TEPI-2 and UBI: Designs for Optimal Immuno-oncology and Cell Therapy Dose Finding with Toxicity and Efficacy

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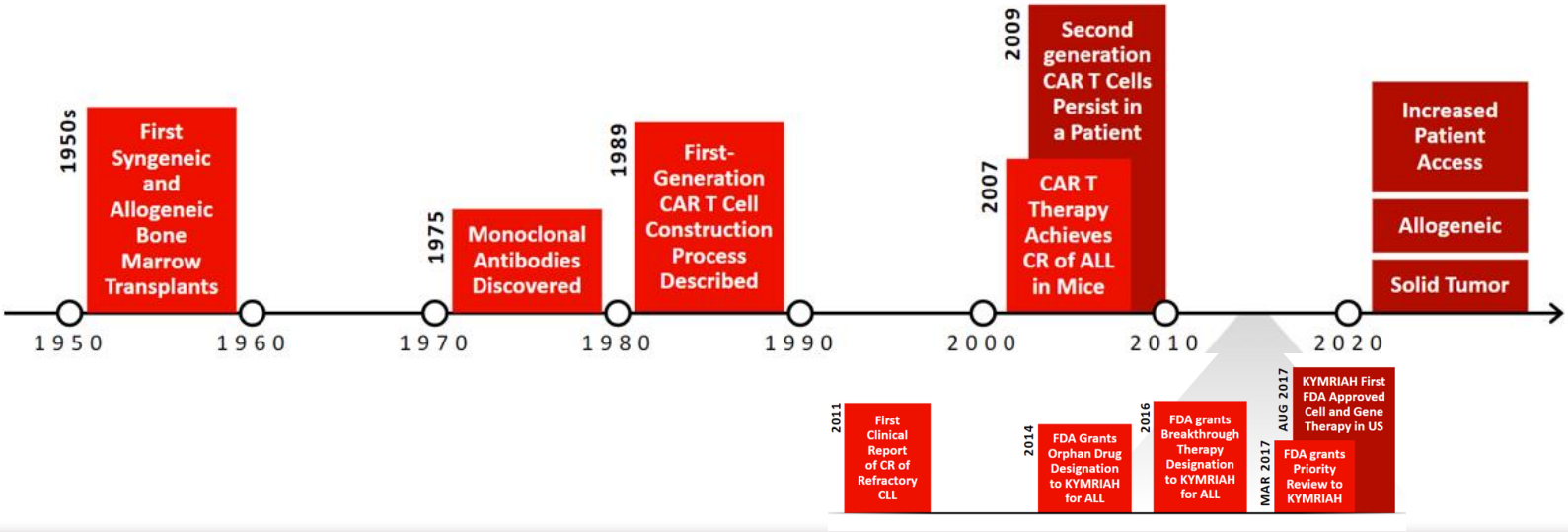
Better Health, Brighter Future

Outline

- **Background**
- TEPI2: Toxicity Efficacy Probability Interval-2 design
- UBI: Utility Based Interval design
- Simulation study
- Case study
- Summary

Cell Therapy Development

- An incredibly promising cellular immunotherapy approach for treating cancers with unmet medical needs:
  - chimeric antigen receptor (CAR) T cell
  - engineered T-cell receptor (TCR)
  - tumor infiltrating lymphocytes (TILs)
  - natural killer (NK)
  - others
- FDA Guidance on “Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products”



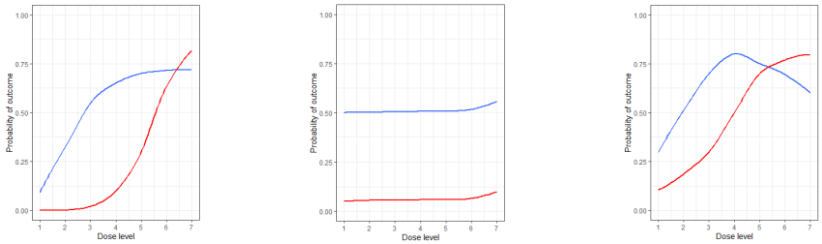
Challenges in Cell Therapy Early Phase Designs

High risk in safety	Complex manufacture	Infeasible to establish dose-response relationship
• prolonged biological activity • high potential for immunogenicity • relatively invasive procedures for dose administration	• lead to limited dose levels • increase the subject variability • patient loss during manufacturing waiting time • Uncertain safety/efficacy correlation between cryopreserved and fresh 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

- Traditional oncology Phase I dose finding study
  - Identify **dose-limiting toxicities** (DLTs)
  - Find **maximum tolerated dose** (MTD)
  - Underlying assumption: both safety and efficacy increases with dose
- Not optimal for the cell therapy

New Paradigm of Dose Finding Design

- Problem: 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



- Proposal: seamless phase I/II dose finding study
  - Incorporating the toxicity and efficacy outcomes simultaneously.
  - Find **optimal biological dose** (OBD): the dose that possesses the highest efficacy probability while inducing acceptable toxicity.
  - Phase I and II are merged using a coherent approach for optimal dosing

Time efficient | Patient saving | Lower cost | Optimal dose

Ref: FDA draft guidance on considerations for the design of early-phase clinical trials of cellular and gene therapy products (2013)

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TEPI: Toxicity Efficacy Probability Interval

- Proposed by Ji et al.(2017) to combine efficacy and toxicity in dose finding

- Assume the toxicity probability p_i increase with dose level i and efficacy probability q_i is not monotone with dose level $i, p_i \perp q_i$
  - 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

$$JUPM_{(a,b)}^{(c,d)} = \frac{\Pr(p_i \in (a,b), q_i \in (c,d) | D)}{(b-a) \times (d-c)}, 0 < a < b < 1, 0 < c < d < 1$$

TEPI

- 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, 1
Toxicity rate	Low	0, 0.15	E	E	E	E
	Moderate	0.15, 0.33	E	E	E	S
	High	0.33, 0.4	D	S	S	S
	Unacceptable	0.4, 1	D	D	D	D

- **Safety rule**
  - To exclude any dose with excessive toxicity
  - If $\Pr(p_i > p_T|D) > \eta$, exclude dose i, i +1, …, d from future use
- **Futility rule**
  - To exclude any dose with unacceptable efficacy
  - If $\Pr(q_i > q_E|D) < \xi$, exclude dose i from future use

TEPI

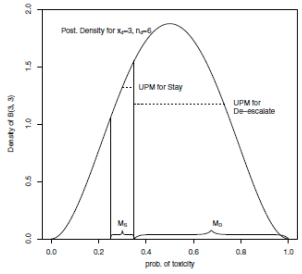
- Pre-calculated TEPI dose-finding decision table
- Ockham's razor may provide unrealistic decision

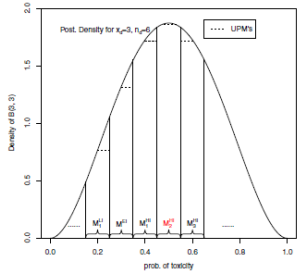
Table 2. Dose-finding table of the TEPI design

Number of patients treated at current dose level	Number of DLTs	Number of responders			
3	0	0	1–3		
	1	E	E		
	2	D	S		
	3	D	D		
		DU_T	DU_T		
		0	1–4	5–6	
6	0	EU	E	E	
	1	EU	E	S	
	2–3	DU_E	D	S	
	4	DU_E	D	D	
	5–6	DU_T	DU_T	DU_T	
		0	1	2–6	7–9
9	0–1	EU	E	E	E
	2	EU	E	E	S
	3–4	DU_E	D	S	S
	5–6	DU_E	D	D	D
	7–9	DU_T	DU_T	DU_T	DU_T
		0–1	2	3–7	8–12
12	0–1	EU	E	E	E
	2	EU	E	E	S
	3–5	DU_E	D	S	S
	6	DU_E	D	D	D
	7–12	DU_T	DU_T	DU_T	DU_T

Toxic to stay

Could be improved!





TEPI2

- Divide into equal length, each block has the same area, 13*5

			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

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TEPI-2 and UBI: designs for optimal immuno-oncology and cell therapy dose finding with toxicity and efficacy

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TEPI vs TEPI2

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

N=6

TEPI

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

TEPI2

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

EU: E with unacceptable efficacy; DUE: D with unacceptable efficacy; DUT: D with unacceptable toxicity

- TEPI2 is safer than TEPI
  - Avoid undesirable decisions, such as S 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

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BOIN: Bayesian Optimal Interval Design

- Only consider safety in dose escalation and optimal dose selection

- Let $\hat{p}_i = x_i/n_i$ denote the observed DLT rate at the current dose level i. To assign a dose to the next cohort of patients,
  - If $\hat{p}_i \leq \lambda_e$, escalate to the next higher dose.
  - If $\hat{p}_i \geq \lambda_d$, de-escalate to the next lower dose.
  - Otherwise, i.e., $\lambda_d < \hat{p}_i < \lambda_e$. stay at the current dose.

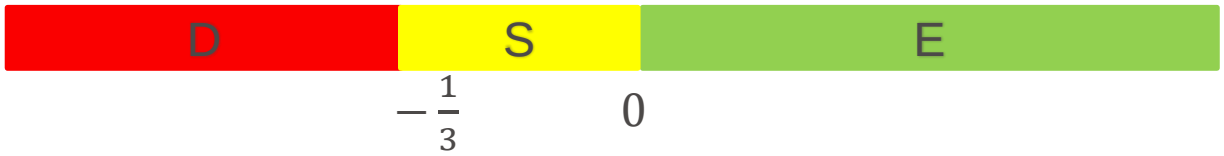
  - $\phi_1 = 0.6p_T$ and $\phi_2 = 1.4p_T$
  - $\lambda_e = \dfrac{\log(\frac{1-\phi_1}{1-p_T})}{\log\{\frac{p_T(1-\phi_1)}{\phi_1(1-p_T)}\}}, \lambda_d = \dfrac{\log(\frac{1-p_T}{1-\phi_2})}{\log\{\frac{\phi_2(1-p_T)}{p_T(1-\phi_2)}\}}$

	Target DLT rate ϕ					
Boundaries	0.15	0.2	0.25	0.3	0.35	0.4
λ_e	0.118	0.157	0.197	0.236	0.276	0.316
λ_d	0.179	0.238	0.298	0.358	0.419	0.479

Proposed design: UBI

- 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.



$f_E(\hat{q}_i)$ is function of efficacy probability, $f_T(\hat{p}_i)$ is function of toxicity probability

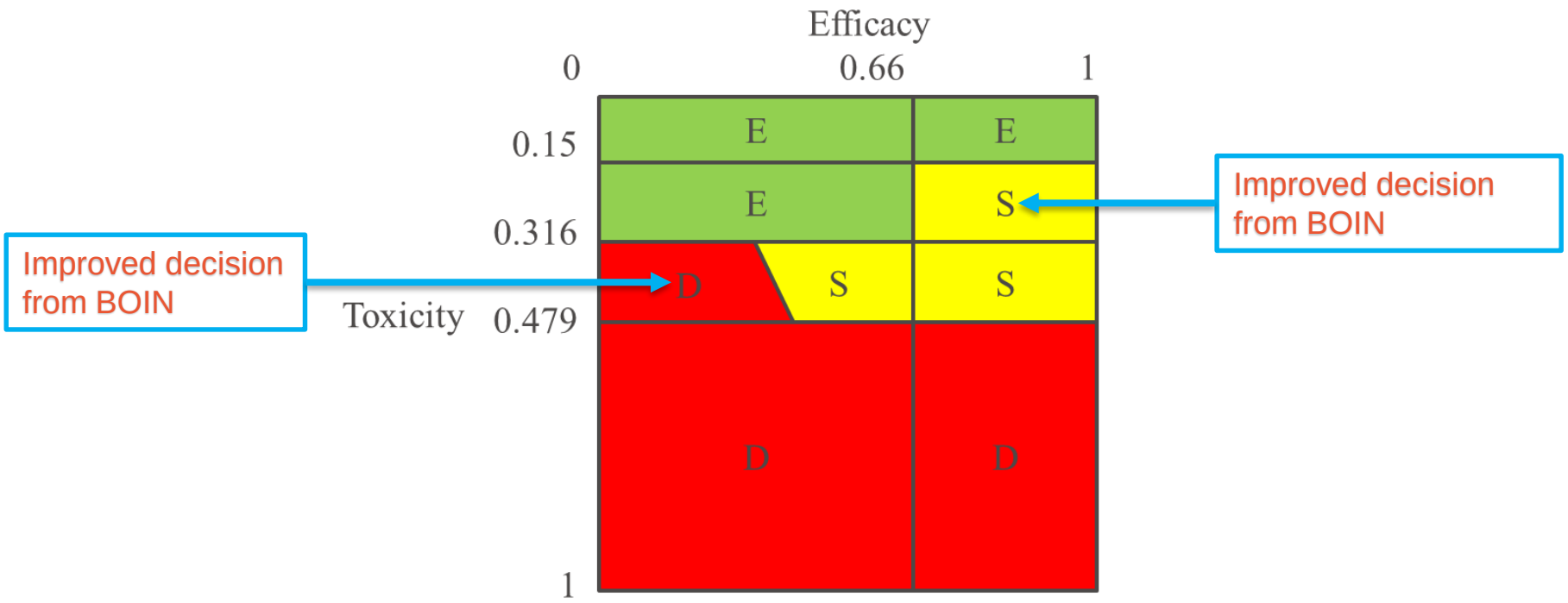
Ref: Li, P., Lin, J., Ji, Y. and Liu, R. (2020) TEPI-2 and UBI: Designs for Optimal Immuno-oncology and Cell Therapy Dose Finding with Toxicity and Efficacy. *Journal of Biopharmaceutical Statistics* (in press)

Proposed design: UBI

- Different efficacy-toxicity trade-off depending on efficacy profile
- Efficacy Utility:
  - $\hat{q}_i = y_i/n_i,\ f_E(\hat{q}_i) = \begin{cases} 0, \hat{q}_i > Eff \\ \hat{q}_i, \hat{q}_i \leq Eff \end{cases}, Eff = 0.66$
- Toxicity Utility
  - When $\hat{q}_i > Eff,\ f_T(\hat{p}_i) = \begin{cases} 0, \hat{p}_i \leq Tox \\ 1, \hat{p}_i \geq \lambda_d \\ \hat{p}_i/3, else \end{cases}, Tox = 0.15$ "Superb" Efficacy
  - 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.

UBI

- An example of UBI decision table based on p_T=0.4 and q_E=0.2.



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

TEPI N=6 UBI

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

UBI		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

- TEPI2 is safer than TEPI, and UBI is in between
  - Avoid undesirable decisions, such as S 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 an important role

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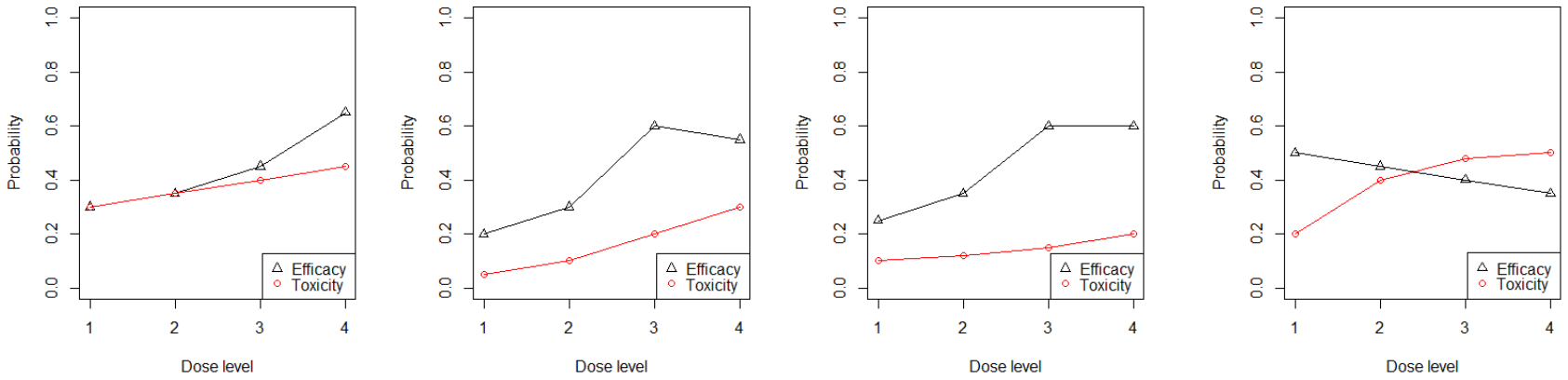
Simulation

- Maximum tolerated toxicity rate $p_T = 0.4$ and cutoff probability $\eta = 0.95$, minimum acceptable efficacy rate $q_E = 0.2$ and cutoff probability $\xi = 0.3$.
- The parameters in the utility functions are $(p_1^*, p_2^*) = (0.15, 0.4)$, $(q_1^*, q_2^*) = (0.2, 0.6)$
- Starting dose =1 with a total of 4 dose levels, maximum sample size of 21 patients and cohort size of 3.
- For Beta priors, $\alpha_p = \alpha_q = \beta_p = \beta_q = 1$.



Simulation

	Dose	Tox	Eff	Selection probability (%)					Number of subjects treated				
				BOIN	TEPI	TEPI2	UBI	EffTox	BOIN	TEPI	TEPI2	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	**0.2**	**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

- Reliability: TEPI2 and UBI have higher OBD selection probability
- Safety: TEPI2 and UBI have less patients treated above OBD

Comparison

Properties	BOIN	TEPI	TEPI2	UBI	EffTox
Incorporates both toxicity and efficacy		X	X	X	X
Rule based design	X	X	X	X	
Transparent decision table		X	X	X	
Avoid undesirable decisions at high toxicity			X	X	
Not risk patients to higher dose at high efficacy			X	X	

- Propose safer and more efficient designs to combine safety and efficacy in OBD identification in immunotherapy and cell therapy.

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Case Study

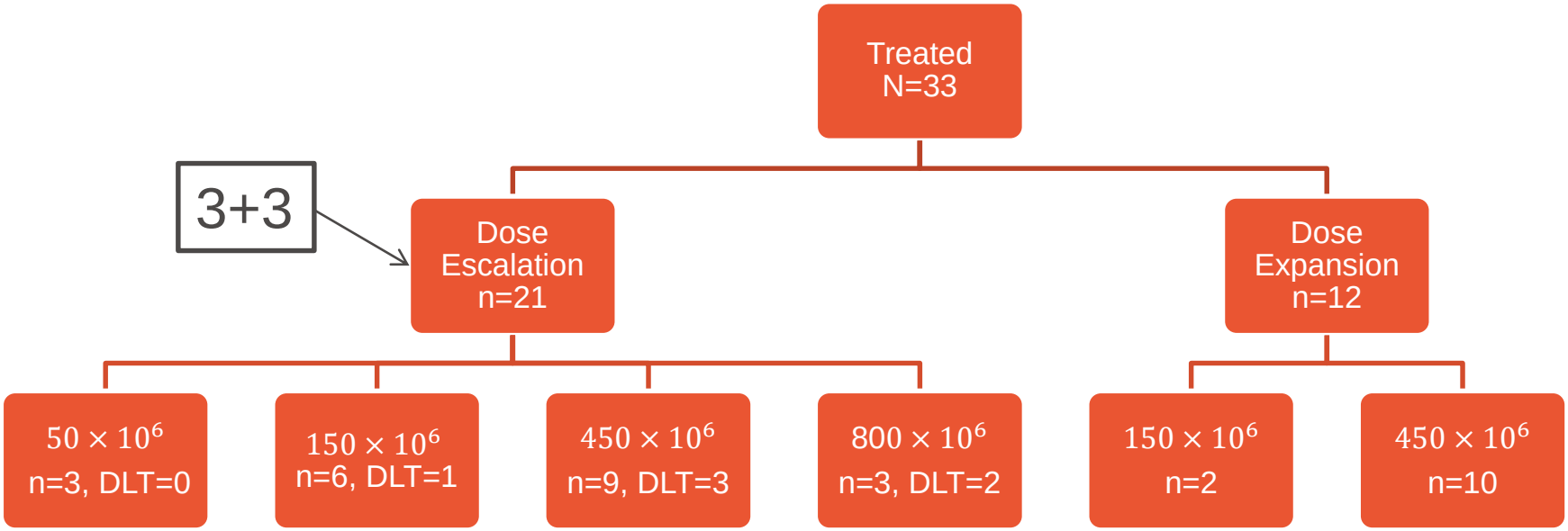
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma

Noopur Raje, M.D., Jesus Berdeja, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Sundar Jagannath, M.D., Deepu Madduri, M.D., Michaela Liedtke, M.D., Jacalyn Rosenblatt, M.D., Marcela V. Maus, M.D., Ph.D., Ashley Turka, Lyh-Ping Lam, Pharm.D., Richard A. Morgan, Ph.D., Kevin Friedman, Ph.D., Monica Massaro, M.P.H., Julie Wang, Pharm.D., Ph.D., Greg Russotti, Ph.D., Zhihong Yang, Ph.D., Timothy Campbell, M.D., Ph.D., Kristen Hege, M.D., Fabio Petrocca, M.D., M. Travis Quigley, M.S., Nikhil Munshi, M.D., and James N. Kochenderfer, M.D.

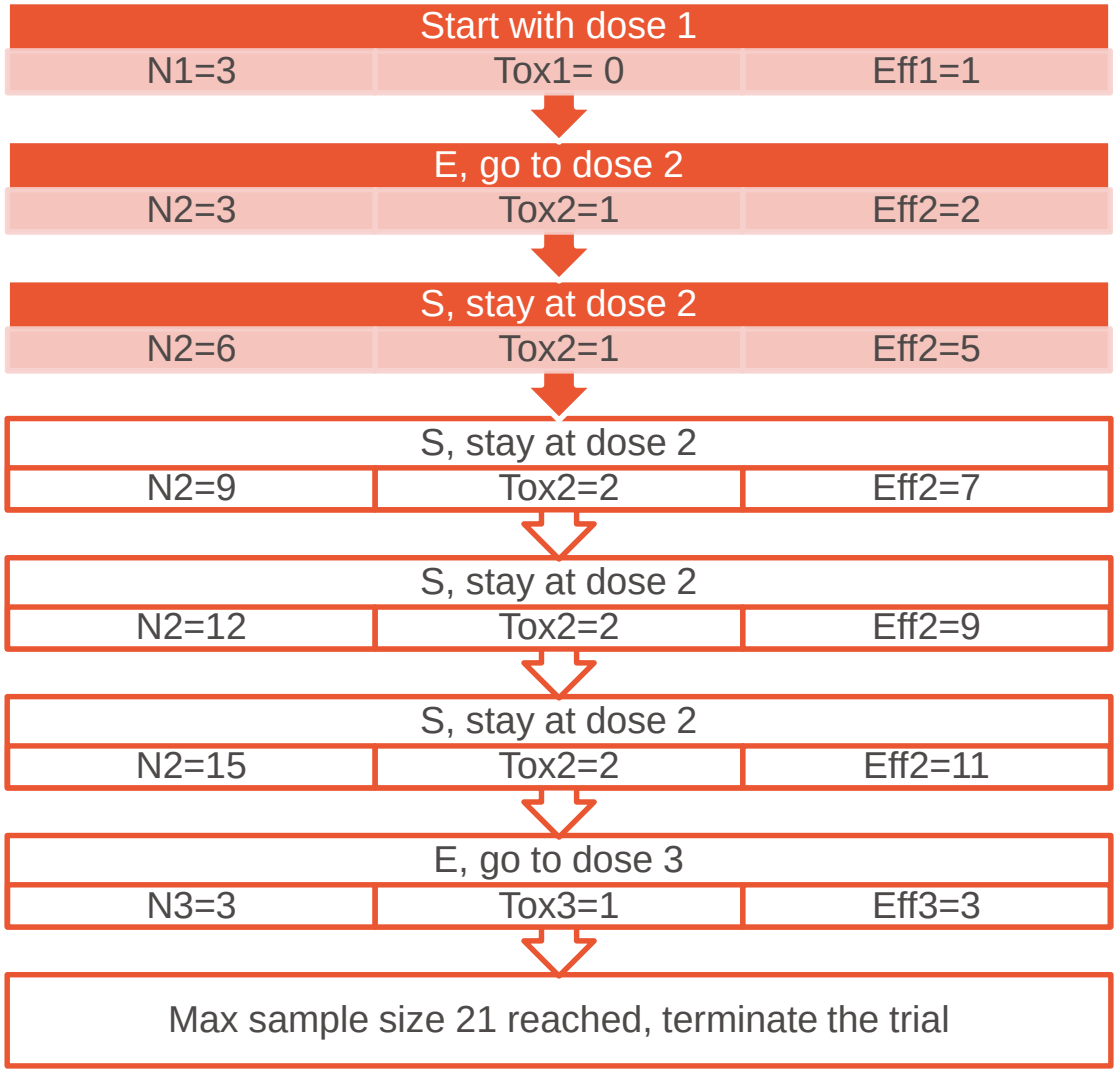
Case Study



- **Safety:** adverse events of grade 3 or higher occurring within the 21 days after infusion, estimated DLT rate of **0, 0.17, 0.33, 0.67**
- **Efficacy:** clinical response within the first 8 weeks, reported response rate of **0.33, 0.75, 0.95, 1.0**

Case Study

Redesign the study using proposed TEPI2 and UBI design



Case Study

Dose level	1	2	3	4
N of patients by 3+3	3	6	9	3
N of patients by TEPI2 and UBI	3	15	3	0
Estimated DLT rate	0	0.13	0.33	0
Estimated Response rate	0.33	0.73	1.0	0

TEPI2 and UBI:

- Recommend dose level 2 as OBD, 150×10^6 CAR+ T cells
- Fewer patients at dose level 3 and 4
- Seamlessly integrating dose escalation and dose expansion cohorts

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Summary

- Proposed two optimal designs to identify OBD in phase I/II trials:
  - TEPI2: equal length intervals in the JUPM table
  - UBI: rule based with utility function for safety and efficacy trade off
- TEPI2 and UBI design are safer than TEPI.
  - Avoid escalation with sufficient efficacy signal
  - Less patients to be dosed at toxic dose levels
- Rule based designs with straightforward and transparent decision table.
- The monotone assumption between efficacy and dose is **NOT** needed, a key and unique feature in immunotherapy and cell therapy.
- Efficient phase I/II designs to accelerate clinical development.

Reference

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Thank you!

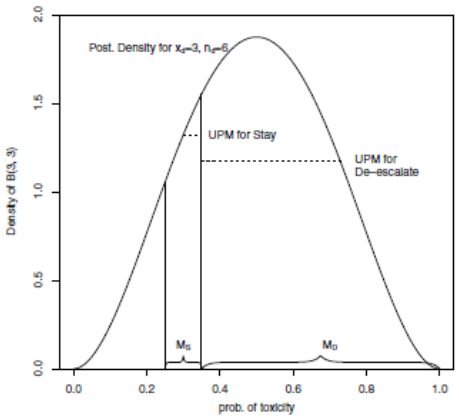
Background

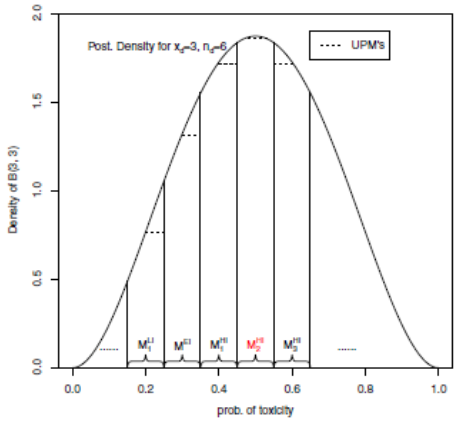
- Existing model-based designs for toxicity
  - Continual reassessment method (CRM)
  - Dose escalation with overdose control (EWOC)
  - Bayesian logistic regression model (BLRM)
- Existing model-assisted designs for toxicity
  - Modified toxicity probability interval (mTPI)
  - Bayesian optimal interval (BOIN)
  - Keyboard designs
- Existing model-based designs for toxicity and efficacy
  - Efficacy-toxicity trade-off (EffTox)
- Existing model-assisted designs for toxicity and efficacy
  - Toxicity efficacy probability interval (TEPI)

TEPI2

- For TEPI, 4*4 matrix, the intervals are not in equal length

			Efficacy rate			
			Low	Moderate	High	Superb
			0, 0.2	0.2, 0.4	0.4, 0.6	0.6, 1
Toxicity rate	Low	0, 0.15	E	E	E	E
	Moderate	0.15, 0.33	E	E	E	S
	High	0.33, 0.4	D	S	S	S
	Unacceptable	0.4, 1	D	D	D	D





TEPI vs TEPI2

N=9

TEPI

TEPI		E									
		0	1	2	3	4	5	6	7	8	9
T	0	EU	E	E	E	E	E	E	E	E	E
	1	EU	E	E	E	E	E	E	E	E	E
	2	EU	E	E	E	E	E	E	S	S	S
	3	DUE	D	S	S	S	S	S	S	S	S
	4	DUE	D	S	S	S	S	S	S	S	S
	5	DUE	D	D	D	D	D	D	D	D	D
	6	DUE	D	D	D	D	D	D	D	D	D
	7	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT
	8	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT
	9	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT

TEPI2

TEPI2		E									
		0	1	2	3	4	5	6	7	8	9
T	0	EU	E	E	E	E	E	E	E	E	E
	1	EU	E	E	E	E	E	E	E	E	E
	2	EU	E	E	E	E	E	S	S	S	S
	3	DUE	D	S	S	S	S	S	S	S	S
	4	DUE	D	D	D	D	D	D	D	D	D
	5	DUE	D	D	D	D	D	D	D	D	D
	6	DUE	D	D	D	D	D	D	D	D	D
	7	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT
	8	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT
	9	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT

- TEPI2 is safer than TEPI
  - Avoid undesirable decisions, such as S 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

TEPI vs UBI

N=9

TEPI

TEPI		E									
		0	1	2	3	4	5	6	7	8	9
T	0	EU	E	E	E	E	E	E	E	E	E
	1	EU	E	E	E	E	E	E	E	E	E
	2	EU	E	E	E	E	E	E	S	S	S
	3	DUE	D	S	S	S	S	S	S	S	S
	4	DUE	D	S	S	S	S	S	S	S	S
	5	DUE	D	D	D	D	D	D	D	D	D
	6	DUE	D	D	D	D	D	D	D	D	D
	7	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT
	8	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT
	9	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT

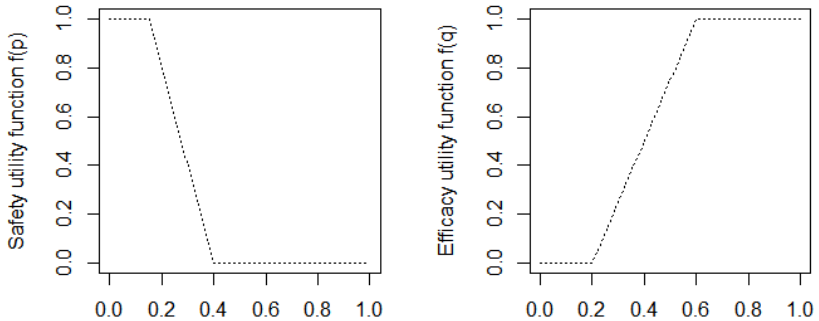
UBI

UBI		E									
		0	1	2	3	4	5	6	7	8	9
T	0	EU	E	E	E	E	E	E	E	E	E
	1	EU	E	E	E	E	E	E	E	E	E
	2	EU	E	E	E	E	E	S	S	S	S
	3	DUE	D	D	S	S	S	S	S	S	S
	4	DUE	D	D	D	D	S	S	S	S	S
	5	DUE	D	D	D	D	D	D	D	D	D
	6	DUE	D	D	D	D	D	D	D	D	D
	7	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT
	8	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT
	9	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT	DUT

- TEPI2 is safer than TEPI, and UBI is in between
  - Avoid undesirable decisions, such as S 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

TEPI OBD selection

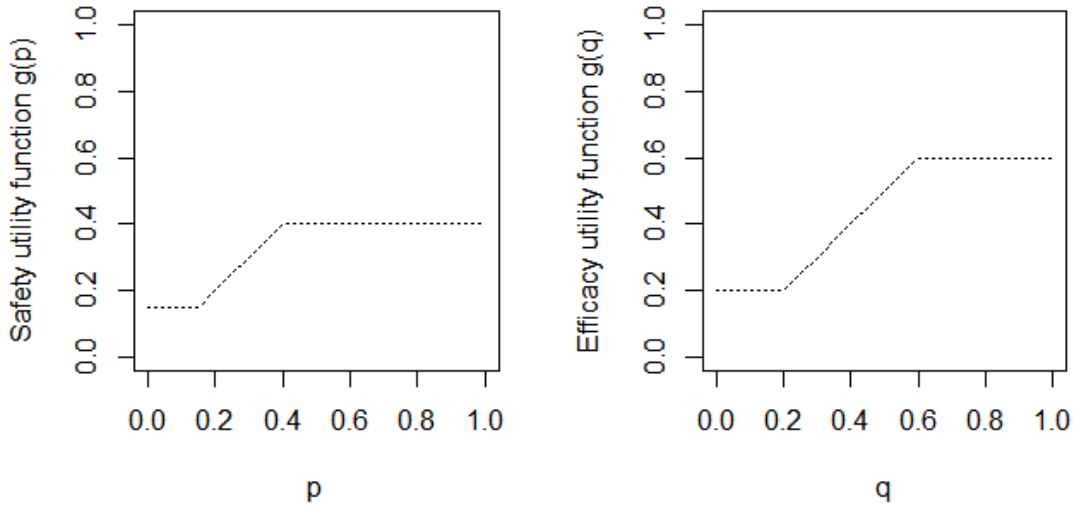
- At end of the trial, get the posterior distribution of efficacy and toxicity.
- For each sample t, generate $p^t = (p_1^t, \ldots, p_d^t)$, $q^t = (q_1^t, \ldots, q_d^t)$
  - PAVA isotonic transformation to make p^t non-decreasing.
- At each dose i, calculate $U^t(\hat{p}_i^t, q_i^t) = f_T(\hat{p}_i^t)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

Case Study

- Simulation to compare the performance
- Reliability: TEPI2 and UBI have higher OBD selection probability

	Selection probability (%)						Number of subjects treated					
Dose	3+3	BOIN	TEPI	TEPI2	UBI	Efftox	3+3	BOIN	TEPI	TEPI2	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