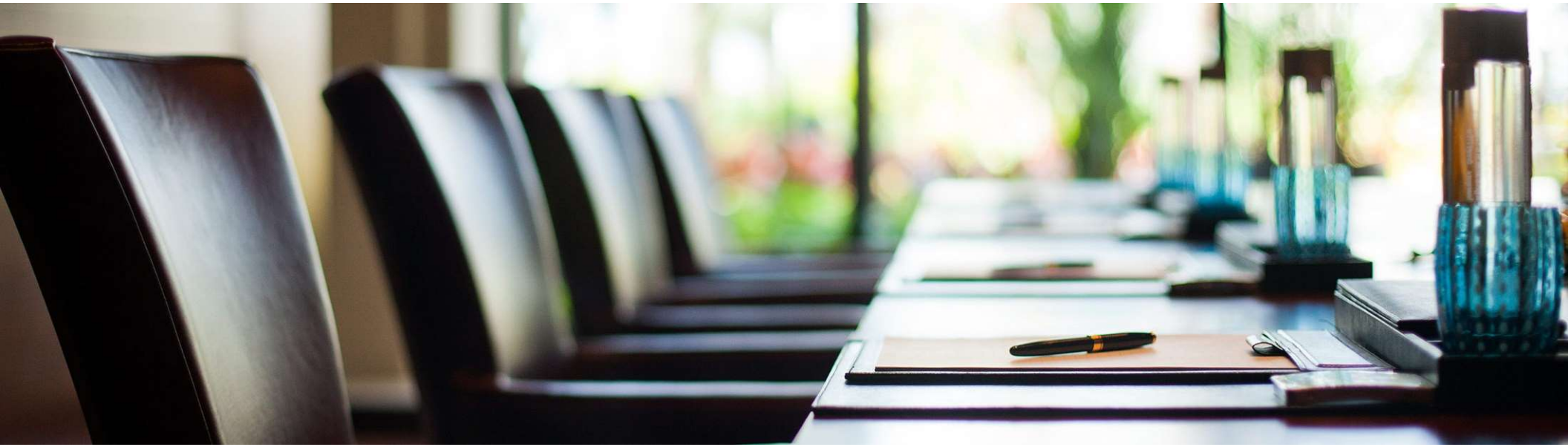


Adaptive Designs for Optimal Dose Determination in I-O and Cell Therapy

Rachael Liu
Takeda Pharmaceuticals

2021 Pharmaceutical Symposium of the Boston Chapter of ASA

Better Health, Brighter Future

AGENDA

- Introduction
- Designs focusing on DLT in Cycle I
- Designs considering late-onset toxicity
- Dose finding in basket and umbrella trials
- Dose finding incorporating multiple endpoints
- Concluding remarks

Immuno-oncology and Cell Therapy Development

- I-O has been an essential pillar for cancer treatment.
- Utilize immune system to fight against foreign threats: innate immunity and adaptive immunity
- Evolving and accelerated development of I-O pipelines globally

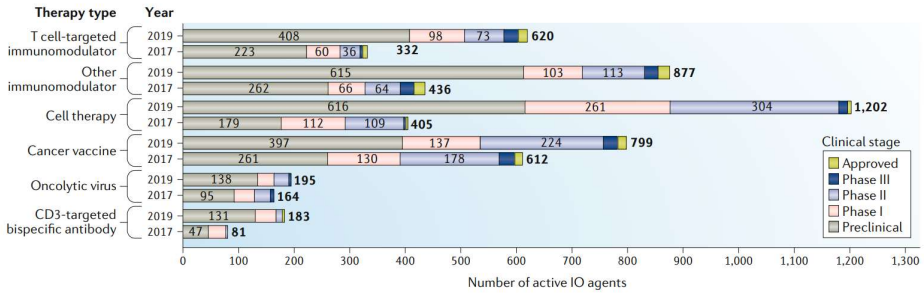
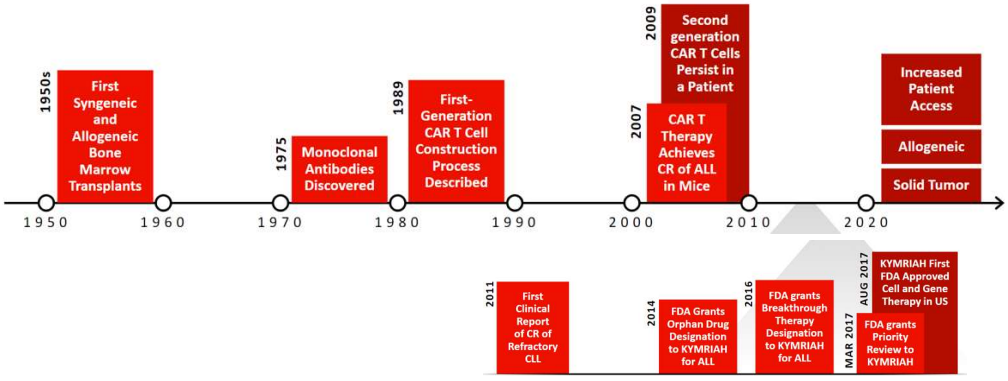


Fig. 1 | **Overview of all 3,876 active IO agents in the current global drug development pipeline.** In the past 2 years, 1,846 new agents have been added to the immuno-oncology (IO) pipeline, an increase of 91%.

- Cell therapy as the largest growth category within I-O has been approved to treat patients with several cancers.
- Rapidly growing area including chimeric antigen receptor (CAR) T cell, TCR, TILs, NK and others.
- FDA Guidance on “Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products”



Phase I Dose Escalation Study Designs in I-O and Cell Therapy

Conventional Dose Finding

- Identify dose-limiting toxicities (DLTs)
  - toxicity that is considered unacceptable (due to severity and/or irreversibility) and limits further dose escalation
- Find maximum tolerated dose (MTD)
  - dose with target DLT rate (e.g., < 33%)
- Establish recommended phase II dose (RP2D)
  - combining safety, efficacy, PK and PD information

Patient-Focused Dose Optimization

- Identify safety signal beyond DLT at cycle 1
- Identify signal of efficacy or biological activity
- Identify optimal effective dose
- Smart designs allow efficient characterization of safety and efficacy/activity profiles.
  - Patient population selection
  - Seamless Ph I/II design
  - Dosing schedules exploration
  - Combination partners exploration

Challenges in I-O and Cell Therapy Early Phase Designs

Risk of toxicity	Complex manufacturing procedure*	Infeasible to establish dose-response relationship
• Prolonged biological activity • Challenging to predict from animal models • High potential for immunogenicity • Relatively invasive procedures for dose administration*	• Lead to limited dose levels • Increased variability • Estimand considerations • Uncertain safety/efficacy differences between versions of the products	• Toxicity could be insubstantial in the predicted therapeutic dose range • Potential benefit may appear to plateau above a certain dose • Preclinical data is often not informative • Unclear exposure-response relationship

*: Cell therapy specific issues

Traditional oncology dose finding study aims to:

- Identify **dose-limiting toxicities** (DLTs)
- Find **maximum tolerated dose** (MTD)
- Underlying assumption: both safety and efficacy increases with dose

Not optimal for I-O and cell therapy!

Dose Optimization Designs are under Increasing Scrutiny

US FDA's 'Project Optimus' Will Encourage Move Away From Conventional Dose-Finding For Modern Cancer Therapies

26 May 2021 | **ANALYSIS**

by Kate Rawson | kate@previsionpolicy.com

Executive Summary

Simply carrying forward the maximum tolerated dose into later-stage trials does not account for the importance of long-term tolerability – and the fact that higher doses are not necessarily better for patients.

FDA'S PREPARES TO TAKE THE WHEEL AND TRANSFORM ONCOLOGY DOSING. *Source: Raymond*

Pursue multiple dose expansion cohorts after initial dose escalation, or randomize patients between two or more doses to gain information about preliminary efficacy or safety and tolerability. "These data can help support a more informed decision on which dose or which doses to carry forward to pivotal studies." Shah noted that even in a single-arm study, patients could be randomized to two or more doses.

A comprehensive exploration on drug candidates and population before pivotal trials is encouraged and "to-be" expected following a patient-centric principal

US FDA Plans To Get Tougher On Oncology Dose Optimization

FDA'S PAZDUR SAYS CANCER PROGRAMS MAY SOON BE REQUIRED TO DO MORE DOSE FINDING

One problem the FDA runs into is that the agency is presented with data on varying doses with very small patient populations – 10 or 15 patients at best – leading to overlapping confidence intervals, Pazdur said.

"What needs to be done is a randomized study, looking at these various doses, looking at response rates to determine which one would be the one that they want to carry forward. Even with single arm trials, if that is their preferred method of getting their drug approved on a single arm trial, they could do a randomized study early on looking at two or three doses, at an interim analysis select a dose, and then continue that onward in a single arm study, utilizing those patients and counting those patients that were entered already at that dose level. So you have a continuum going on," Pazdur said.

AGENDA

- Introduction
- Designs focusing on DLT in Cycle I
- Designs considering late-onset toxicity
- Dose finding in basket and umbrella trials
- Dose finding incorporating multiple endpoints
- Concluding remarks

Overview of the Dose Finding Designs using DLT for MTD Recommendation

3+3 is outdated

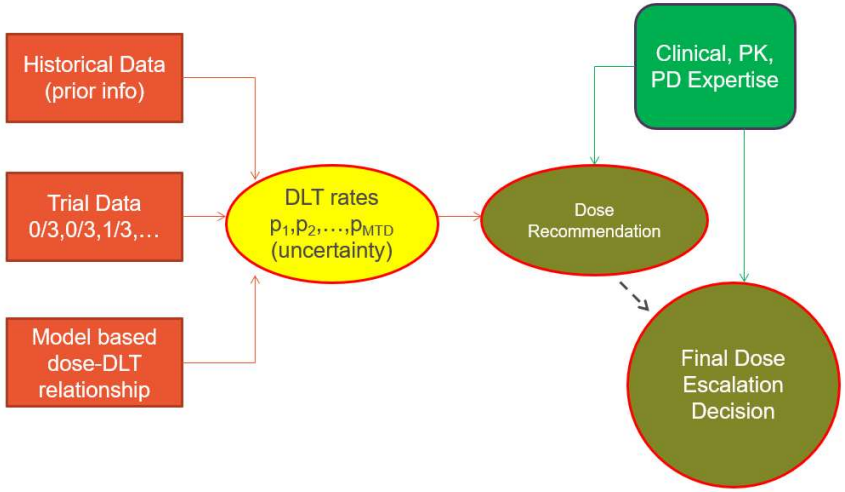
- Low probability and high variability in MTD estimates (Thall and Lee 2003, Goodman et al 1995)
- Operational inconvenience due to cohort tied to 3 patients at a time
- Risk of missing the target by random chance and rule-based decision

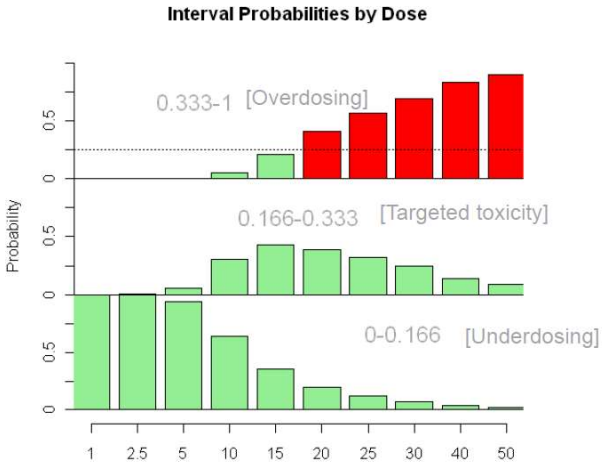
Improved designs

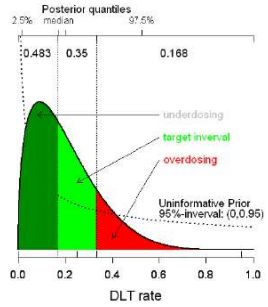
- Model Based design:
  - Bayesian Logistic Regression Model (BLRM)
  - Rely on dose-DLT relationship assumption
- Model Assisted design
  - mTPI, mTPI2 (modified toxicity probability interval design), BOIN (Bayesian optimal interval design), keyboard, etc.
  - No dose-DLT relationship
  - Transparent dose escalation decision table available before the trial

Model Based Design: Bayesian Logistic Regression Model (BLRM)

Neuenschwander et al.(2008) proposed the BLRM design:







Bayesian Logistic Regression Model

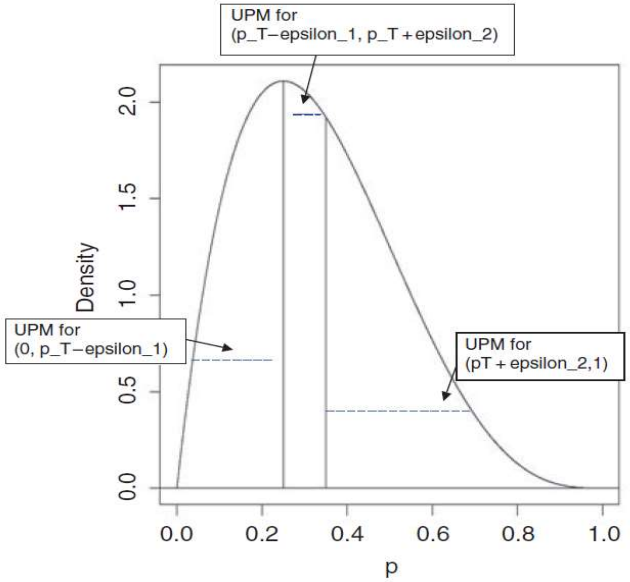
$$\log\left(\frac{P_i}{1-P_i}\right) = \log(\alpha) + \beta \log\left(\frac{D_i}{D^*}\right)$$

where P_i is the DLT rate, D_i is the ith dose, D^* is the reference dose, allowing the interpretation of α as the odds of a DLT at D^*

- A model that can utilize all available information as prior (preclinical, historic studies as well as incoming data from ongoing trials).
- Studies with data from a range of doses to establish the dose-DLT relationship
- Implementation of escalation with over-dose control (EWOC)
- Flexible cohort size, potential exploration of intermediate dose levels, operationally convenient

Model Assisted Design: Modified Toxicity Probability Interval Design (mTPI)

Ji et. al (2010) proposed the mTPI design



- The next cohort of doses is selected by the interval with largest UPM $UPM\,(i,\,d) = \frac{Pr\,(M_i|\{x_d,\,n_d\})}{S\,(M_i)}$
- MTD is selected as the dose with the smallest difference $|\widehat{p_i} - p_T|$

Transparent and convenient dose escalation decision table

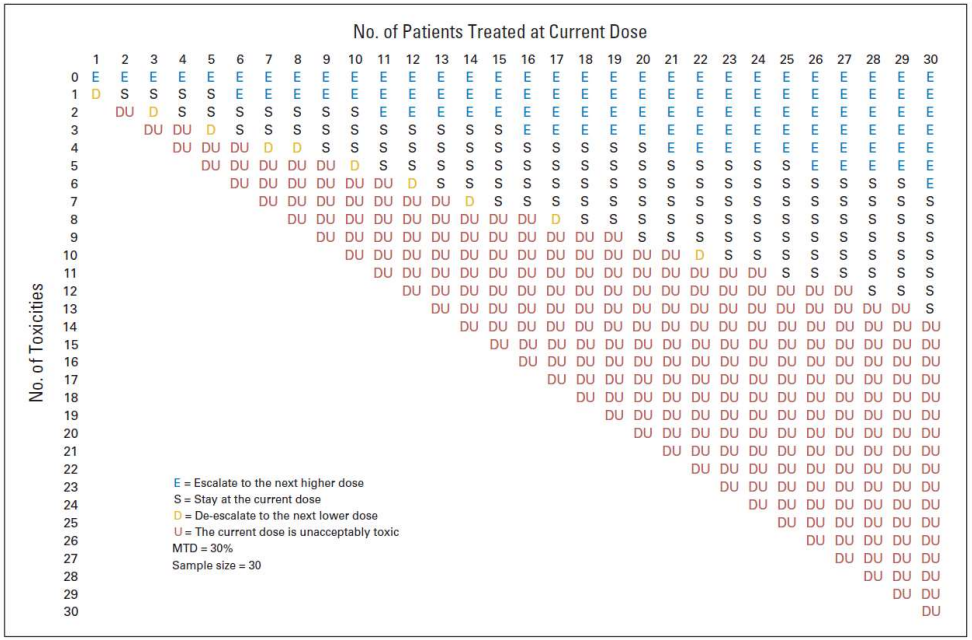


Fig 2. Dose-finding spreadsheet of the modified toxicity probability interval (mTPI) method. The spreadsheet is generated based on a beta/binomial model and precalculated before a trial starts. The letters in different colors are computed based on the decision rules under the mTPI method and represent different dose-finding actions. In addition to actions de-escalate the dose (D), stay at the same dose (S), and escalate the dose (E), the table includes action unacceptable toxicity (U), which is defined as the execution of the dose-exclusion rule in mTPI. MTD, maximum-tolerated dose.

Model Assisted Design: Modified Toxicity Probability Interval Design (mTPI2)

An extension of mTPI by Guo et. al (2017) to address the undesirable decision under mTPI due to consequences of Ockham's razor.

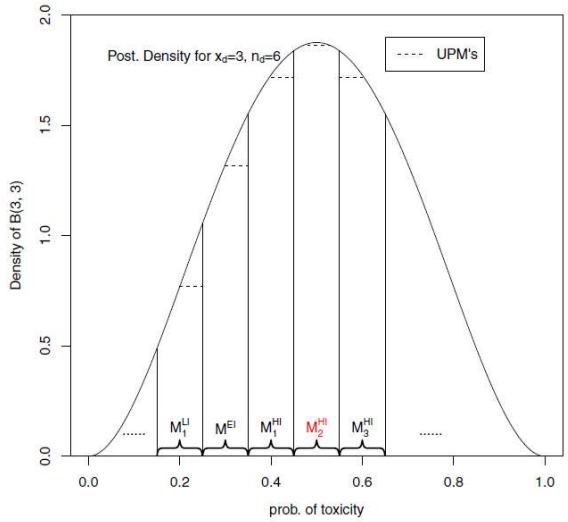


Fig. 2. An example demonstrating the new framework of mTPI-2. Here, *EI* is the equivalence interval $(p_T - \epsilon_1, p_T + \epsilon_2)$, *LI* denotes the intervals below *EI*, and *HI* denotes the intervals above *EI*. Interval M_2^{HI} exhibits the largest UPM and therefore the decision is now *D*, to de-escalate.

	1		2		3		4		5		6		7		8		9		10	
	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	S	D	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E
2			D	D	D	D	S	D	S	D	S	S	S	S	S	S	S	E	S	E
3					DU	DU	DU	DU	D	D	S	D	S	D	S	D	S	S	S	S
4							DU	DU	DU	DU	DU	DU	D	D	D	D	S	D	S	D
5									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D
6											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
7													DU	DU	DU	DU	DU	DU	DU	DU
8															DU	DU	DU	DU	DU	DU
9																	DU	DU	DU	DU
10																			DU	DU

* **Column** indicates the number of patients treated. **Row** indicates the number of patients with DLTs

* **E**: Escalate to the next higher dose; **S**: Stay at the same dose; **D**: De-escalate to the previous lower dose; **DU**: De-escalate to the previous lower dose and the current dose will never be used again in the trial;

$$p_T = 0.3, and\ \varepsilon_1 = \varepsilon_2 = 0.05$$

Model Assisted Design: Bayesian Optimal Interval Design (BOIN)

- A transparent and straightforward design (Liu and Yuan 2015)by comparing the observed DLT rate with pre-specified dose escalation and de-escalation boundaries (λ_e, λ_d)
- Pre-specify max sample size and target DLT rate ϕ
- Input to obtain the boundaries
  - ϕ_1: the highest DLT probability that dose escalation is required; general use value $\phi_1 = 0.6\phi$
  - ϕ_2: the lowest DLT probability that dose de-escalation is required; general use value $\phi_2 = 1.4\phi$

- The optimal boundaries are obtained by minimizing the decision errors

$$\alpha(\lambda_{1j}, \lambda_{2j}) = \text{pr}(H_{0j})\text{pr}(\bar{\mathcal{R}}|H_{0j}) + \text{pr}(H_{1j})\text{pr}(\bar{\mathcal{E}}|H_{1j}) + \text{pr}(H_{2j})\text{pr}(\bar{\mathcal{D}}|H_{2j})$$

$$\begin{aligned} H_{0j}: &\quad p_j = \phi \\ H_{1j}: &\quad p_j = \phi_1 \\ H_{2j}: &\quad p_j = \phi_2, \end{aligned}$$

$$\lambda_{1j} = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right) + n_j^{-1}\log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)}$$

$$\lambda_{2j} = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right) + n_j^{-1}\log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)}.$$

Table 1. Dose escalation/deescalation rule for the BOIN Design

Number of patients treated at the current dose	1	2	3	4	5	6	7	8	9
Escalate if # of DLT <=	0	0	0	0	1	1	1	1	2
Deescalate if # of DLT >=	1	1	2	2	2	3	3	3	4
Eliminate if # of DLT >=	NA	NA	3	3	4	4	5	5	5

Note: # of DLT is the number of patients with at least 1 DLT.

BOIN example: target toxicity =0.3, boundary (0.236, 0.358)

Other Designs Focusing on Cycle 1 DLT

- iBOIN (Zhou et. al, 2020)
  - Incorporate prior study DLT information
  - Generate dose specific decision-making tables
  - Safe/toxic dose in previous study may trigger more aggressive/conservative decision making compared with BOIN design

- Keyboard Design (Yan et. al, 2017)
  - Resolves the overdosing issue of the mTPI by defining a series of equal-width dosing intervals(or keys)
  - Using the interval (or key) with the highest posterior probability to guide dose escalation and de-escalation

- i3+3 design (Liu et. al, 2020): improved rule-based design than 3+3

- Cumulative cohort design (Ivanova et. al, 2007): non-parametric dose-finding procedure

Dose Finding Design Focusing on DLT in Cycle I

- Overview of multiple design options
- Good judgment based on understanding of
  - Potential toxicity profiles
  - Rational of planned dose ranges
  - Study objective and outcomes
- Simulations are important to select most appropriate designs under various scenarios via close collaboration

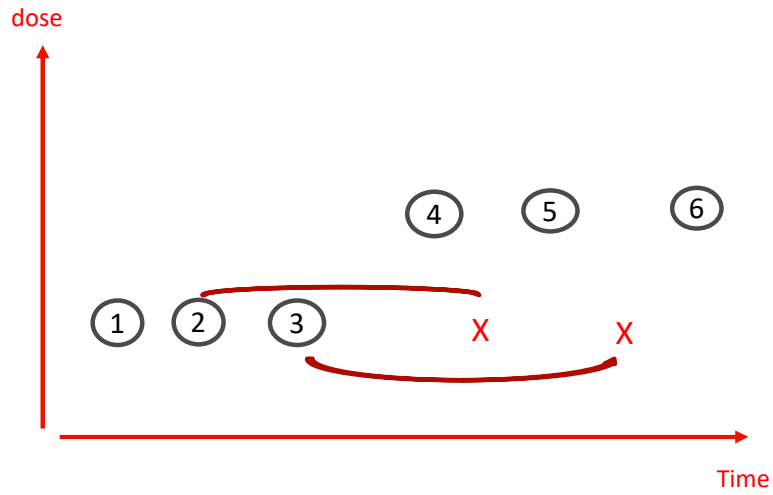
AGENDA

- Introduction
- Designs focusing on DLT in Cycle I
- Designs considering late-onset toxicity
- Dose finding in basket and umbrella trials
- Dose finding incorporating multiple endpoints
- Concluding remarks

Designs Incorporating Late Onset Toxicity

- Some I-O trials have the risk of late onset toxicity beyond cycle 1
- Define window and specify the target toxicity rate
- Decision making is using accumulative data, no enrolment pause is preferred
- Designs options:
  - TITE-CRM by Cheung and Chappell (2000)
    - Assume a dose-DLT relationship
    - Weights the outcomes according to the extend to which patients have completed the evaluation period.
    - Risk of mis-specification
  - TITE-BOIN by Yuan et. al (2018)
    - No assumption of dose-DLT relationship
    - Evaluate the average follow up time for patients to decide the maturity of information on decision making (STFT)
    - Dose escalation decision table can be generated before the trial

Example of late onset toxicity



AGENDA

- Introduction
- Designs focusing on DLT in Cycle I
- Designs considering late-onset toxicity
- Dose finding in basket and umbrella trials
- Dose finding incorporating multiple endpoints
- Concluding remarks

All-comers Trial or Early-on Implementation of Master Protocol Concept

- Multiple indications and/or drug candidates in early phases of drug development
  - Common question in I-O and Cell Therapy
- Heterogeneity in patient population might lead to incorrect decision making
- Exploration of dosing schedule and combination partners
- Implication in regulatory decisions on appropriate dosage and/or dosing schedules

Amgen's Sotorasib Updates Raise New Questions For KRAS Program

Lower Dose Being Tested Against Higher Dose Under FDA Review

The FDA has asked the company to evaluate a lower dose than the 960mg dose it approved in an ongoing clinical trial as a post-marketing requirement. Amgen announced the initiation of that Phase II trial comparing the 960mg dose against a 240mg dose both given one daily, in a 27 April earnings report. (Also see "Amgen's Sotorasib Updates Raise New Questions For KRAS Program" - Scrip, 28 Apr, 2021.)

- Emerging need for innovations on appropriate dose finding designs in the early phase of the development
  - Implementation of basket trial or umbrella trial concept

Benefit of Basket or Umbrella Trials for Patient-centric Dose Decision Making

- Commonly used in practice
  - Naive pooling
    - Estimate an overall MTD
    - Inaccurate estimation
  - Stratification
    - Estimate MTD for indications/drug candidates separately
    - Increase of variability

- Proposals for innovative dose finding
  - Basket trials: indication specific
  - Umbrella trials: combination partner/dosing schedules specific
  - Borrowing information across similar arms
  - Less number of patients and accelerated timeline
  - More accurate estimation of dose-toxicity relationship

Exchangeability-nonexchangeability Model

- Neuenschwander et. al proposed EXNEX design that assumes indication-specific parameter to be partially exchangeable with parameters from other indications

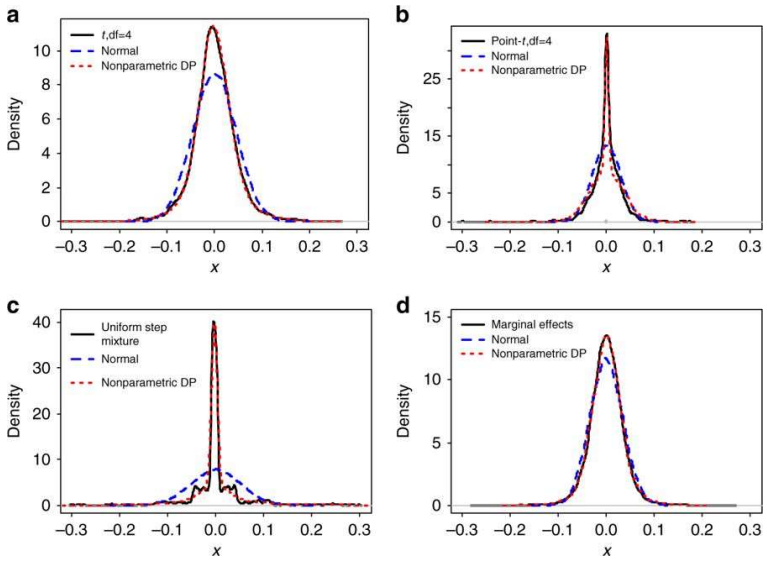
- Exchangeability-nonexchangeability model (EXNEX)
  - With probability $p_j, \theta_j \sim N(\mu, \Sigma)$
  - With probability $1 - p_j, \theta_j \sim N(v_j, S_j)$

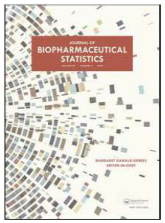
- Allow borrowing information across similar strata while avoiding too optimistic borrowing for extreme strata

- Limitations:
  - Parameter misspecification on prior distribution leads to inaccurate MTD
  - Estimation highly depends on weight p

Semi-parametric Dose Finding Designs

- Li et. al(2019) proposed Bayesian semi-parametric design (BSD) framework for dose-finding with multiple indications or drug candidates
- Utilzing non-parametric Dirichlet process for prior approximation
  - Used in ML and computer vision
  - Draw a distribution G from $DP(H, \alpha)$
  - Adaptively learn distribution from data
  - Capable of fitting a broad spectrum of distributions





Journal of Biopharmaceutical Statistics

ISSN: 1054-3406 (Print) 1520-5711 (Online) Journal homepage: https://www.tandfonline.com/loi/lbps20

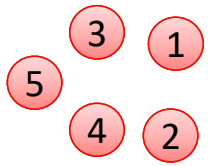
Bayesian Semi-parametric Design (BSD) for adaptive dose-finding with multiple strata

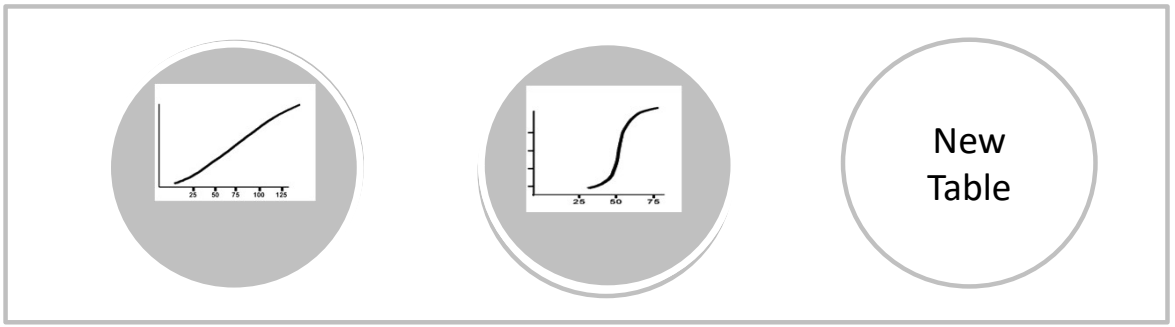
Mo Li, Rachael Liu, Jianchang Lin, Veronica Bunn & Hongyu Zhao

Bayesian Semi-parametric Design I (BSD1)

- Belief of relatively homogeneity across strata
- Prior distribution:
  - $\theta_j \sim G, G \sim DP(H, \alpha), H = N(\mu, \Sigma)$
  - The prior distribution of θ_j is generated by DP itself and is able to infer from data.

Implemented by Chinese Restaurant Process (CRP)

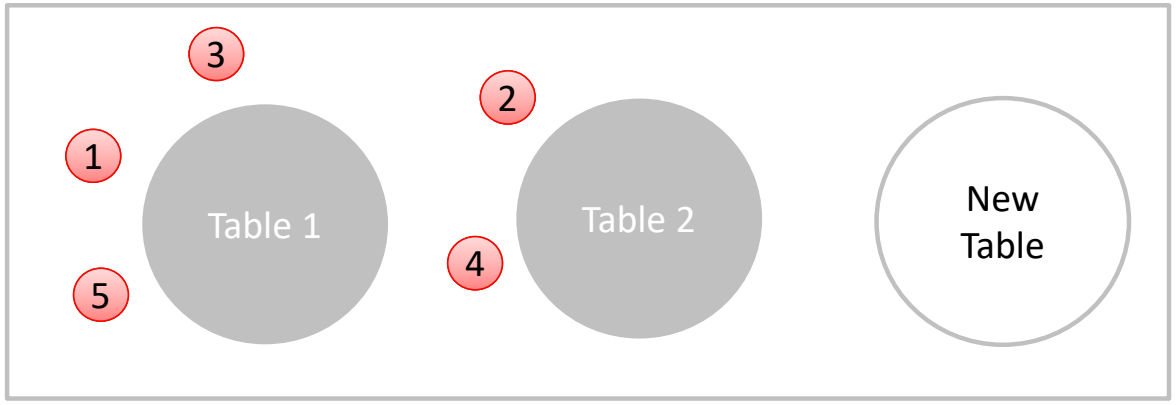




- Cluster assignment of indications
  - $P(z_j = k | z_1, \ldots, z_{j-1}, \alpha) = \begin{cases} \frac{N_k}{N-1+\alpha} & if\ \ k\ is\ an\ old\ cluster \\ \frac{\alpha}{N-1+\alpha} & if\ k\ is\ a\ new\ cluster \end{cases}$
- Indications in the same cluster, eg: $\theta_1 = \theta_3$
- Indications in different clusters, eg: $\theta_1, \theta_2 \sim H$

Bayesian Semi-parametric Design II (BSD2)

- No prior assumption on the extent of heterogeneity
- Prior distribution:
  - $\theta_j|\mu_j,\Sigma_j \sim N(\mu_j,\Sigma_j)$, with $\mu_j=(\mu_{j1},\mu_{j2})$, $\Sigma_j=\begin{pmatrix}\tau_{j1}^2 & \rho_j\tau_{j1}\tau_{j2}\\ \rho_j\tau_{j1}\tau_{j2} & \tau_{j2}^2\end{pmatrix}$.
  - For convenience, denote $\theta_j \sim F(\phi_j)$ where $\phi_j=(\mu_{j1},\mu_{j2},\tau_{j1},\tau_{j2},\rho_j)$
- Hyper-parameters
  - $\phi_j \sim G, G \sim DP(H,\alpha)$
  - $\mu_{j1},\mu_{j2} \sim G_1, G_1 \sim DP(H_1,\alpha), H_1=N(\mu_0,\sigma_0^2)$,
  - $\tau_{j1},\tau_{j2} \sim G_2, G_2 \sim DP(H_2,\alpha), H_2=Lognormal(v_0,\tau_0^2)$,
  - $\rho_j \sim G_3, G_3 \sim DP(H_3,\alpha), H_3=Unif(-1,1)$.
- Indications in the same cluster
  - eg: $\phi_1=\phi_3=\phi, \theta_1,\theta_3 \sim F(\phi)$
- Indications in different clusters
  - eg: ϕ_1,ϕ_2 follow identical distribution, $\theta_1 \sim F(\phi_1), \theta_2 \sim F(\phi_2)$



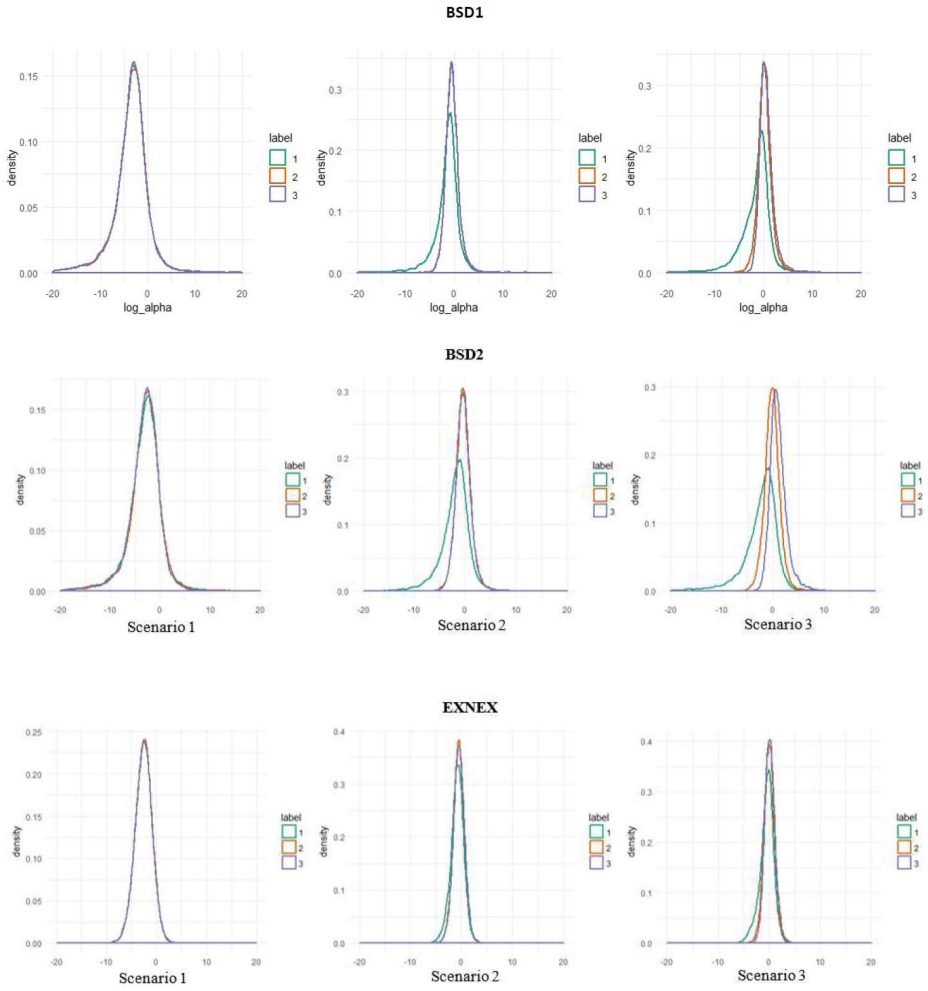
Illustrative Example

Heterogeneity

Scenario 1		
Indi1	Indi2	Indi3
6mg: 0/3	6mg: 0/3	6mg: 0/3

Scenario 2		
Indi1	Indi2	Indi3
6mg: 0/3	6mg: 1/3	6mg: 1/3

Scenario 3		
Indi1	Indi2	Indi3
6mg: 0/3	6mg: 1/3	6mg: 2/3



Illustrative Example

Scenario	Cohort	Indication 1	Indication 2	Indication 3
1	1	6mg: 0/3	6mg: 0/3	6mg: 0/3
	2	12mg: 1/3	12mg: 1/3	12mg: 0/3
		→[1] →[2] →[3] →[4] →[5]	→ → → → →	↑ → → → ↑
2	1	6mg: 0/3	6mg: 0/3	6mg: 0/3
	2	12mg: 1/3	12mg: 0/3	12mg: 0/3
		→ ↑ ↑ → →	↑ ↑ ↑ ↑ ↑	↑ ↑ ↑ ↑ ↑

(1) Stratified; (2) EX; (3) EXNEX; (4) BSD1; (5) BSD2

Overall, BSD1 & BSD2 have better dose escalation decision

Dose Finding in Basket and Umbrella trials

- It is not uncommon to explore multiple indications and multiple treatment candidates
- Appropriate designs to incorporate the complex elements to
  - Accelerate the development
  - Increase the efficiency
  - Comprehensive exploration before committing to pivotal trials
- Designs with borrowing feature will be able to address this issue in master protocol concept
  - Basket trial and umbrella trial
  - Avaible designs such as BSD1, BSD2, EX, EXNEX designs
  - Important to avoid mis-specification and allow learning form data

AGENDA

- Introduction
- Designs focusing on DLT in Cycle I
- Designs considering late-onset toxicity
- Dose finding in basket and umbrella trials
- Dose finding incorporating multiple endpoints
- Concluding remarks

When MTD ≠ Optimal Dose

- Dose finding with limited data and heterogeneity is likely to miss the efficacy signal during exploration
- The highest “safe” dose is not always optimal
  - Potential benefit may appear to plateau above a certain dose
  - Lower doses are as efficacious as higher doses
- Efficacy should be considered for optimal dose in future clinical development: e.g., clinical response, biomarkers, etc.
- Phase I/II dose finding study
  - Incorporate the toxicity and efficacy outcomes simultaneously.
  - Find **optimal biological dose** (OBD): the dose that possesses the highest efficacy probability while inducing acceptable toxicity.
- An optimal and efficient design to identify the right dose level with maximum efficacy potential and tolerable toxicity is the key factor to success

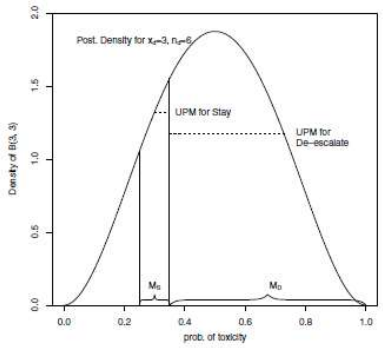
Designs Incorporating Both Safety and Efficacy Endpoints

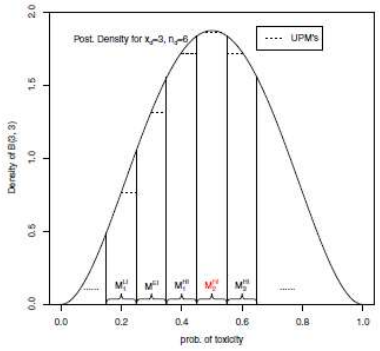
- Model based designs:
  - Thall and Cook (2004) proposed efficacy-toxicity trade off designs
  - Sato, Hirakawa, and Hamada (2016) proposed the SHH design.
  - Strong model and distribution assumption

- Model assisted designs:
  - Ji et al.(2017) proposed TEPI design
  - Takeda et. al (2018) proposed BOIN-ET design
  - Lin et. al (2020) proposed BOIN-12 design
  - Li et. al (2020) proposed TEPI-2 and UBI designs
  - Relaxed model assumption but mostly need the utility trade off function

TEPI-2: Toxicity Efficacy Probability Interval-2 Design

- Assume the toxicity probability p_i increase with dose level i and efficacy probability q_i is not monotone with dose level i
  - Prior: $p_i \sim beta(\alpha_p, \beta_p)$, $q_i \sim beta(\alpha_q, \beta_q)$
  - Data: $x_i|p_i \sim Bin(n_i, p_i)$, $y_i|q_i \sim Bin(n_i, q_i)$
  - Posterior: $p_i \sim beta(a + x_i, b + n_i - x_i)$, $q_i \sim beta(a + y_i, b + n_i - y_i)$
  - Joint Unit Probability Mass (JUPM) is defined as ratio between the probability of the region and the size of the region
- TEPI design can provide unrealistic decision due to Ockham's razor
- To improve, Li et. al proposed TEPI-2 design by calculating the JUPM in equal interval





TEPI-2: Dose Escalation Decision based on Intervals of Toxicity and Efficacy

Based on the preset table, calculate JUPM, find the maximum and get the decision E, S or D

Table 1. An example of TEPI decision table based on p_T=0.4 and q_E=0.2. "E", "S", and "D" denote escalation, stay, and de-escalation, respectively.

			Efficacy rate				
			Low	Moderate	High	Superb	
			0, 0.2	0.2, 0.4	0.4, 0.6	0.6,0.8	0.8, 1
Toxicity rate	Low	0, 0.08	E	E	E	E	E
		0.08, 0.16	E	E	E	E	E
	Moderate	0.16, 0.24	E	E	E	S	S
		0.24, 0.32	E	E	E	S	S
	High	0.32, 0.4	D	S	S	S	S
	Unacceptable	0.4, 0.48	D	D	D	D	D
		0.48, 0.56	D	D	D	D	D
		....	D	D	D	D	D
		0.88, 0.96	D	D	D	D	D
		0.96, 1	D	D	D	D	D

- Safety Rule:
  - To exclude any dose with excess toxicity if $\Pr(p_i > p_T|D) > \eta$
- Futility Rule:
  - To exclude any dose with unacceptable efficacy if $\Pr(q_i > q_E|D) < \xi$

TEPI-2: Transparent Decision Tables

- Use $p_T = 0.4$, $q_E = 0.2$ for safety and futility rule

TEPI		E						
		0	1	2	3	4	5	6
T	0	EU	E	E	E	E	E	E
	1	EU	E	E	E	E	S	S
	2	DUE	D	S	S	S	S	S
	3	DUE	D	S	S	S	S	S
	4	DUE	D	D	D	D	D	D
	5	DUT	DUT	DUT	DUT	DUT	DUT	DUT
	6	DUT	DUT	DUT	DUT	DUT	DUT	DUT

TEPI

TEPI2		E						
		0	1	2	3	4	5	6
T	0	EU	E	E	E	E	E	E
	1	EU	E	E	E	S	S	S
	2	DUE	D	S	S	S	S	S
	3	DUE	D	D	D	D	D	D
	4	DUE	D	D	D	D	D	D
	5	DUT	DUT	DUT	DUT	DUT	DUT	DUT
	6	DUT	DUT	DUT	DUT	DUT	DUT	DUT

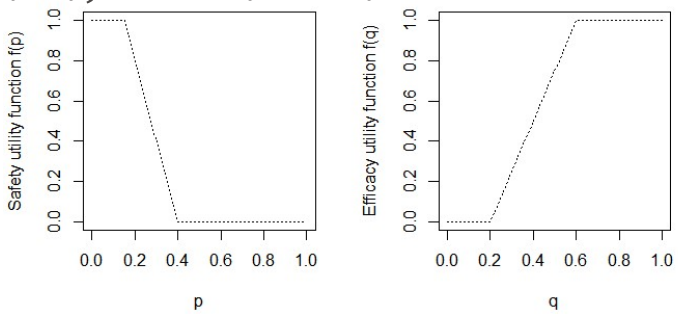
TEPI-2

TEPI2 is safer than TEPI

- Avoid undesirable decisions, such as when 3 out of 6 patients experience DLT at a given dose
- Won't risk more patients to a higher dose when efficacy is good

TEPI-2: Optimal Dose Selection

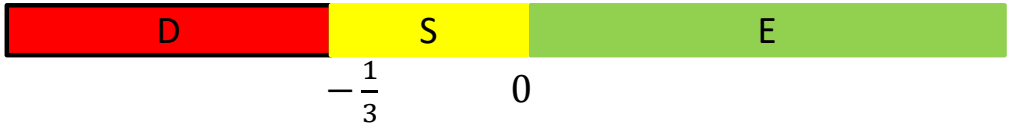
- Calculate the posterior distribution of efficacy and toxicity.
- For each sample t, generate $p^t = (p_1^t, \ldots, p_d^t)$, $q^t = (q_1^t, \ldots, q_d^t)$
  - PAVA isotonic transformation to make p^t non-decreasing.
- At each dose i, calculate $U^t(\hat{p}_i^t, q_i^t) = f_T(\hat{p}_i^t) f_E(q_i^t)$, where



- The estimated posterior expected utility at dose i is given by $\hat{E}[U(p_i, q_i)|D] = \frac{1}{T}\sum_{t=1}^{T} U^t(\hat{p}_i^t, q_i^t)$.
- OBD selection: $\hat{d} = argmax_i \hat{E}[U(p_i, q_i)|D]$, selected the optimal dose with the maximum utility

UBI design: BOIN based Utility Design Incorporating Safety and Efficacy

- Propose UBI to consider efficacy and toxicity simultaneously
- Construct Utility function $U = f_E(\hat{q}_i) - \theta f_T(\hat{p}_i)$, e.g., trade-off parameter θ=2
  - If $U \geq 0$, escalate to the next higher dose.
  - If $U < -\frac{1}{3}$, de-escalate to the next lower dose.
  - Otherwise, i.e., $-\frac{1}{3} \leq U < 0$. stay at the current dose.



$$\hat{q}_i = y_i/n_i,\ f_E(\hat{q}_i) = \begin{cases} 0, \hat{q}_i > Eff \\ \hat{q}_i, \hat{q}_i \leq Eff \end{cases}, Eff = 0.66$$

When $\hat{q}_i > Eff,\ f_T(\hat{p}_i) = \begin{cases} 0, \hat{p}_i \leq Tox \\ 1, \hat{p}_i \geq \lambda_d \\ \hat{p}_i/3, else \end{cases}, Tox = 0.15$

When $\hat{q}_i \leq Eff,\ f_T(\hat{p}_i) = \begin{cases} 0,\ \hat{p}_i \leq \lambda_e \\ 1, \hat{p}_i \geq \lambda_d \\ \hat{p}_i, else \end{cases}$, λ_e and λ_d are from BOIN

TEPI vs UBI

- Use $p_T = 0.4$, $q_E = 0.2$ for safety and futility rule
- Dose escalation/de-escalation rule and final dose selection use empirical toxicity and efficacy rate instead of Bayesian

N=6

TEPI		E						
		0	1	2	3	4	5	6
T	0	EU	E	E	E	E	E	E
	1	EU	E	E	E	E	S	S
	2	DUE	D	S	S	S	S	S
	3	DUE	D	S	S	S	S	S
	4	DUE	D	D	D	D	D	D
	5	DUT	DUT	DUT	DUT	DUT	DUT	DUT
	6	DUT	DUT	DUT	DUT	DUT	DUT	DUT

TEPI

U-BOIN		E						
		0	1	2	3	4	5	6
T	0	EU	E	E	E	E	E	E
	1	EU	E	E	E	S	S	S
	2	DUE	D	S	S	S	S	S
	3	DUE	D	D	D	D	D	D
	4	DUE	D	D	D	D	D	D
	5	DUT	DUT	DUT	DUT	DUT	DUT	DUT
	6	DUT	DUT	DUT	DUT	DUT	DUT	DUT

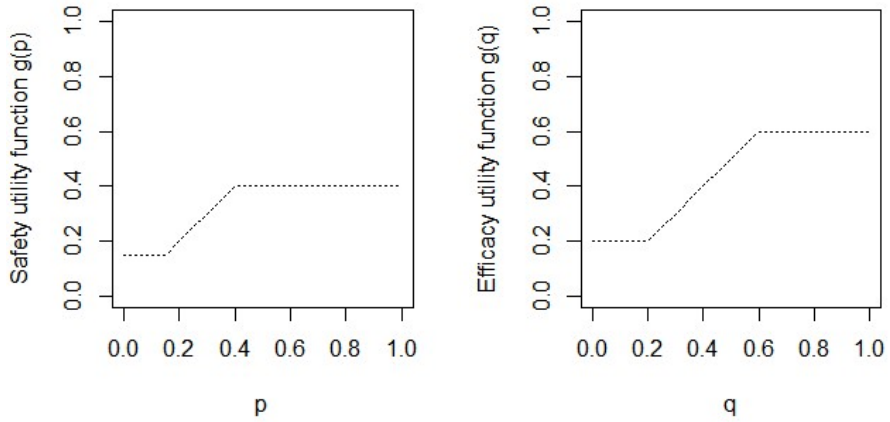
UBI

U-BOIN is safer than TEPI, similar as TEPI-2

- Avoid undesirable decisions, such as when 3 out of 6 patients experience DLT at a given dose
- Won't risk more patients to a higher dose when efficacy is high
- Trade-off between efficacy and toxicity plays a role

UBI: Optimal Dose Selection

- The toxicity $\hat{p} = (\hat{p}_1, \ldots, \hat{p}_d)$ and efficacy rate $\hat{q} = (\hat{q}_1, \ldots, \hat{q}_d)$ are calculated at the end of the trial
  - PAVA isotonic transformation was applied on $\hat{p}$ to obtain the isotonic estimates.
- For each dose i, calculate Utility score $U(\hat{p}_i, \hat{q}_i) = g_E(\hat{q}_i) - \theta g_T(\hat{p}_i)$,



- Select the optimal dose with the maximum utility score.

TEPI2 and UBI: Model Performance

- TEPI-2 and UBI have higher OBD selection probability -> better reliability
- Dose mis-specification cause unfavorable results for EffTox in some scenarios.
- Designs incorporating efficacy have superior reliability than toxicity-based designs.
- TEPI-2 and UBI have fewer patients treated above OBD

Table 5. Simulation results comparing the BOIN, TEPI, EffTox, TEPI-2, and UBI under different scenarios.

				Selection probability (%)					Number of subjects treated				
	Dose	Tox	Eff	BOIN	TEPI	TEPI-2	UBI	EffTox	BOIN	TEPI	TEPI-2	UBI	EffTox
S1	1	**0.25**	**0.3**	40.5	67.5	68.2	70.2	16	8.7	11.4	11.8	11.6	5.3
	2	0.35	0.35	31.4	17.8	15.4	13.2	23	6.2	5.6	5.2	5.5	5.9
	3	0.4	0.45	14.4	2.4	2.9	3.8	19	2.3	2.0	1.8	1.9	4.6
	4	0.45	0.65	5.8	0.3	0.5	0.5	34	0.6	0.4	0.5	0.4	4.3
S2	1	0.05	0.2	0.3	24.7	24.5	24.5	2	3.6	4.0	4.0	4.1	3.3
	2	0.1	0.4	6.3	26.3	22.2	29.3	7	4.9	4.7	4.8	4.9	4.1
	3	**0.2**	**0.6**	30.9	42.6	44.7	44.2	43	6.2	6.5	6.9	6.9	7.3
	4	0.3	0.55	62.7	5.5	4.3	6.1	48	6.2	5.7	5.2	5.0	6.3
S3	1	0.1	0.25	1.9	23.2	24.4	22.6	4	4.4	4.7	4.8	4.7	3.6
	2	0.12	0.35	5.3	24.5	23.5	24.6	5	4.7	4.7	4.9	4.8	3.9
	3	**0.15**	**0.6**	16.3	38.6	39.7	40.6	24	4.8	5.0	5.3	5.3	5.6
	4	0.2	0.6	76.4	11.3	10.1	10.1	68	6.9	6.3	5.7	5.9	7.8
S4	1	0.07	0.2	0.7	23.4	23.6	22.1	3	3.9	4.1	4.1	4.2	3.6
	2	0.1	0.35	3.3	34.6	32.5	31.2	4	4.5	4.5	4.7	4.7	3.7
	3	**0.15**	**0.5**	32.0	35.7	37.5	37.9	38	6.1	5.9	6.3	6.2	6.5
	4	0.35	0.55	63.9	4.7	5.1	7.1	55	6.5	6.2	5.7	5.7	7.1
S5	1	**0.2**	**0.5**	46.6	89.2	90.6	90.3	50	9.0	9.9	11.4	11.1	8.8
	2	0.4	0.45	36.9	8.8	7.2	7.7	30	7.2	8.7	7.6	7.8	7.6
	3	0.48	0.4	10.7	0.4	0.6	0.9	8	2.0	1.9	1.6	1.7	2.7
	4	0.5	0.35	2.2	0	0	0	8	0.3	0.3	0.3	0.2	1.4

Case Study: a Hypothetical CAR-T Study

- Hypothetical CART study with four dose levels
- Maximum sample size 21

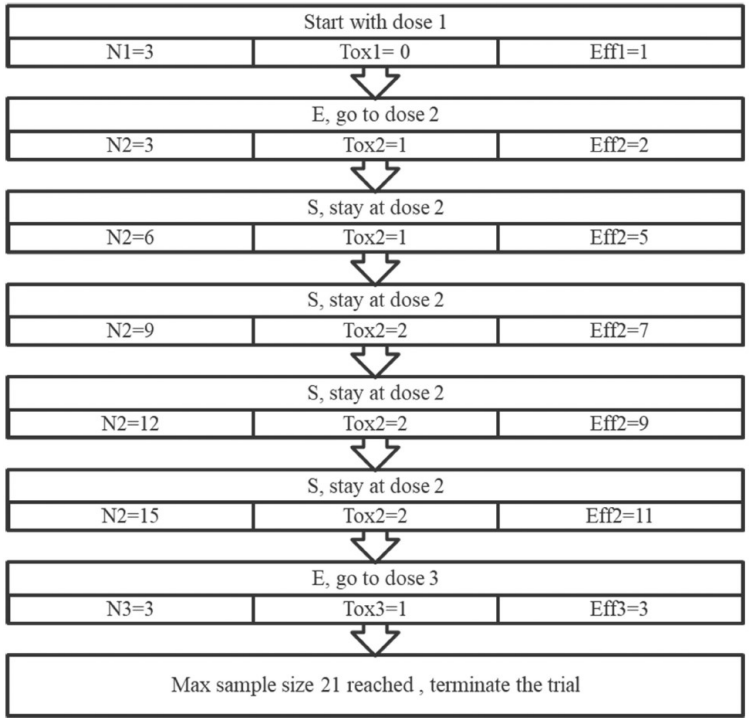


Table 6. Simulation results comparing the 3 + 3, BOIN, TEPI, EffTox, TEPI-2, and UBI incase study.

	Selection probability (%)						Number of subjects treated					
Dose	3 + 3	BOIN	TEPI	TEPI-2	UBI	EffTox	3 + 3	BOIN	TEPI	TEPI-2	UBI	EffTox
1	22.7	1.6	26.7	22.9	29.9	1	3.1	3.6	3.5	3.7	3.6	3.2
2	44.6	32.9	65.0	69.0	65.4	74	4.0	7.3	8.1	9.4	9.0	11.5
3	31.4	58.7	8.1	8.0	4.6	25	3.4	7.7	8.1	6.8	7.2	5.7
4	1.2	6.9	0	0	0	0	1.2	2.0	1.2	1.1	1.1	0.6

Dose Finding Incorporating Multiple Endpoints

- In I-O and Cell therapy, MTD is not always the optimal dose
  - Complex dose-toxicity, dose-efficacy relationship
  - Unnecessary to push to MTD for RP2D decision making

- A design incorporating multiple endpoints during dose escalation is beneficial
  - Ensure appropriate number of patients allocated to various dose levels
  - Increase the reliability of the optimal dose recommendation
  - Reduce the sample size and accelerate the development

- Available design options in model-based and model-assisted fashions
  - Require input on the trade-off between safety and efficacy endpoints
  - Various assumptions on the dose related relationship
  - Better option compared with the DLT driven designs

AGENDA

- Introduction
- Designs focusing on DLT in Cycle I
- Designs considering late-onset toxicity
- Dose finding in basket and umbrella trials
- Dose finding incorporating multiple endpoints
- Concluding remarks

Concluding Remarks

- In I-O and Cell Therapy, early development is especially complex with prominent scientific questions to be addressed
  - Pre-clinical models are not informative
  - Unclear relationship between doses and activity
  - Careful selection of planned dosage and dosing schedules
  - Identification of optimal dose with tolerable profile and clinical activity
  - Heterogeneity of the patient population
  - Exploration of combination partners
- Patient-focused innovative designs are in great need to handle
  - DLT or beyond
  - Reliability of MTD or OBD determination
  - Implementation of basket trial and umbrella trial early-on
    - Allow dynamic borrowing to improve the efficiency
  - Incorporating both safety and efficacy endpoints
- Carefully examine the designs through simulation practices for optimal implementation

Well begun is half done!

Thank You!

Takeda Pharmaceutical Company Limited

References

1. Li, P., Lin, J., Ji, Y. and Liu, R. (2020) TEPI-2 and UBI: Designs for Optimal Immuno-oncology and Cell Therapy Dose Finding with Toxicity and Efficacy. *Journal of Biopharmaceutical Statistics* (in press)
2. Liu, R., Lin, J., and Li, P. (2020) Design considerations for phase I/II dose finding clinical trials in Immuno-oncology and cell therapy. *Contemporary Clinical Trials* (in press).
3. Li, M., Liu, R., Lin, J., Bunn, V., and Zhao, H. (2020) Bayesian Semi-parametric Design (BSD) for adaptive dose-finding with multiple strata. *Journal of Biopharmaceutical Statistics*, 30:5, 806-820
4. Bottino, D., Liu, R., Bazzazi, H., and Venkatakrishnan, K. (2020). Quantitative translation in Immuno-oncology research and development. Clinical Pharmacology & TherapeuticsVolume 108, Issue 3 p. 430-433
5. B. Allard, et al., Immuno-oncology-101: overview of major concepts and translational perspectives, Semin. Cancer Biol. 52 (Pt 2) (2018 Oct).
6. Stephan Kruger, et al., Advances in cancer immunotherapy 2019-latest trends, J Exp. Clin. Cancer Res. 38 (2019) 268.
7. K.S. Campbell, A.K. Purdy, Structure/function of human killer cell immunoglobulin like receptors: lessons from polymorphisms, evolution, crystal structures and mutations, Immunology. 132 (2) (2011) 315–325.
8. L.L. Lau, B.D. Jamieson, T. Somasundaram, R. Ahmed, Cytotoxic T-cell memory without antigen, Nature. 369 (6482) (1994) 648–652.
9. Jia Xin Yu, M. Vanessa, Hubbard-Lucey and Jun tang, from the Analyst's couch, Immuno-oncology drug development goes global, Nat. Rev. Drug Discov. 18 (2019) 899–900.
10. U.S. Department of Health and Human Services, Food and Drug Administration Center for Biologics Evaluation and Research, Guidance for Industry: considerations for the design of early-phase clinical trials of cellular and gene therapy products, June 2015, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-early-phase-clinical-trials-cellular-and-gene-therapy-products
11. L. Rosenbaum, Tragedy, perseverance, and chance—the story of CAR-T therapy, N.Engl. J. Med. 377 (14) (2017) 1313–1315.
12. S. Gill, M.V. Maus, D.L. Porter, Chimeric antigen receptor T cell therapy: 25 years in the making, Blood Rev. 30 (2016) 157–167.
13. Thall PF, Lee SJ. Practical model-based dose-finding in phase I clinical trials: methods based on toxicity. Int J Gynecol Cancer. 2003 May-Jun;13(3):251-61. doi: 10.1046/j.1525-1438.2003.13202.x. PMID: 12801254.
14. SN. Goodman, ML. Zahurak, S. Piantadosi. Some practical improvements in the continual reassessment method for phase I studies. Statistics in MedicineVolume 14, Issue 11 (1995) p. 1149-1161

References

16. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008 Jun 15;27(13):2420-39. doi: 10.1002/sim.3230. PMID: 18344187.
17. Y Ji and S-J Wang, "Modified Toxicity Probability Interval Design: A Safer and More Reliable Method Than the 3 3 Design for Practical Phase I Trials"
18. Y Ji, P Liu, Y Li, and BN Bekele, "A modified toxicity probability interval method for dose finding trials", Clin Trials. 2010 Dec; 7(6): 653–663. Guo, S-J Wang, S Yang, H Lynn, and Y Ji, "A Bayesian interval dose-finding design addressing Ockaham's razor: mTPI-2", Contemporary Clinical Trials 58(2017) 23-33
19. Liu S. and Yuan, Y. (2015). Bayesian optimal interval designs for phase I clinical trials, Journal of the Royal Statistical Society: Series C , 64, 507-523.
20. Zhou, Y., Lee, J. J., Wang, S., Bailey, S., & Yuan, Y. (2020). Incorporating historical information to improve phase I clinical trial designs. arXiv preprint arXiv:2004.12972.
21. Yan F, Mandrekar SJ, Yuan Y. Keyboard: a novel bayesian toxicity probability interval design for phase I clinical trials. Clin Cancer Res. 2017;23:3994-4003.
22. Liu M, Wang SJ, Ji Y. The i3+3 design for phase I clinical trials. J Biopharm Stat. 2020 Mar;30(2):294-304. doi: 10.1080/10543406.2019.1636811. Epub 2019 Jul 15. PMID: 31304864.
23. Ivanova, A., Flournoy, N., and Chung, Y. (2007). Cumulative cohort design for dose-finding. Journal of Statistical Planning and Inference 137, 2316–2327.
24. van Werkhoven, E., Hinsley, S., Frangou, E. et al. Practicalities in running early-phase trials using the time-to-event continual reassessment method (TiTE-CRM) for interventions with long toxicity periods using two radiotherapy oncology trials as examples. BMC Med Res Methodol 20, 162 (2020).
25. Yuan, Y., Lin, R., Li, D., Nie, L. and Warren, K.E. (2018). Time-to-event Bayesian Optimal Interval Design to Accelerate Phase I Trials. Clinical Cancer Research 24(20): 4921-4930.
26. Neuenschwander, B., M. Branson, and T. Gsponer. 2008. Critical aspects of the Bayesian approach to phase I cancer trials. Statistics in Medicine 27:2420–2439. doi:10.1002/(ISSN)1097-0258.
27. Neuenschwander, B., S. Wandel, S. Roychoudhury, and S. Bailey. 2016. Robust exchangeability designs for early phase clinical trials with multiple strata. Pharmaceutical Statistics 15:123–134. doi:10.1002/pst.v15.2.
28. Thall, P. F., and J. D. Cook. 2004. Dose-finding based on efficacy-toxicity trade-offs. Biometrics 60:684–693.
29. Sato H, Hirakawa A, Hamada C. An adaptive dose-finding method using a change-point model for molecularly targeted agents in phase I trials. Stat Med. 2016 Oct 15;35(23):4093-109. doi: 10.1002/sim.6981. Epub 2016 May 11. PMID: 27221807.
30. Raje, N., J. Berdeja, Y. Lin, D. Siegel, S. Jagannath, D. Madduri, M. Liedtke, J. Rosenblatt, M. V. Maus, A. Turka, et al. 2019. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. New England Journal of Medicine 380 (18):1726–1737.