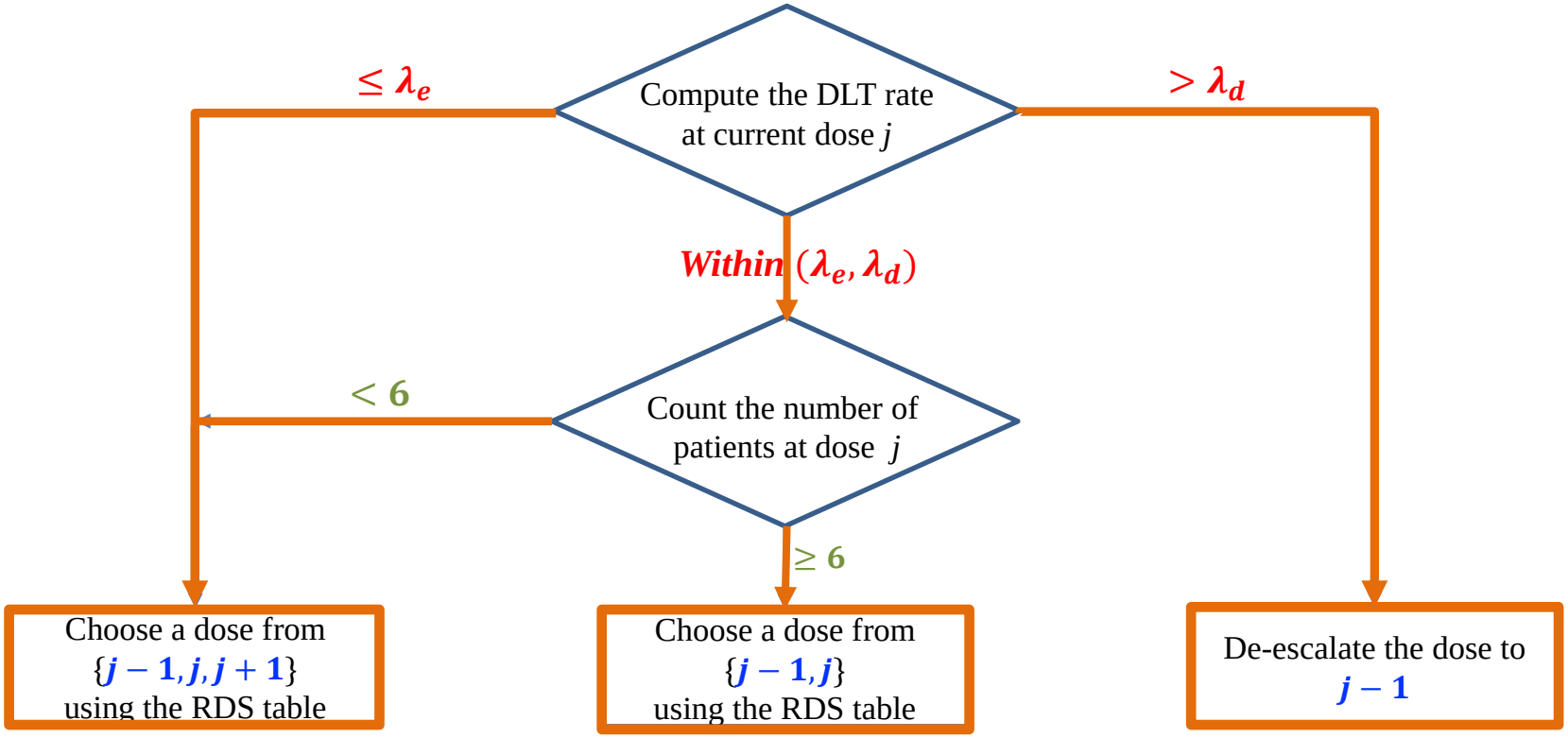


Table 1. Optimal dose escalation and de-escalation boundaries

	Target toxicity rate for the MTD						
Boundary	0.1	0.15	0.2	0.25	0.3	0.35	0.4
l_e (escalation)	0.078	0.118	0.157	0.197	0.236	0.276	0.316
l_d (de-escalation)	0.119	0.179	0.238	0.298	0.358	0.419	0.479

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

Rank-Based Desirability Score (RDS)

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
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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

Model-Assisted Design

Back End

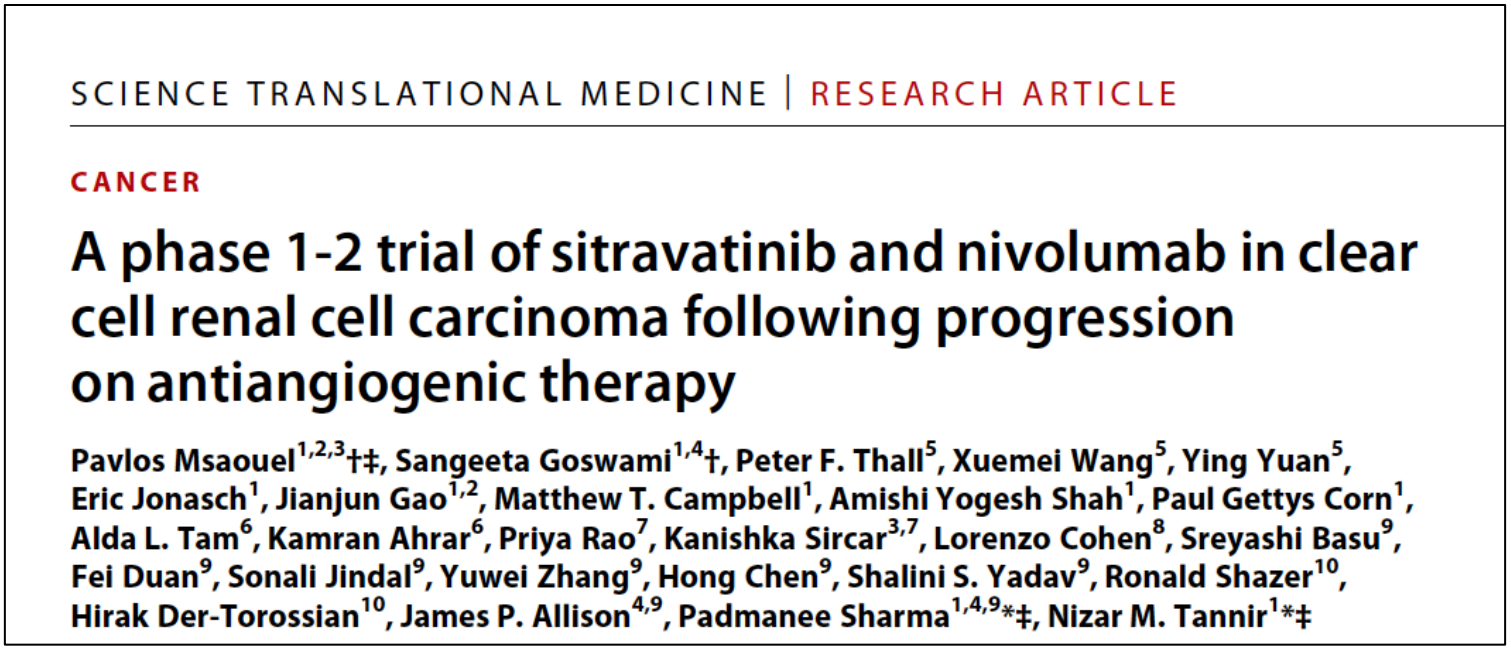
Model-Assisted Design

Front End

Yuan Y, Lee JJ, Hilsenbeck SG. Model-Assisted Designs for Early-Phase Clinical Trials: Simplicity Meets Superiority. JCO Precis Oncol. 2019 Oct 24;3:PO.19.00032. doi: 10.1200/PO.19.00032.

Applications

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



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

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A Phase I-II Renal Cell Carcinoma Trial

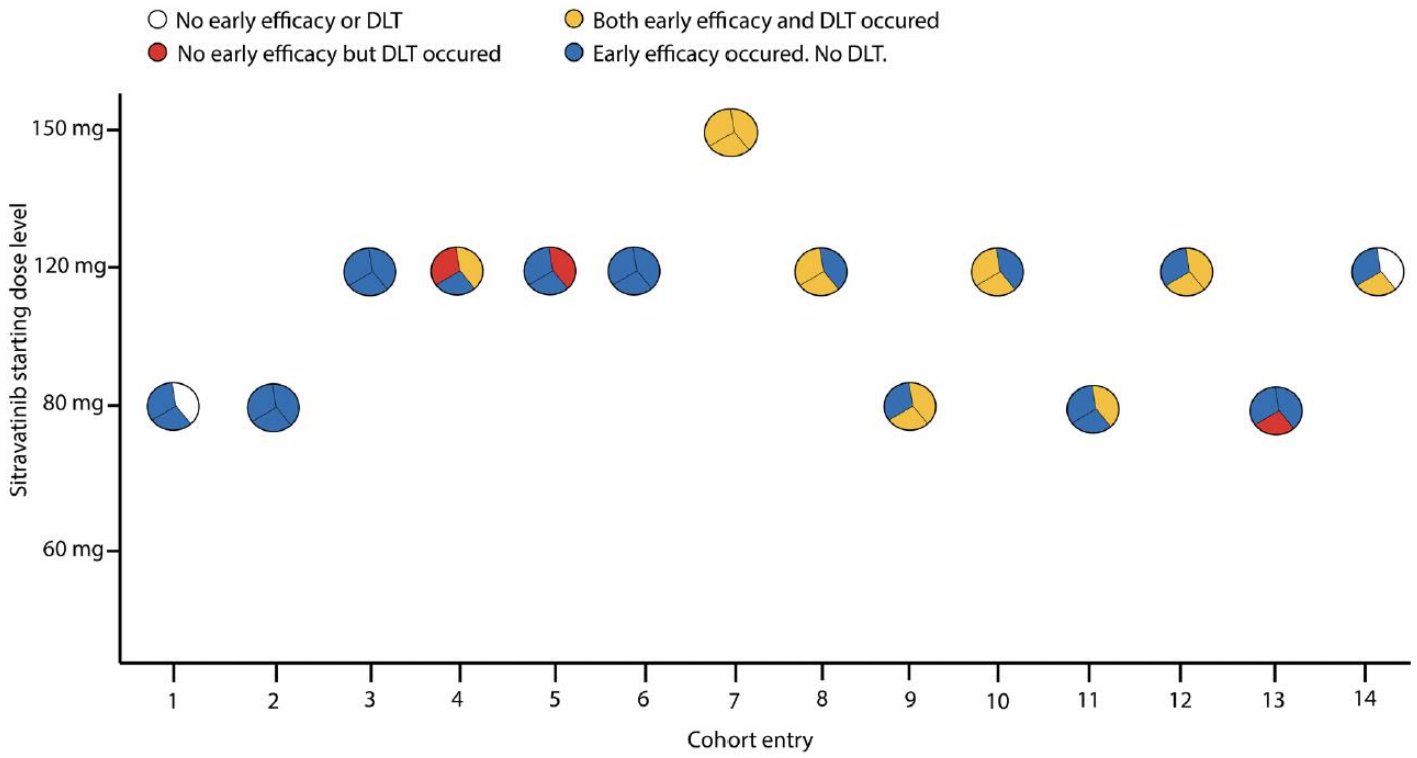

Fig. 1. Illustration of trial conduct to determine the optimal starting dose of sitravatinib in combination with nivolumab. Each circle represents a cohort of three patients whose DLT and early efficacy outcomes are indicated by different colors. The first cohort of three patients started at a sitravatinib dose of 80 mg daily, and subsequent cohorts started at a sitravatinib dose selected by the LO-EffTox design based on the DLT and early efficacy outcomes of all prior cohorts. The sitravatinib starting dose of 60 mg daily was never selected, whereas the sitravatinib starting dose of 150 mg was only selected on cohort 7 and subsequently found to be too toxic to be selected again based on the prespecified trade-off between DLT and early efficacy.

A pancreatic cancer trial

LO-EffTox design

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STATISTICAL ANALYSIS

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Lessons Learned From Implementing a Novel Bayesian Adaptive Dose-Finding Design in Advanced Pancreatic Cancer

Rebecca S. S. Tidwell, MS[1]; Peter F. Thall, PhD[1]; and Ying Yuan, PhD[1]

PURPOSE Novel Bayesian adaptive designs provide an effective way to improve clinical trial efficiency. These designs are superior to conventional methods, but implementing them can be challenging. The aim of this article was to describe what we learned while applying a novel Bayesian phase I-II design in a recent trial.

METHODS The primary goal of the trial was to optimize radiation therapy (RT) dose among three levels (low, standard, and high), given either with placebo (P) or an investigational agent (A), for treating locally advanced, radiation-naive pancreatic cancer, deemed appropriate for RT rather than surgery. Up to 48 patients were randomly assigned fairly between RT plus P and RT plus A, with RT dose-finding done within each arm using the late-onset efficacy-toxicity design on the basis of two coprimary end points, tumor response and dose-limiting toxicity, both evaluated at up to 90 days. The random assignment was blinded, but within each arm, unblinded RT doses were chosen adaptively using software developed within the institution.

Tidwell RSS, Thall PF, Yuan Y. (2021) JCO Precis Oncol. 1719-1726. doi: 10.1200/PO.21.00212.

Applications

- U-BOIN (NCT05334329)
  - Genetically Engineered Cells (COH06) With or Without Atezolizumab for the Treatment of Non-small Cell Lung Cancer Previously Treated With PD-1 and/or PD-L1 Immune Checkpoint Inhibitors
- 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

CAR T-cell Therapy

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HEMATOLOGIC MALIGNANCIES—LEUKEMIA, MYELODYSPLASTIC SYNDROMES, AND ALLOTRANSPLANT

Phase I study of donor-derived CD5 CAR T cells in patients with relapsed or refractory T-cell acute lymphoblastic leukemia.

Jing Pan, Yue Tan, Lingling Shan, Biping Deng, Zhuojun Ling, Weiliang Song, ...

Background: Despite the manageable safety and encouraging efficacy of donor-derived CD7 chimeric antigen receptor (CAR) T cells in relapsed or refractory T-cell acute lymphoblastic leukemia (r/r T-ALL) (Pan et al. *J Clin Oncol* 2021;39:3340-3351), a considerable proportion of responding patients eventually relapsed with CD7 antigen loss. CAR T cells targeting another antigen, CD5, which is expressed on blasts of over 80% T-ALL cases, may be capable of treating these patients. Here we present early safety and efficacy results of a phase I trial of donor-derived CD5 CAR T cells in T-ALL. **Methods:** CD5 CAR T cells that resist fratricide by deletion of CD5 gene (Preclinical data in Dai et al. *Mol Ther* 2021;29:2707-2722) were manufactured. Patients with prior stem cell transplantation (SCT) (group A) received CAR T cells from prior SCT donors, while patients without SCT history (group B) received CAR T cells from new donors who also provided stem cells for transplantation post CAR T therapy. The trial using bayesian optimal interval phase I/II design to explore optimal biological dose (OBD) from the initial dose of 1×10^6 (±20%) CAR T cells/kg in each group. If manufactured cells were not sufficient, patients could be treated at a low dose of 5×10^5 (± 20%)/kg. The primary endpoint was safety with efficacy secondary. **Results:** Five patients who had CD7-negative relapsed after CD7 CAR therapy

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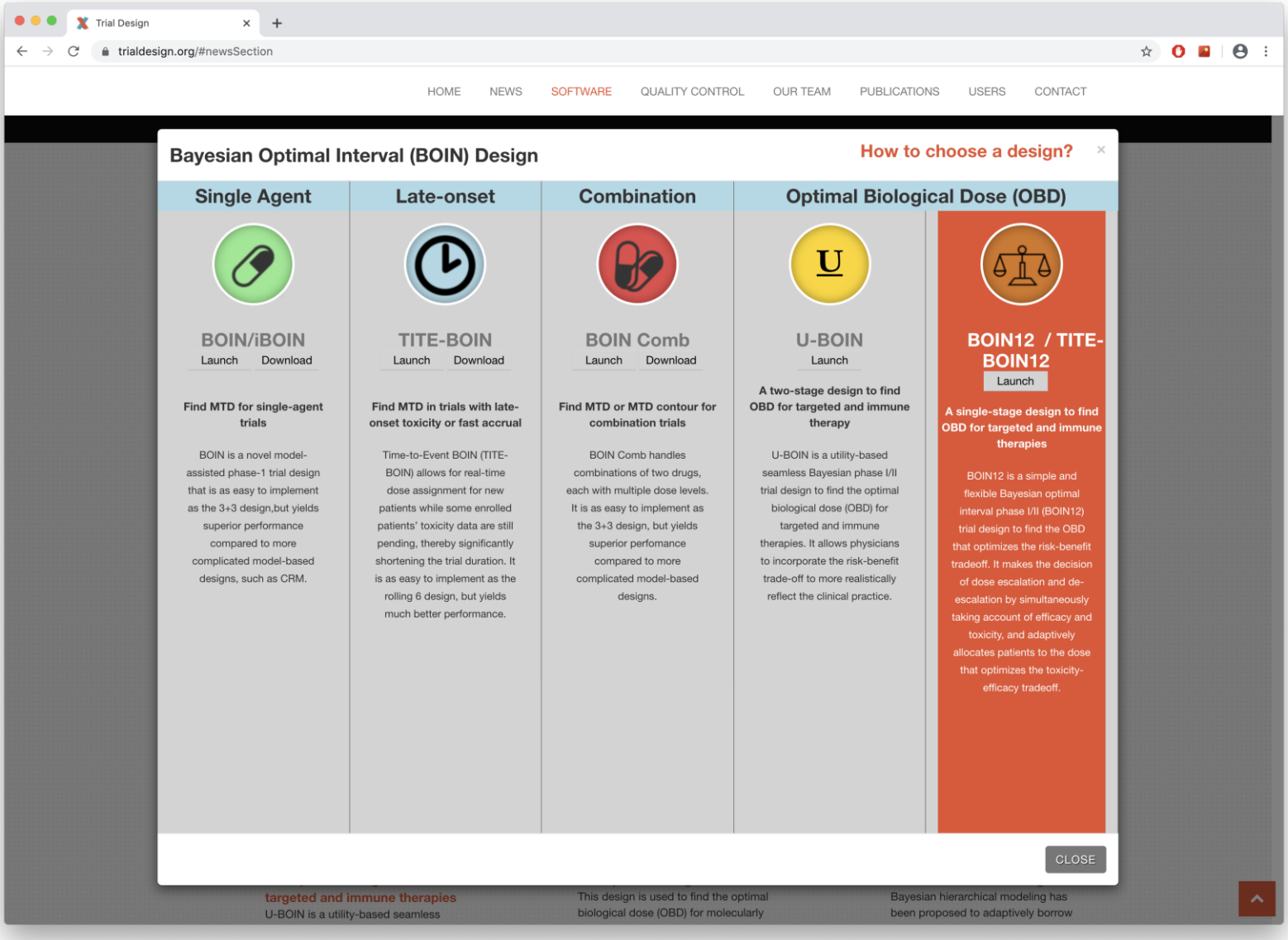
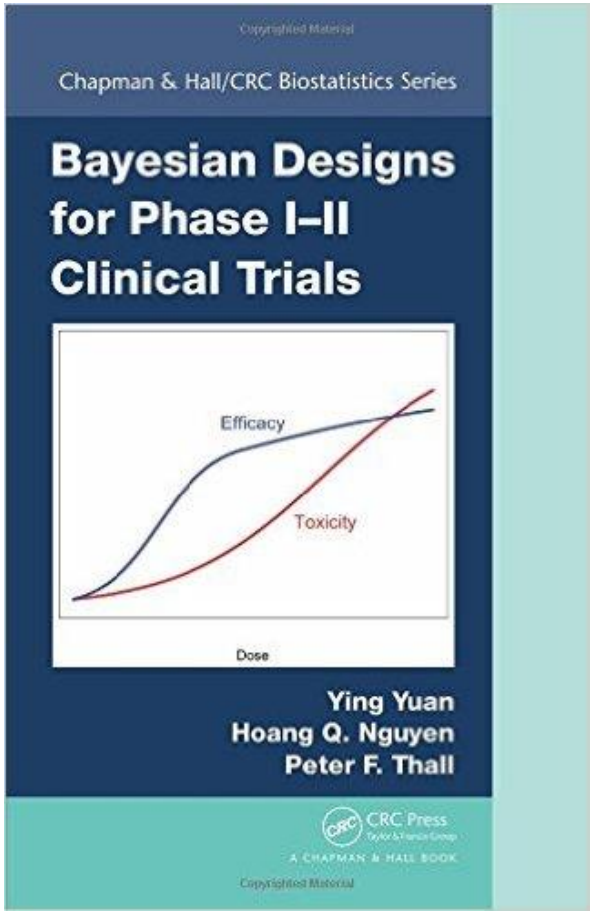


Discussion

- Dose transition and dose selection are relatively independent
  - Dose transition based on quick toxicity/efficacy read-outs, and dose selection based on clinically relevant endpoints
- Statistical methods provide a simplified description to complicated real-world trials that captures the most important features of interest. The decision may be made based on design recommendation and the totality of the data (e.g., dose interruption, late-onset toxicity, PK/PD)

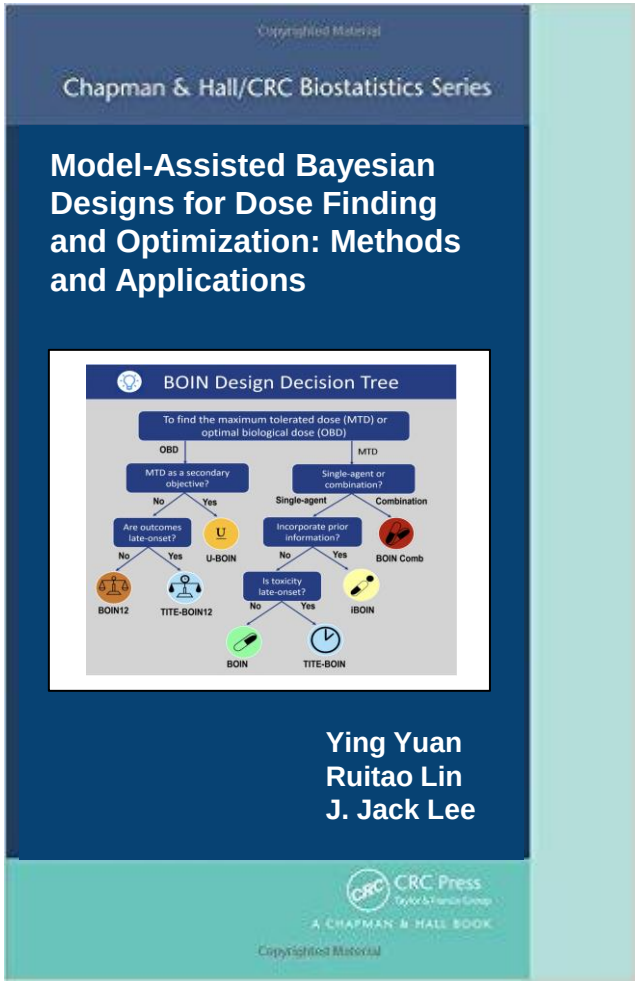
References

Model-based designs



Model-assisted designs

(available late summer)



References

- Yan, F., Thall PF, Lu KH, Gilbert MR and Yuan, Y. (2018) Phase I-II clinical trial design: A state-of-the-art paradigm for dose finding. *Annals of Oncology* , 29, 694-699. [**An easy-to-read review on the phase I-II paradigm**]
- Thall PF, Cook JD (2004) Dose-finding based on efficacy-toxicity trade-offs. Biometrics 60:684-693. [**EffTox design**]
- Jin, I.H., Liu, S., Thall, P. and Yuan, Y. (2014) Using data augmentation to facilitate conduct of phase I/II clinical trials with delayed outcomes. Journal of the American Statistical Association, 109, 525-536. [**LO-EffTox**]
- Tidwell RSS, Thall P and Yuan Y. (2021) Lessons Learned From Implementing a Novel Bayesian Adaptive Dose-Finding Design in Advanced Pancreatic Cancer, JCO Precision Oncology 5, 1719-1726. DOI: 10.1200/PO.21.00212. [**Implementation of LO-EffTox**]
- Zhou Y, Lee JJ, Yuan Y. (2019) A utility-based Bayesian optimal interval (U-BOIN) phase I/II design to identify the optimal biological dose for targeted and immune therapies. Stat Med. 2019 Dec 10;38(28):5299-5316. [**U-BOIN**]
- Lin R, Zhou Y, Yan F, Li D and Yuan Y (2020) BOIN12: Bayesian Optimal Interval Phase I/II Trial Design for Utility-Based Dose Finding in Immunotherapy and Targeted Therapies, JCO precision oncology, revision invited. [**BOIN12**]
- Zhou Y, et al. (2022) TITE-BOIN12: A Bayesian phase I/II trial design to find the optimal biological dose with late-onset toxicity and efficacy, Statistics in Medicine, 41(11):1918-1931. [**TITE-BOIN12**]

Thank You!