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Abstract

To save valuable time and resources in new drug development, Phase I/II clinical trials with toxicity control and drug efficacy as dual primary endpoints have become increasingly popular. Escalation with over-dose control (the EWOC) is a Bayesian adaptive Phase I clinical trial design that can accurately estimate the maximum tolerated dose (MTD) level and control the probability of overdosing patients during the dose allocation phase. In this paper, we extend EWOC to Phase I/II clinical trials by controlling for under-dosing with a Gumbel Copula model to provide patients with at least minimum drug efficacy. We propose a utility function to measure the composite effect of toxicity and efficacy and select the optimal dose. To deal with the common issue that the efficacy endpoint often cannot be quickly ascertained, we employ Bayesian data augmentation to handle delayed efficacy and allow for flexible patient accrual without a waiting period. Extensive simulations demonstrate that the proposed new design not only provides better therapeutic effect by reducing the probability of treating patients at under-dose levels while protecting patients from being overdosed, but also improves trial efficiency and increases the accuracy of dose recommendation for subsequent clinical trials. We apply the proposed design to a Phase I/II solid tumor trial.

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Keywords

Escalation with over-dose control; Escalation with under-dose control; Gumbel copula model; Phase I/II clinical trial; Bayesian data augmentation

1. Introduction

The primary objective of a Phase I clinical trial is to find the maximum tolerated dose (MTD), defined as the dose at which the probability of dose limiting toxicity (DLT) is equal or close to the target toxicity level (TTL, i.e., 33%).Among numerous existing Phase I trial designs, escalation with overdose control (EWOC), proposed by [1], is considered to be a useful Bayesian dose finding method. Like the continual reassessment method (CRM) proposed by [2], the EWOC uses the idea of accumulating data to adaptively make the decision of dose assignment for new patients. In addition, by incorporating over-dose control, EWOC treats patients with an optimal Bayesian-feasible dose sequence that minimizes the expected risk of over-dosing (doses higher than the MTD). Various extensions of the EWOC have been proposed to further improve its performance and accommodate more complicated dose-finding problems. For example, [3] extended the EWOC method by incorporating covariates in their model in order to estimate individual MTDs for different patient subgroups. In addition, [4] have developed a hybrid method that varies the feasibility bound in the EWOC design. Whereas [5] proposed a novel normalized equivalent toxicity score (NETS) system and integrated NETS with EWOC to develop an extended design, called EWOC-NETS, which can improve the accuracy of the EWOC estimation. Recently, [6] proposed another extended version of the EWOC, called the TITE-EWOC, to allow staggered patient enrollment and utilize partially completed toxicity data in new dose estimation. Furthermore, [7] incorporated a modified TITE to their EWOC-NETS and developed an improved version of their design entitled the EWOC-NETS-TITE.

Clinical trials in general aim to achieve two goals: insure patient safety and efficacy, i.e., the dose chosen to treat patients should be safe and efficacious. Meanwhile, for conventional cytotoxic agents, toxicity and efficacy preassembly monotonically increase with the dose level. Therefore, to achieve the goals of safety and efficacy, we should avoid treating patients not only at excessively high doses that are toxic (i.e., over-dosing), but also not treat patients at excessively low doses that often have only a negligible therapeutic effect (i.e., under-dosing). The EWOC and the aforementioned extensions only consider toxicity as the primary endpoint. They achieve safety through over-dose control, but overlook the problem of under-dosing. Therefore, in this manuscript, we propose a Bayesian dose-finding design that utilizes both over-dose and under-dose controls to achieve the goals to insure patient safety and efficacy. Our design considers toxicity and efficacy as dual endpoints. We employ the Gumbel copula to jointly model the toxicity and efficacy, which marginally follows a logistic model. Similar to the EWOC, we re-parameterize the toxicity and efficacy models to achieve over-dose and under-dose controls. In our design, we continuously update the model estimate based on the accumulated data, and adaptively make the decision of dose assignment based on a utility function that accounts for the trade-off between toxicity and efficacy. We refer to the new design as the Escalation with Over-dose and Under-dose

Controls (EWOUC). Since the proposed EWOUC simultaneously considers toxicity and efficacy, it can be classified as a Phase I/II trial design. Several methods have been proposed for the design of Phase I/II cancer trials using DLT and efficacy endpoints [8–16].

In practice, a common barrier to the success of Phase I/II clinical trial is the delay in the estimation of efficacy. That is, the efficacy outcome cannot be observed quickly enough to apply the adaptive decision rule to determine a dose for new patients. In order to overcome this delay in efficacy outcome, we further extend our methodology using the data augmentation (DA) approach proposed by [17]. We refer to the resulting new design as the EWOUC-DA. The EWOUC-DA is more general and contains the EWOUC as a special case when the efficacy outcome is immediately observable. Note that we here only consider delayed efficacy and assume that toxicity is quickly ascertainable because toxicity of cytotoxic agents is often acute. However, the data-augmentation approach can also be readily extended to handle delayed toxicity outcomes as well, see for example [18].

Our research is motivated by one of our collaborative projects; namely, a Phase I/II clinical trial to assess the safety and efficacy of the BKM120 when administered with Everolimus (10 mg) in patients with advanced solid malignancies. We re-designed the trial to establish the Phase II Dose (RP2D) of BKM120 based on its composite effect of toxicity and preliminary efficacy. Toxicity in terms of DLT was defined during cycle 1 only and included any grade 3 non-hematologic toxicity or any grade 4 hematologic toxicity according to Common Terminology Criteria for Adverse Events version CTCAE v. 4.02 criteria. The target tolerated level is 33%. Efficacy in the terms of tumor response was to be assessed by cross-sectional imaging after every 2 cycles using the RECIST criteria. Responders were to be defined as the patients with complete response (CR) or partial response (PR). Non-responders were to be the patients with stable disease (SD) or progressive disease (PD). In this trial, a total of 5 dose levels will be investigated with 3 patients per cohort being enrolled. We would like to enroll patients in staggered time intervals as they are accrued without suspending the trial. The efficacy is expected to be delayed (at 2 cycles) compared with the observation window of DLT (at 1 cycle). Therefore, the non-ignorable missing value assumption of efficacy due to late-onset is another issue to deal with in this trial. The EWOC design is one of the Phase I designs commonly used at the Winship Cancer Institute of Emory University. The EWOC design provides over-dose control to protect patients from being exposed to over-toxic dosages, but ignores the efficacy of treatment and cannot provide under-dose control to optimize the therapeutic effect for patients. This motivated us to develop new designs, aimed to: (1) provide over-dose control to guarantee safety; (2) provide under-dose control to achieve a better therapeutic effect; and (3) accommodate the issue of delayed efficacy in order to support continual patient enrollment.

The remainder of the manuscript is organized as follows. In Section 2, we describe our probability models, dose finding algorithm and data augmentation method to handle delayed efficacy outcome. In Section 3, extensive simulations are presented to evaluate the performance of the EWOUC and the EWOUC-DA. In Section 4, an application of the EWOUC-DA to a real trial is provided. Finally, in Section 5, we summarize the operating characteristics of our new design.

2. Methods

2.1. Outcome model and Re-parameterization

Let Y_E and Y_T denote the toxicity and efficacy outcomes with $Y_E = 1$ if the patient experiences an efficacy event and $Y_T = 1$ if the patient experiences a DLT event, respectively. We use the Farlie–Gumbel–Morgenstern copula model ([8]) to model the joint distribution of Y_E and Y_T. The copula model is chosen because with this model, the joint distribution of Y_E and Y_T can be conveniently expressed as a function of their marginal distributions. Specifically, we assume that the marginal distributions of Y_E and Y_T follow logistic regression models (1) and (2) below,

$$\pi_T = P(Y_T = 1 | X = x) = \frac{1}{1+\exp[-(\beta_{0,T} + \beta_{1,T} x)]} \quad (1)$$

$$\pi_E = P(Y_E = 1 | X = x) = \frac{1}{1+\exp[-(\beta_{0,E} + \beta_{1,E} x)]} \quad (2)$$

where X is the dose level, and $\beta_{0,T}$, $\beta_{1,T}$, $\beta_{0,E}$, $\beta_{1,E}$ are unknown regression parameters. Define $\pi_{ab} = P(Y_T = b, Y_E = a | X = x)$, a and $b \in \{0, 1\}$.Under the Farlie–Gumbel–Morgenstern copula model [8], the joint distribution of Y_E and Y_T conditional on the dose level X is given by (3) below

$$\pi_{11} = \pi_T \pi_E \left[1 + \frac{e^{\varphi} - 1}{e^{\varphi} + 1}(1 - \pi_T)(1 - \pi_E)\right] \quad (3)$$

where $\frac{e^{\varphi} - 1}{e^{\varphi} + 1}$ represents the association between toxicity events and efficacy events from −1 to 1. When $\phi = -\infty$ or $\phi = \infty$, toxicity events and efficacy events are completely dependent. When $\phi = 0$, toxicity events and efficacy events are independent [10]. Similarly, $\pi_{01} = \pi_T - \pi_{11}$, $\pi_{10} = \pi_E - \pi_{11}$, $\pi_{00} = 1 - \pi_{01} - \pi_{10} - \pi_{11}$.

The marginal logistic models (1) and (2) are familiar to statisticians and practitioners. However, the parameters ($\beta_{0,T}$, $\beta_{1,T}$, $\beta_{0,E}$, $\beta_{1,E}$) do not possess the interpretations that are directly related to finding the target of dose level. Following the EWOC approach, we re-parameterize ($\beta_{0,T}$, $\beta_{1,T}$, $\beta_{0,E}$, $\beta_{1,E}$) with new parameters (γ_T, γ_E, ρ_T, ρ_E) such that the model parameters have intuitive clinical interpretations. This re-parameterization facilitates the implementation of the over-dose and under-dose controls described later. Specifically, let θ_T and θ_E be the probabilities of having toxicity and efficacy, respectively. θ_T is the toxicity upper bound (like the target tolerated toxicity level in a Phase I clinical trial). θ_E is the efficacy lower bound (like the target efficacy probability in a Phase II clinical trial). These parameters should be pre-specified in the study design stage. We define γ_T as the MTD, at which the toxicity probability is θ_T, and define γ_E as the minimum efficacious dose (MED), at which the efficacy probability is θ_E. Clearly, the dose above the MTD is deemed unacceptably toxic, and the dose below the MED is deemed clinically futile. We further define ρ_T and ρ_E as the probability of toxicity and the probability of efficacy when the

patient is treated at a minimum dose X_{min} under investigation, respectively. Mathematically, (γ_T, γ_E, ρ_T, ρ_E) satisfy the following Eqs. (4) and (5):

$$\begin{cases} \text{logit}(\rho_T)=\beta_{0,T}+\beta_{1,T}X_{\min} \\ \text{logit}(\theta_T)=\beta_{0,T}+\beta_{1,T}\gamma_T \end{cases} \quad (4)$$

$$\begin{cases} \text{logit}(\rho_E)=\beta_{0,E}+\beta_{1,E}X_{\min} \\ \text{logit}(\theta_E)=\beta_{0,E}+\beta_{1,E}\gamma_E \end{cases} . \quad (5)$$

Therefore, the original parameters ($\beta_{0,T}$, $\beta_{1,T}$, $\beta_{0,E}$, $\beta_{1,E}$) can be re-parameterized in terms of (γ_T, γ_E, ρ_T, ρ_E) as given in Eqs. (6) and (7)

$$\beta_{0,j}(\gamma_j,\rho_j)=\frac{1}{\gamma_j-X_{\min}}\left[\gamma_j\ \text{logit}(\rho_j)-X_{\min}\ \text{logit}(\theta_j)\right] \quad (6)$$

$$\beta_{1,j}(\gamma_j,\rho_j)=\frac{1}{\gamma_j-X_{\min}}\left[\text{logit}(\theta_j)-\text{logit}(\rho_j)\right] \quad (7)$$

where $j \in \{T, E\}$. This re-parameterization is a one-to-one transformation. Each set of values for ($\beta_{0,T}$, $\beta_{1,T}$, $\beta_{0,E}$, $\beta_{1,E}$) corresponds to a unique set of values for (γ_T, γ_E, ρ_T, ρ_E).

For the ith patient treated at dose x_i, define $Y_{ab,i} = 1$ if $Y_{E,i} = a$, and $Y_{T,i} = b$, $a, b \in \{0, 1\}$; otherwise $Y_{ab,i} = 0$. Suppose that n patients has been treated in the trial, resulting in the toxicity and efficacy data $\boldsymbol{D_n} = [(y_{E,1}, y_{T,1}), \ldots, (y_{E,n}, y_{T,n})]$. The likelihood function under the copula model is given by (8) as

$$L(\mathbf{V})=\prod_{i=1}^{n}\prod_{a=0}^{1}\prod_{b=0}^{1}\pi_{ab,i}{}^{y_{ab,i}}, \quad (8)$$

where $\mathbf{V} = (\rho_T, \rho_E, \gamma_T, \gamma_E, \phi)$ and $\pi_{ab,i}$ is $P(Y_T = b, Y_E = a|X = x_i)$. Let $p(\mathbf{V})$ denote the prior distribution of $\mathbf{V}$, then the posterior distribution of $\boldsymbol{V}$ is given by (9) to be

$$p(\mathbf{V}|\boldsymbol{D_n}) \propto L(\mathbf{V})p(\mathbf{V})=\prod_{i=1}^{n}\prod_{a=0}^{1}\prod_{b=0}^{1}\pi_{ab,i}{}^{y_{ab,i}}p(\mathbf{V}). \quad (9)$$

To define $p(\mathbf{V})$,we assign ρ_T and ρ_E uniform prior distributions in the interval $[0, \theta_T]$ and $[0, \theta_E + \delta]$, where δ is a small positive value. We assign γ_T and γ_E non-informative uniform prior distributions in the interval $[X_{min}, X_{max}]$,where X_{max} is the maximum dose under investigation or determined by pre-clinical studies. In clinical trial practice, there are several scenarios under which γ_T and γ_E are outside of the interval $[X_{min}, X_{max}]$. When $\gamma_T < X_{min}$, the trial will be terminated early because of high toxicity. When $\gamma_E > X_{max}$, the trial will be terminated early without a dose level being recommended, or new higher dose levels need to be added because no pre-specified dose levels meet the minimum efficacy requirement. When $\gamma_T > X_{max}$ and $\gamma_E < X_{min}$, the trial will choose the dose with the best utility in the interval.

2.2. Over-dose control and under-dose control

To achieve maximum patient benefit, we should avoid exposing patients to either overly toxic doses (i.e., doses above γ_T, the MTD) or to low doses that are deemed therapeutically futile (i.e., doses below γ_E, the MED). Ideally, we want to treat patients at doses between (γ_E, γ_T). The relationship between the true MTD and the true MED should be considered to decide whether a drug should be moved forward for further study. If the MTD is lower than the MED, we should terminate the trial without selecting any investigational dose for further study because none of the doses are both safe and efficacious. On the other hand, if the MTD is higher than the MED, i.e., there is an interval between the MED and the MTD, we should treat patients with a dose within that interval. This is the basic idea behind the over-dose and under-dose controls, which can be formally described as follows.

Suppose that n patients have been treated in the trial. To select a dose x_{n+1} for the incoming $(n+1)^{\text{th}}$ patient, we require that x_{n+1} satisfies both the over-dose control condition (10),

$$P(x_{n+1} \geq \gamma_T | \boldsymbol{D_n}) \leq \alpha_T, \quad (10)$$

and the under-dose control condition (11),

$$P(x_{n+1} \leq \gamma_E | \boldsymbol{D_n}) \leq \alpha_E, \quad (11)$$

where α_T and α_E are called feasibility bounds for toxicity and efficacy, respectively. Under these two conditions, the probability of over dosing is less than α_T and the probability of under dosing is less than α_E for the $(n+1)^{\text{th}}$ patient based on the observed data. In practice, it is desirable to let the cutoffs α_T and α_E vary during the trial. This is because at the beginning of the trial, there is very limited information to estimate the MTD and the MED, and thus we prefer conservative over-dose and under-dose controls by setting α_T at a smaller value and α_E at a larger value, respectively. During the trial, as more data about the MTD and the MED are accumulated, we can afford relatively more liberal over-dose and under-dose controls. For over-dose control, we usually start α_T at 0.25 and increase its value by a step size of 0.05 after each new cohort is enrolled until α_T reaches 0.5. [4] showed that using their varying feasibility bound improves the speed for the posterior estimators of the MTD to converge to the true MTD, and leads to good operating characteristics. Accordingly, we let α_E decrease from 0.75 by a step size of 0.05 until it reaches 0.5 when we enroll each new cohort.

It is possible that multiple investigational doses satisfy the over-dose and under-dose control criteria. For convenience, we call these doses an *acceptable dose set*. In order to choose a dose from the acceptable dose set to treat the $(n+1)^{\text{th}}$ patient, we define a utility function $U(x)$ to measure the utility of a dose x as follows,

$$U(x) = \pi_E(x) - W\pi_T(x),$$

where W represents the penalty induced by toxicity. That is, $U(x)$ measures the tradeoff between toxicity and efficacy. A large value of W indicates that we want to heavily penalize toxicity and strongly prefer a dose with low toxicity. Among doses in the acceptable dose

set, we choose the one with the highest utility (i.e., the highest value of $U(x)$) to treat the $(n + 1)^{th}$ patient.

The dose-finding algorithm for the proposed design can be summarized as follows:

1. Treat the first cohort at the lowest dose, $d_1 = x_1$.
2. Based on the cumulative data $\boldsymbol{D_i}$, update the posterior distribution $p(\rho_T, \rho_E, \gamma_T, \gamma_E, \phi|\boldsymbol{D_i})$, and assign the next cohort of patients to the dose that satisfies both over-dose and under-dose control conditions (10) and (11) and has the highest posterior mean of $U(x)$. If no doses satisfy conditions (10) and (11), stop the trial.
3. Repeat steps 1 to 2 until the maximum sample size is reached. Select the dose with the highest posterior mean of $U(x)$ as the final recommended dose, called the optimized utility dose (OUD).

2.3. Accommodation of delayed efficacy

The design proposed above requires that toxicity and efficacy are quickly observable such that the adaptive dose-finding rule can be used to pick a dose for new patients. However, in many cases, the efficacy outcome is not immediately ascertainable and takes a relatively long time to evaluate, resulting in the so-called delayed efficacy. We assume that toxicity is quickly ascertainable, as often the case in practice for cytotoxic agents. A direct consequence of delayed efficacy is that at the moment of decision making for the dose assignment, some patients who have enrolled into the trial might have not finished their time to follow up yet, and thus, their efficacy outcomes are missing. [17] showed that such missing outcomes are non-ignorable and proposed a Bayesian data augmentation approach to account for these missing data. By taking the approach of [17], we extend our methodology here to accommodate delayed efficacy. The problem we tackle is more complicated due to our bivariate distribution of toxicity and efficacy, while [17] focus only on a univariate distribution for delayed toxicity. Although we assume that toxicity is immediately observed, because of the bivariate structure of the data, the observed toxicity outcome affects the imputation (or data argument) of the missing efficacy outcome, as we show below.

Let T denote a follow-up window (or time frame) for assessing efficacy, such that $Y_{E,i} = 1$ if the ith patient experiences efficacy events in (0, T); otherwise $Y_{E,i} = 0$. Let r_i denote the time to efficacy and u_i denote the actual follow-up time at the moment that we need to make the decision of dose assignment for a new patient. Clearly, if $u_i < T$ and $u_i < r_i$ (i.e., the patient has not finished the follow-up assessment and the actual follow-up time is shorter than the time to efficacy), $Y_{E,i}$ is missing. We denote M_i as a missing indicator with $M_i = 1$ indicating that $Y_{E,i}$ is missing. Following [17], we specify a piecewise exponential model for r_i. We partition the follow-up window (0, T) into K intervals $[0, h_1), \ldots, [h_{K-1}, h_K]$ ($h_K = T$), and assume a constant hazard λ_k for the kth interval. K is number of the knots in the piecewise exponential model. The choice of K can affect the smoothness of the model. With greater K, the fitted curve will be smoother. We can choose K by Deviance Information Criterion. Define $t_i = min(r_i, u_i)$ as the observed time-to-event. The likelihood function of $\boldsymbol{\lambda} = (\lambda_1, \ldots, \lambda_K)$ based on $\boldsymbol{t} = (t_1, \ldots, t_n)$ from n treated patients is given by (12) to be

$$L(\boldsymbol{\lambda})=P(\boldsymbol{t}|\boldsymbol{\lambda})=\prod_{i=1}^{n}\prod_{k=1}^{K}\lambda_{\mathrm{k}}{}^{\delta_{ik}}e^{-y_{E,i}\lambda_{\mathrm{k}}s_{ik}} \quad (12)$$

where $s_{ik} = h_k - h_{k-1}$, if $t_i > h_k$, and $t_i - h_{k-1}$, if $h_{k-1} \le t_i < h_k$, otherwise 0. δ_{ik} is defined as 1 if the ith patient experienced an efficacy event in $[h_{k-1}, h_k)$ or 0 otherwise. The posterior of $\boldsymbol{\lambda}$ is still unimodal distribution so that $\boldsymbol{\lambda}$ is identifiable by its posterior median. When data are limited, the number of $\boldsymbol{\lambda}$ in the model should be decreased in order to reduce the risk of over-fitting.

Our strategy for handling delayed efficacy is to "impute" the missing values of y_{E}, thereby converting the missing data problem into a standard complete-data problem. This is achieved by a Bayesian data augmentation algorithm, which consists of two steps; namely, an imputation step I and a posterior step P. In the I step, we impute the missing values of $y_{\mathrm{E,\,i}}$ conditional on the model parameters; and in the P step, we draw samples from the posterior distribution of the model parameters conditional on the "imputed" complete data. Specifically, at the I step, conditioning on $\boldsymbol{\theta} = (\rho_T, \rho_E, \gamma_T, \gamma_E, \phi, \boldsymbol{\lambda})$ and the observed toxicity outcome $y_{T,i} = b$, where $b \in \{0, 1\}$, we draw the missing value of $y_{E,i}$ from its posterior predictive distribution, which is the distribution of unobserved observations (prediction) conditional on the observed data and the posterior distribution of parameters, to obtain the posterior predictive distribution (13)

$$f(y_{E,i}|\boldsymbol{\theta}, M_i=1, Y_{T,i}=b, \boldsymbol{t}) = \mathrm{Bernoulli}\left(\frac{\pi_{1b,i}\,\exp\left(-\sum_{k=1}^{K}\lambda_k s_{ik}\right)}{\pi_{1\mathrm{b,i}}\,\exp\left(-\sum_{k=1}^{K}\lambda_k s_{ik}\right)+1-\pi_{0b,i}}\right). \quad (13)$$

The derivation of this posterior predictive distribution is given in the Appendix A. Note that the posterior predictive distribution of the missing efficacy outcome $Y_{E,i}$ depends on the observed toxicity outcome $Y_{T,i} = b$ through $\pi_{1b,i}$. After imputing the missing data at the P step, we essentially handle a standard complete-data problem, and sample $\boldsymbol{\theta}$ from its posterior distribution (conditional on the imputed complete data). A Gibbs sampler of the missing outcomes and parameters is formed by iteratively sampling between the I and P steps. We iterate the Gibbs sampling algorithm until the MCMC chain converges.

3. Simulations

3.1. Simulation settings

We compare EWOC to three different versions of EWOUC, EWOUC-DA (EWOUC using DA to handle missing efficacy data), EWOUC-Comp (EWOUC with complete data, which waits for the patient's efficacy outcome to be fully observed before enrolling the next new patient), and EWOUC-NW (EWOUC not waiting, which treats the unobserved efficacy outcome as a non-response and enrolls patients in real time without waiting). Similar to EWOUC-Comp, EWOC also requires waiting for complete data before enrolling new patients. Here, the EWOUC-Comp serves two purposes. First, the comparison between the EWOUC-Comp and the EWOC provides a fair evaluation on the performance of the additional under-dose control characteristic because the EWOC and the proposed EWOUC-

Comp are both based on the complete data. Second, the EWOUC-Comp serves as a benchmark (or upper bound) to evaluate how efficiently the EWOUC-DA and the EWOUC-NW handle the delayed outcome of efficacy as the EWOUC-Comp represents the ideal case of no missing efficacy data (i.e., complete data). The comparison between the EWOUC-DA and the EWOUC-NW evaluates the contribution of utilizing incomplete efficacy data with DA instead of ignoring these data.

The designs are compared based upon three main aspects: dose recommendation accuracy, therapeutic effects, and trial duration, under 5 different scenarios (Table 1). These scenarios correspond to different situations that we may encounter in the solid tumor trial. Fig. 1 depicts the dose–response curves for these scenarios. Scenario 1 (S1) corresponds to an extremely good agent, with a steep increasing dose–efficacy curve and a flat dose–toxicity curve. Scenario 2 (S2), Scenario 3 (S3), Scenario 4 (S4) and Scenario 5 (S5) correspond to a good agent, a moderate agent, a bad agent and an extremely bad agent, respectively. Following the setting of the solid tumor trial, five dose levels (0.2, 0.4, 0.6, 0.8, and 1.0) are investigated. The highest tolerated toxicity rate is $\theta_T = 0.33$ and the minimum efficacy bound is $\theta_E = 0.3$. The corresponding MTDs and MEDs under each scenario are indicated in Fig. 1. We assume that toxicity is quickly observed, but efficacy takes three months to be evaluated (i.e., T = 3 months). We simulate the time to efficacy from a piecewise exponential model with $(\lambda_1, \lambda_2, \lambda_3) = (0.4, 0.67, 2.0)$ for three equally spaced intervals. These parameters are chosen so that 70% efficacy response occurs in the later half of follow-up [T/2, T]. As for the utility function, W is 3 for all scenarios. We assign ρ_T a uniform prior distribution (0, 0.33), ρ_E a uniform prior distribution (0, 0.5), γ_T and γ_E both an independent uniform prior distribution (0.2, 1.2), and ϕ a standard normal distribution. Following [17], we take the priors for $\lambda_1, \lambda_2, \lambda_3$ as Gamma(0.2, 0.5),Gamma(0.33, 0.5) and Gamma(1, 0.5), respectively, such that a priori the time to efficacy is approximately uniformly distribution in (0, T). The number of patients used for each simulated trial is set as 30 unless the trial pre-stops. The Metropolis–Hastings algorithm is used to sample from the posterior distribution. The first 1000 iterations are used as burn-in period and the next 1000 iterations are used as the sample from posterior distribution. We repeat 1000 simulations for each scenario to evaluate the performance of the designs. We further study different time to efficacy and different correlation models in Section 3.5 to evaluate the robustness of the DA algorithm for our design and the sensitivity of our prior selection.

3.2. Dose identification accuracy

One of the most important factors in evaluating the performance of the design is the accuracy of final dose identified. We first compare the EWOUC-comp and the EWOC design based on complete data to evaluate the additional advantage by incorporating under-dose control. The EWOUC and the EWOC differ in their ability to identify the final dosage (OUD vs MTD). For all scenarios, the EWOUC-Comp tends to identify a dose level with the best utility and the true OUD for S1, S2, and S3 are the dose level 3, dose level 3, and dose level 4, respectively (Table 1). Under these three scenarios, the EWOUC-Comp tends to identify the true OUD with the highest accuracy rate among all 4 designs. The dose identified percentages for the true OUD by the EWOUC-Comp are 91.9%, 91%, and 67.9% in the S1, S2, and S3, respectively (Table 1). The trial designed with EWOUC-Comp should

be terminated early under S4 and S5. The EWOC tends to identify a dose level in the vicinity of the true MTD instead of the OUD; e.g., in S1, 50.3% for dose level 4 and 45.4% for dose level 5 (the true MTD). The MTD identified by the EWOC is more effective than the OUD, but at the cost of being more toxic for further clinical trials. By contrast, the EWOUC-Comp tends to identify doses with better utility: e.g., in S1, 91.9% for dose level 3, the true OUD and 6.1% for dose level 4. The dose level chosen by EWOUC designs is less toxic while guaranteeing the minimum efficacy and optimizing the utility.

Next, we evaluate the performance of the DA algorithm in dealing with missing efficacy data and allowing flexible patient enrollment by comparing the EWOUC-DA to the EWOUC-Comp and the EWOUC-NW. The EWOUC-Comp can serve as an upper bound with the maximum accuracy assuming availability of complete data and the EWOUC-NW can serve as the lower bound with the minimum accuracy when discarding all incomplete data at the moment of new dose level decision. From the simulation results (Table 1), we can see that the EWOUC-DA is much better than the EWOUC-NW, but not as good as EWOUC-Comp. For example, in S1, the probability of correctly recommending the dose level 3 as final the OUD is 49.6% for the EWOUC-NW, 72.3% for the EWOUC-DA, and 91.9% for the EWOUC-Comp, respectively. The EWOUC-DA is more accurate than the EWOUC-NW by fully utilizing incomplete data with DA. Another interesting finding is that ignoring incomplete data tends to over-estimate the OUD as suggested by the simulation results that the EWOUC-NW has a higher probability than the EWOUC-DA to recommend dose levels higher than the true OUD (Table 1). For example in S1, the EWOUC-NW selects a total of 48.1% (47.3% for dose level 4 and 0.8% for dose level 5) over the OUD selection compared to a total of 26.0% (25.9% for dose level 4 and 0.1% for dose level 5) for the EWOUC-DA. Similar conclusions are also observed in S2 and S3. In the S4 and S5, the accuracy of the OUD cannot be compared between the 3 EWOUC designs because of no true OUD. The better accuracy of the EWOUC-Comp over the EWOUC-DA is a result of its complete data at the decision moment. However, in the practice it may take too long a waiting period to obtain complete data. The EWOUC-DA does not require complete data to make a decision so that it makes the trial more efficient and quicker in time to complete without sacrificing too much accuracy in estimating the OUD.

3.3. Therapeutic efficacy

Therapeutic efficacy is another important aspect in the evaluation of performance of Phase I clinical trial design. Therapeutic efficacy should be composed of not only the efficacy of drug, but also the severity of the toxicity that patients suffer, especially permanent adverse consequences of a severe toxicity event. Moreover, the toxicity of a dose will increase when the efficacy increases so that the utility score proposed in Section 2 should be a better measurement of the composite therapeutic effect rather than the drug efficacy alone. Under all scenarios in this manuscript, the EWOC always completes a trial with fixed sample size (36). The EWOUC trials with pre-specified sample sizes (36) perform well in cases with good agents, but may terminate a trial early as the consequence of no dose levels meeting the MED in the case of bad agents.

The simulation results for DLT rates and utility by different designs and scenarios are summarized in Table 2. The advantage of the EWOUC-Comp over the EWOC is that the EWOUC-Comp keeps a balance between toxicity and efficacy by treating patients at the optimized utility. Consequently, the expected utility is increased from 0.21 to 0.28 (increased about 34%) in S1 under the EWOUC-Comp design, as shown in Table 2. More clearly, the expected utility increased sharply (from 0.02 to 0.14) in S2 under the EWOUC-Comp design. The EWOC loses utility because it treats many patients near the MTD and the rate of DLT is high at such dose levels. We evaluate the contribution of the under-dose control on the therapeutic effect by the comparison between the EWOUC-Comp and the EWOUC, both of which are based on complete observed outcomes. For S1, S2 and S3, most patients are treated at the OUD under the EWOUC-Comp design with 73.01% in S1, 70.81% in S2, 47.73% in S3, respectively (Table 3). The EWOC tends to treat patients at higher toxicity and efficacy dose levels close to the MTD. For example, 40.46% patients are treated at dose level 4 in S1 and 37.71% patients are treated at the MTD (also dose level 4) in S2. By contrast, the EWOUC-Comp treats only 4.95% and 3.84% of patients at such a dose level 4 in S1 and S2 so that the risk of over-dose is lowered and patients are guaranteed the minimum efficacy rate. The EWOUC-Comp optimizes the proposed utility function under a high utility dose level. For “good” agents (S1, S2, and S3), fewer patients are treated under the MED, compared with the EWOC, which indicates that the under-dose control introduced in the EWOUC-Comp lowers the probability that patients are treated at futile doses (S1: 0.2% vs 0.0%. S2: 0.4% vs 0.2%). For S4 (bad agent) and S5 (extremely bad agent) with high toxicity, although the EWOUC-Comp tends to treat a higher percentage of patients at or above the MTD than the EWOC, the risk is even lower in the EWOUC-Comp than the EWOC because the EWOUC-Comp terminates the trial earlier with a smaller sample size of 15.86 than the EWOC (36) and treats fewer total number of patients at or above the MTD.

From the simulation results (Table 3), the DA algorithm has improved the trial therapeutic effect substantially, compared to EWOUC-NW. Based on the same data at the moment of a new dosage decision, the EWOUC-DA design treats many more patients at the OUD than the EWOUC-NW (56.13% vs 28.94% in S1, 58.23% vs 38.76% in S2, and 47.37% vs 40.17% in S3). The EWOUC-NW is more aggressive and treats more patients above the OUD. The EWOUC-DA with the DA algorithm can fix the problem of over-estimating by imputing the efficacy response, resulting in better therapeutic effects with respect to the utility. The therapeutic effect of the EWOUC-DA is not as good as that of the EWOUC-Comp which is based on complete data to make more accurate estimation. In the case of bad (S4) or extremely bad agents (S5), the 3 versions of EWOUC designs terminates the trial quite early because no dose levels meet the MED. The average sample sizes are 15.86 for the EWOUC-Comp, 13.80 for the EWOUC-NW, 20.36 for the EWOUC-DA. The sample size is the smallest for the EWOUC-NW because the EWOUC-NW tends to overestimate the MED by ignoring incomplete data.

Overall, without under-dosing control, the EWOC cannot guarantee the minimum efficacy. In contrast, the EWOUC designs treat most patients under optimized utility dose level utility while guaranteeing the minimum efficacy rate. The DA algorithm helps fully utilize incomplete efficacy data and improves the probability of identifying the correct OUD.

3.4. Trial duration

The EWOUC-DA and the EWOUC-NW are the same in the trial duration as they allow flexible patient enrollment without a waiting period. But the EWOUC-Comp waits for the complete data before a new dose level determination. The simulation results on the trial length of the EWOUC-DA and the EWOUC-Comp based on different mean cohort inter-arrival times under the scenario S1 are summarized in Table 4. The follow-up window is 3 months and the inter-cohort arrival time is assumed to be exponentially distributed with average inter-patient arrival times of 0.25, 0.5, 1, 2, and 3 months, respectively. The trial length of the EWOUC-DA has been substantially shortened in the range from 8.24% to 78.65% compared to the EWOUC-Comp (Table 4). The percentage reduction in the length of trial decreases as the relative ratio between the observation window and inter-cohort arrival time increases. When the inter-cohort arrival time is higher, the durations of two designs become similar. The reason is that all responses of previous cohorts have been confirmed when the next cohort arrives so that there is nearly no delay in treating the next cohort. The DA algorithm allows flexible patient enrollment and has an advantage of shortening the trial duration when patients are available early.

3.5. Sensitivity studies

We further investigate the robustness of the EWOUC under the good agent scenarios (S1, S2, and S3) by conducting more simulations with different combinations of (ϕ, θ_E) where ϕ is set to be 1, 2 or 3 in the copula model to generate the patients' responses and θ_E is set to be 0.3 or 0.4. Under all these 3 scenarios, the EWOUC-DA design can detect the correct OUD in at least 68% of the cases and treats more than 48% of patients at the true OUD dose level (dose level 3). The accuracy of the OUD and the therapeutic effects are not sensitive to the value of ϕ, but both improve with higher values of θ_E (data not shown).

We investigate the robustness of the EWOUC with different distributions used to model the true time to efficacy and find that both accuracy of the OUD and therapeutic effect are very similar when the log logistic or the Weibull distribution are employed under S1 and S2 (data not shown). We also study the sensitivity of λ, W, and priors. The posterior distributions of λ should not be sensitive because vague priors are used for λ. W is subjectively chosen. The choice of W will affect the true utility of the dose level and the posterior distribution of utility should be different with different W. Therefore, the assumed piece-wise exponential models are shown to work well in the EWOUC-DA with different time to efficacy distributions. Moreover, our simulation results also show that the behavior of the EWOUC-DA is very similar to that of the EWOUC-Comp (data not shown).

4. Application using a real trial example

The Phase I/II clinical trial described in Section 2 has been redesigned with the EWOUC-DA in which 30 patients in 10 cohorts will be enrolled and treated. As the study is still in the design stage, no real study data are available yet, therefore, we have used the sample size n = 30 for the real study setting. All the estimates are from simulation studies for prospective planning purposes. The dose levels for the trial are summarized in Table 5. The trial will start with the dose level 1, BKM120 (20 mg) and everolimus (10 mg), which have been

previously established as safe single agent doses. In the trial, the target tolerated level (TTL), θ_T, is set as 0.33 and the minimum efficacy bound, θ_E, is chosen as 0.3. The MTD and the MED are assumed to follow uniform distributions (20, 120). The true correlation between toxicity probability and efficacy probability ϕ is 0 for the copula model. The prior ρ_T and ρ_E, at the starting dose level are chosen as 0.03 and 0.08, respectively. Considering the time to efficacy distribution, hazards are assigned by $\lambda_k = K/\{T(K - k + 0.5)\}$ (K = 2, T = 3). The priors for the piecewise exponential model are Gamma (0.3, 0.5), Gamma (0.5, 0.5) and Gamma (1.5, 0.5), respectively. If 2 or 3 out of the first 3 patients in the first cohort show DLT status, the clinical trial should be suspended and reevaluated. Otherwise, the trial will continue with the next patient cohort. Based on the cumulative data, $\boldsymbol{D_i}$, the posterior distribution $p(\theta|\boldsymbol{D_i})$ will be updated and the next cohort of patients will be assigned to the dose level which has the highest estimate of utility $\hat{U} = E\{U|\boldsymbol{D_i}\}$ among all dose levels that satisfy both over-dose and under-dose control conditions. If no dose levels satisfy conditions of under-dose and over-dose controls and $P(\gamma_T > \gamma_E|\boldsymbol{D_i}) < 0.25$, the trial will stop. Otherwise, we will continue to treat patients at the MTD for under-dose control, assuming that the MTD is the most efficacious dose. The trial will stop when the maximum sample size of 30 patients has been reached. The final OUD will be the dose with the highest utility as the final recommended dose for the next clinical trial. The accrual rate is expected to be approximately 3 patients per month, but it generally takes 2 cycles (2 months) to fully assess efficacy for each patient cohort. By the time of dose assignment for a newly enrolled patient cohort, some patients who have not experienced efficacy thus far may show efficacy later during the remaining follow-up. We assume whether the efficacy is late-onset or not is relative to the patient accrual rate. The EWOUC-DA does not require efficacy in cycle 1 when toxicity is observed, and the update of the posterior estimates and the unobserved efficacy outcomes will be treated as missing data. We iteratively impute the missing data and sample from the posterior distribution of the model parameters based on the imputed data.

We assume that dose level 3 is the OUD. The toxicity is penalized by setting W = 3 in the utility function. A total of 1000 trial replicates were generated. The detailed operating characteristics are shown in Table 5. In brief, the design has a probability of about 82.40% to identify a correct OUD and 57.25% patients are treated under the OUD. The expected (mean) utility is 0.12. About 16% patients will experience DLT events and 57% of the patients will benefit from efficacy events based on our 1000 replicates.

5. Conclusion and discussion

The EWOC is a cutting edge adaptive Phase I clinical trial design. In this paper, we extend the EWOC with additional characteristics of under-dose control to improve the therapeutic effect for patients and employ the DA algorithm to overcome the late onset efficacy problem in early stage Phase I/II clinical trials. Compared to the EWOC, the EWOUC-DA has a better therapeutic effect by reducing the probability of treating patients at under-dose levels while protecting patients from being over-dosed. The application of the DA algorithm in the EWOUC-DA improves trial efficiency and increases the accuracy of dose estimation for subsequent clinical trials.

In the EWOUC, the Farlie–Gumbel–Morgenstern copula model ([8]) is employed to model the joint probability of toxicity events and efficacy outcomes. In the current version of the EWOUC, the model can only estimate a marginal OUD for all patients in the trial. However, it can be extended to include patient covariates so that our design can be applied to find a personalized OUD. There are many other copula models that can be used (see [19]). Through extensive simulation studies, we have found that the EWOUC performs well in detecting a dose between the MED and the MTD with the best utility. For the EWOUC, the preferred dose for a new cohort is the one with optimal utility so that patients will be treated at a dose level with lower toxicity instead of one in the vicinity of the MTD. Thus, the DLT rate in the trial will decrease and the over-dose protection becomes better using the EWOUC rather than using the EWOC. Moreover, most patients will be treated at a dose higher than the MED with under-dose control so that some level of the therapeutic effect is guaranteed for patients given a potentially good drug treatment. Therefore, the EWOUC can provide better over-dose protection and better under-dose control. Another advantage of the EWOUC is that, with dual endpoints, it can identify bad drug treatments that have high toxicity and low efficacy in Phase I clinical trials, thus saving valuable resources at an earlier stage of drug development.

It is fairly common that efficacy information may be missing in the early stages in Phase I clinical trials due to the short follow up time and low starting dose levels. The EWOUC-NW ignores incomplete responses and makes a dose escalation decision based solely on the observed efficacy data, which leads to large biases by underestimating the probability of efficacy and treating more patients at over-doses and under utility dose levels. The EWOUC-Comp is ideal for the assessing the accuracy of a dose decision, but it may not be feasible in practice, especially with long delays in determining efficacy. To address the problem of missing efficacy data, using the DA algorithm is preferable to using a surrogate response in that: (1) the relationship between a surrogate response and a complete response cannot be validated and may be unreliable; (2) there might be no surrogate response for some diseases. Implementation of the DA algorithm in the EWOUC design can solve the problem of underestimating the probability of efficacy while eliminating the lengthy waiting period and shortening the time length of a clinical trial when the accrual rate is high. Therefore, the EWOUC-DA can retain all the advantages of the EWOUC and improve trial efficiency over the EWOUC without sacrificing the waiting time for completion of the data collection.

Neuenschwander et al. (2008) proposed using a utility function to control both under-dosing and over-dosing [20]. They defined under-dosing with respect to toxicity and a patient is considered under-dosed if the predictive toxicity probability of the dose level is in the range of (0, 0.20) [20]. In practice, it is more reasonable to define under-dosing from the efficacy rather than toxicity perspective, because keeping toxicity as low as possible is always a desirable outcome for patients. Therefore, we propose EWOUC in which the under dose control is defined with respect to efficacy instead. Patients being treated at a dose level with lower than the minimum efficacy we want to guarantee will be considered under-dosed. When the efficacy of the low dose level is high, the method of Neuenschwander et al. still tends to choose a high toxicity level to avoid under-dosing. The toxicity probability and severity of adverse events usually increase with increasing dose level. This will become inappropriate and unethical because of unnecessarily high toxicity probability and severe

adverse events. Our EWOUC does not have these issues because it treats both toxicity and efficacy events as pairwise outcomes. The dose level recommended is a balance of toxicity and efficacy so that severe adverse events can be avoided by penalizing the toxicity probability in the utility function. Third, the likelihood and model in our EWOUC are different from those of Neuenschwander et al. [20]. We also incorporate the data augmentation algorithm to make EWOUC more practical. Overall, our EWOUC is substantially different from the method of Neuenschwander et al. and has additional merits.

Our novel design, the EWOUC-DA, can not only be used for regular Phase I clinical trials to improve the therapeutic effect, but is also ideal for Phase I/II clinical trials in order to shorten the development time for a new drug. Some other Bayesian designs have been proposed for Phase I/II clinical trials. For example, [10] proposed a CRM-based Phase I/II clinical trial design, using the trade-off curve drawn by the accepted toxicity and efficacy probability combination. However, CRM has the obvious disadvantage that it treats more patients at dose levels higher than the MTD [21]. CRM-based Phase I/II designs inherit this disadvantage and cannot address the ethical concerns regarding the probability of overdosing patients in a Phase I clinical trial. Another limitation of this design is that it does not consider the common case of missing or incomplete efficacy data, especially at low starting dose levels. [22] have proposed a modified CRM-based Phase I/II clinical trial design in which a surrogate response is employed to represent the ultimate efficacy in order to solve the problem of missing efficacy data. However, the reliability of surrogate responses need to be verified and the availability of reliable surrogates are limited. The EWOUC-DA design is developed to overcome these limitations and can meet the new requirements in upcoming Phase I/II clinical trials. There are also some limitations to the EWOUC-DA methodology, especially when the data are not mature (ie, short follow up), which may reduce the accuracy of estimating lambdas and of estimating the new dose level for the incoming cohort. EWOUC-DA might be biased when the follow-up time is insufficient and the amount of missing data will affect our estimation. This is especially a concern when the study drug has late onset toxicity (ie, safety profile is different in the short-term vs the long term) and/or late efficacy effect. These issues are under investigation and will be addressed in a more advanced version of EWOUC which can deal with incomplete toxicity data as well as incomplete efficacy data.

In summary, we have added under-dose control into the original EWOC and developed a novel Phase I/II clinical trial design, called the EWOUC-DA, in which the Bayesian data augmentation algorithm proposed by [23] is further incorporated to fully utilize the late-onset efficacy. Simulation studies demonstrate that the EWOUC-DA can: (1) improve the therapeutic effect for participants by protecting for under-dose control; (2) address ethical concerns of overdosing patients with over-dose control; (3) recommend an optimal dose for a subsequent clinical trial by maximizing the utility function; (4) increase trial efficiency by using the DA algorithm to solve the problem of late-onset efficacy data while maintaining accuracy for dose estimation without the requirement for complete data; (5) design upcoming Phase I/II clinical trials that can shorten the duration time in drug discovery by combining Phase I and II clinical trials. Therefore, this hybrid design will be of practical use in the field of early phase clinical trials.

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Appendix A

Derivation of predictive distribution of missing efficacy outcome

Given toxicity outcome $Y_{T,i} = b$ and model parameters θ, the predictive probability for a missing efficacy response $y_{E,i} = 1$ is given by

$$\begin{aligned} & p(Y_{E,i}=1|\boldsymbol{\theta}, M_i=1, Y_{T,i}=b) \\ &= \frac{p(Y_{E,i}=1, M_i=1, Y_{T,i}=b|\boldsymbol{\theta})}{p(M_i=1, Y_{T,i}=b|\boldsymbol{\theta})} \\ &= \frac{p(Y_{E,i}=1, Y_{T,i}=b|\boldsymbol{\theta})p(M_i=1|Y_{E,i}=1, Y_{T,i}=b, \boldsymbol{\theta})}{\sum_{a=0}^{1} p(M_i=1, Y_{T,i}=b, Y_{E,i}=a|\boldsymbol{\theta})} \\ &= \frac{\pi_{1b,i} p(M_i=1|Y_{E,i}=1, Y_{T,i}=b, \boldsymbol{\theta})}{\sum_{a=0}^{1} p(Y_{E,i}=a, Y_{T,i}=b|\boldsymbol{\theta})p(M_i=1|Y_{E,i}=a, Y_{T,i}=b, \boldsymbol{\theta})}. \end{aligned}$$

Following [17], we assume conditional independence $p(M_i = 1|Y_{T,i}, Y_{E,i} = a) = p(M_i = 1|Y_{E,i} = a)$. It follows that

$$\begin{aligned} p(Y_{E,i}=1|\boldsymbol{\theta}, M_i=1, Y_{T,i}=b) &= \frac{\pi_{1b,i} p(M_i=1|Y_{E,i}=1, \boldsymbol{\theta})}{\sum_{a=0}^{1} \pi_{ab,i} p(M_i=1|Y_{E,i}=a, \boldsymbol{\theta})} \\ &= \frac{\pi_{1b,i} p(r_i > u_i|Y_{E,i}=1, \boldsymbol{\theta})}{\sum_{a=0}^{1} \pi_{ab,i} p(r_i > u_i|Y_{E,i}=a, \boldsymbol{\theta})} \\ &= \frac{\pi_{1b,i} \exp\left(-\sum_{k=1}^{K} \lambda_k s_{ik}\right)}{\pi_{1b,i} \exp\left(-\sum_{k=1}^{K} \lambda_k s_{ik}\right) + \pi_{0b,i}}. \end{aligned}$$

Hence,

$$f(y_{E,i}|\boldsymbol{\theta}, M_i=1, Y_{T,i}=b, \boldsymbol{t}) = \text{Bernoulli}\left(\frac{\pi_{1b,i} \exp\left(-\sum_{k=1}^{K} \lambda_k s_{ik}\right)}{\pi_{1b,i} \exp\left(-\sum_{k=1}^{K} \lambda_k s_{ik}\right) + 1 - \pi_{0b,i}}\right).$$

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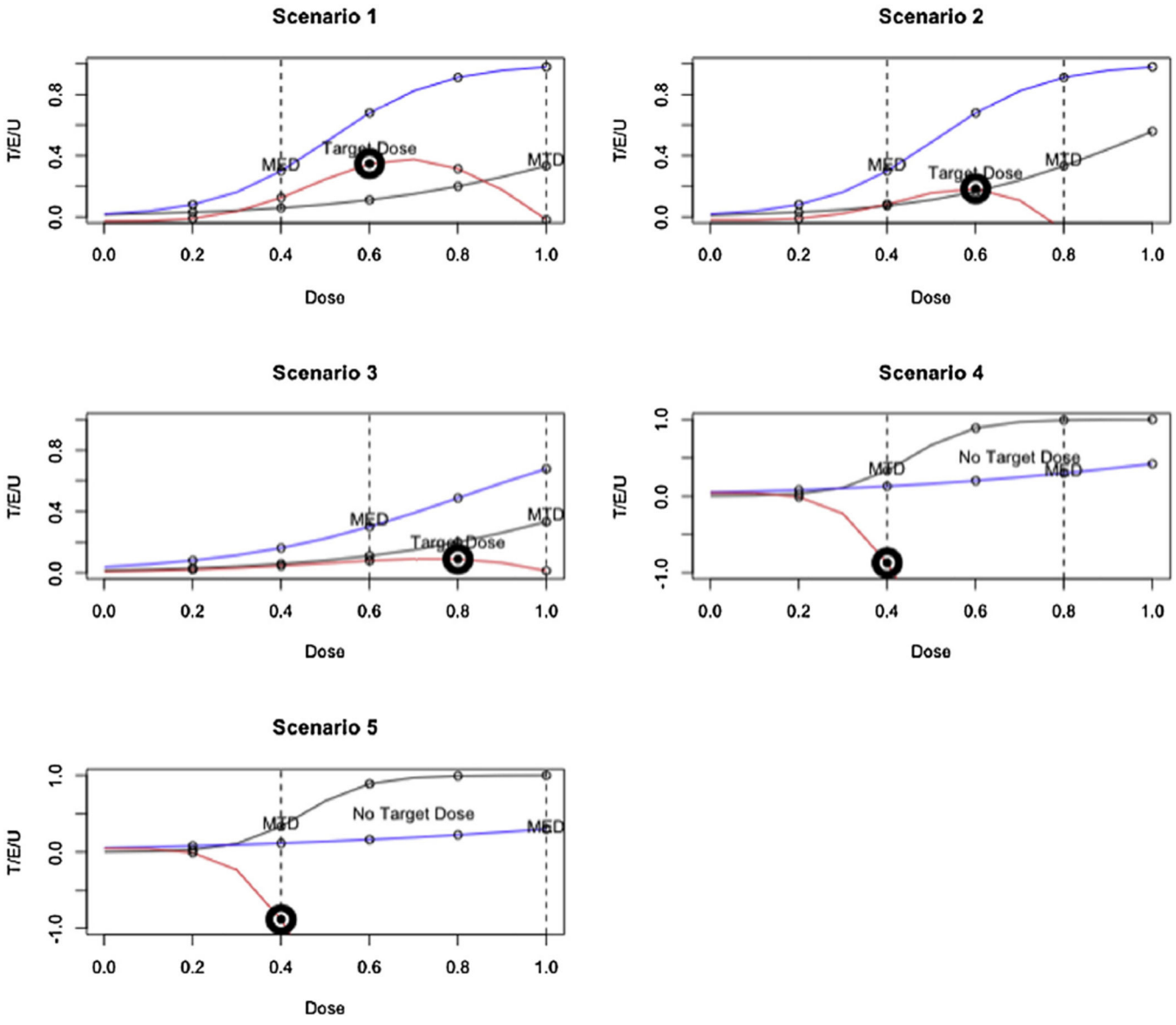

Fig. 1.

Dose response curves for five scenarios. Dose response curves for toxicity (black), efficacy (blue), and utility (red). True MTD and MED are noted on two curves, respectively. Solid dot shows that the dose is the OUD. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1

Dose recommendation percentage of each dose level for 4 designs under 5 scenarios.

S1: Extremely good	Dose Level					
	1	2	3	4	5	None
Probability of DLT	0.03	0.06	0.11	0.2	0.33	NA
Probability of efficacy	0.08	0.3	0.68	0.91	0.98	NA
Utility	−0.01	0.12	0.35	0.31	–0.02	NA
EWOC	0.20	0.60	3.50	50.30	45.40	0.00
EWOUC-NW	0.00	0.90	49.60	47.30	0.80	1.40
EWOUC-DA	0.10	0.90	72.30	25.90	0.10	0.70
EWOUC-Comp	0.00	1.40	91.90	6.10	0.10	0.50
S2: Good						
Probability of DLT	0.03	0.07	0.16	0.33	0.56	NA
Probability of efficacy	0.08	0.3	0.68	0.91	0.98	NA
Utility	−0.01	0.08	0.18	−0.09	–0.69	NA
EWOC	0.40	1.80	29.00	64.80	4.00	0.00
EWOUC-NW	0.00	2.40	67.40	25.90	0.00	4.30
EWOUC-DA	0.00	4.00	81.40	13.80	0.10	0.70
EWOUC-Comp	0.20	3.60	91.00	4.40	0.00	0.80
S3: Moderate						
Probability of DLT	0.03	0.06	0.11	0.2	0.33	NA
Probability of efficacy	0.08	0.16	0.3	0.49	0.68	NA
Utility	0.01	0.01	0.09	0.19	0.31	NA
EWOC	0.10	0.20	0.10	26.00	73.60	0.00
EWOUC-NW	0.00	0.00	3.40	54.90	40.60	1.10
EWOUC-DA	0.00	0.00	9.90	67.00	22.70	0.40
EWOUC-Comp	0.00	0.10	28.50	67.90	2.60	0.90
S4: Bad						
Probability of DLT	0.03	0.33	0.89	0.99	1	NA
Probability of efficacy	0.08	0.13	0.2	0.3	0.42	NA
Utility	−0.01	−0.87	–2.47	−2.68	–2.58	NA

S1: Extremely good	Dose Level					
	1	2	3	4	5	None
EWOC	53.00	43.30	3.70	0.00	0.00	0.00
EWOUC-NW	0.30	0.60	0.00	0.00	0.00	99.10
EWOUC-DA	0.30	4.00	0.20	0.00	0.00	95.50
EWOUC-Comp	0.40	3.70	0.10	0.00	0.00	95.80
S5: Extremely Bad						
Probability of DLT	0.03	0.33	0.89	0.99	1	NA
Probability of Efficacy	0.08	0.11	0.16	0.22	0.3	NA
Utility	−0.01	−0.88	−2.51	−2.75	−2.7	NA
EWOC	53.40	42.70	3.90	0.00	0.00	0.00
EWOUC-NW	0.10	0.40	0.10	0.00	0.00	99.40
EWOUC-DA	0.10	3.00	0.50	0.00	0.00	96.40
EWOUC-Comp	0.10	1.60	0.20	0.00	0.00	98.10

Table 2

Toxicity and expected utility under each design for the 5 scenarios.

Scenario of drug characteristic	DLT				Expected utility			
	EWOC	EWOUC-Comp	EWOUC-DA	EWOUC-NW	EWOC	EWOUC-Comp	EWOUC-DA	EWOUC-NW
S1: extremely good	0.17	0.10	0.11	0.15	0.21	0.28	0.28	0.26
S2: good	0.21	0.14	0.17	0.21	0.03	0.14	0.10	0.04
S3: moderate	0.16	0.08	0.10	0.15	−0.04	0.10	0.08	−0.00
S4: bad	0.22	0.32	0.31	0.32	−0.54	−0.84	−0.82	−0.86
S5: extremely bad	0.21	0.32	0.31	0.32	−0.54	−0.85	−0.82	−0.86

Table 3

Percentage of patients treated at each dose level for the 4 designs under 5 scenarios.

S1: Extremely good	Dose level				
	1	2	3	4	5
EWOC	8.80	11.96	20.83	40.46	17.95
EWOUC-NW	8.59	10.86	28.94	46.36	5.26
EWOUC-DA	8.81	12.77	56.13	22.25	0.04
EWOUC-Comp	8.70	13.32	73.01	4.95	0.03
S2: Good					
EWOC	9.15	14.82	35.64	37.71	2.68
EWOUC-NW	8.75	12.21	38.76	38.88	1.41
EWOUC-DA	9.05	15.39	58.23	17.32	0.02
EWOUC-Comp	9.06	16.29	70.81	3.84	0.00
S3: Moderate					
EWOC	8.62	10.00	11.37	33.51	36.51
EWOUC-NW	8.48	10.67	12.07	40.17	28.62
EWOUC-DA	8.56	10.24	25.11	47.37	8.72
EWOUC-Comp	8.53	10.52	29.43	47.73	3.78
S4: Bad					
EWOC	47.42	47.75	4.83	0.00	0.00
EWOUC-NW	30.07	54.47	15.44	0.02	0.00
EWOUC-DA	28.18	59.90	11.92	0.00	0.00
EWOUC-Comp	29.20	56.68	14.13	0.00	0.00
S5: Extremely Bad					
EWOC	48.18	47.02	4.80	0.00	0.00
EWOUC-NW	30.82	53.78	15.40	0.00	0.00
EWOUC-DA	28.59	59.74	11.67	0.00	0.00
EWOUC-Comp	30.30	55.61	14.09	0.00	0.00

Table 4

Expected time for a trial (months) under different assessment time periods and mean inter-cohort arrival times for 12 cohorts under scenario 1.

Mean inter-arrival time (month)	Assessment period (month)	EWOC-Comp (month)	EWOUC-DA (month)	Change
0.25	3	28.05	5.99	−78.65%
0.5	3	28.27	8.98	−68.23%
1	3	28.36	14.96	−47.25%
2	3	34.65	26.92	−22.31%
3	3	42.37	38.88	−8.24%

Table 5

Simulation results (1000 replicates) of the trial designed with the EWOUC-DA.

Dose level	1	2	3[a]	4	5
BKM120 (mg)	20	40	60	80	100
Everolimus (mg)	10	10	10	10	10
DLT probability	0.03	0.07	0.16	0.33	0.64
Efficacy probability	0.08	0.3	0.68	0.91	0.98
Utility	−0.01	0.09	0.20	−0.08	−0.94
Patient distribution	10.52	17.75	57.25	14.45	0.02
Final dose recommendation	0.10	4.50	82.40	12.00	0.00

[a]The true OUD is dose level 3.