Published in final edited form as:

J Biopharm Stat. 2019 ; 29(2): 271–286. doi:10.1080/10543406.2018.1535497.

An Adaptive Multi-Stage Phase I Dose-finding Design Incorporating Continuous Efficacy and Toxicity Data from Multiple Treatment Cycles*

Yu Du,

Department of Biostatistics, Johns Hopkins University, Baltimore, MD

Jun Yin,

Cancer Center Statistics, Mayo Clinic, Rochester, MN

Daniel J. Sargent, and

Cancer Center Statistics, Mayo Clinic, Rochester, MN

Sumithra J. Mandrekar

Cancer Center Statistics, Mayo Clinic, Rochester, MN, 507-284-2511

Abstract

Phase I designs traditionally use the dose-limiting toxicity (DLT), a binary endpoint from the first treatment cycle, to identify the maximum-tolerated dose (MTD) assuming a monotonically increasing relationship between dose and efficacy. In this article, we establish a general framework for a multi-stage adaptive design where we jointly model a continuous efficacy outcome and continuous/quasi-continuous toxicity endpoints from multiple treatment cycles. The normalized Total Toxicity Profile (nTTP) is used as an illustration for quasi-continuous toxicity endpoints, and we replace DLT with nTTP to take into account multiple grades and types of toxicities. In addition, the proposed design accommodates non-monotone dose-efficacy relationships, and longitudinal toxicity data in effort to capture the adverse events from multiple cycles. Stage 1 of our design uses toxicity data to perform dose-escalation and identify a set of initially allowable (safe) doses; stage 2 of our design incorporates an efficacy outcome to update the set of allowable doses for each new cohort and randomizes the new cohort of patients to the allowable doses with emphasis towards those with higher predicted efficacy. Stage 3 uses all data from all treated patients at the end of the trial to make final recommendations. Simulations showed that the design had a high probability of making the correct dose selection and good overdose control across various dose-efficacy and dose-toxicity scenarios. In addition, the proposed design allows for early termination when all doses are too toxic. To our best knowledge, the proposed dual-endpoint dose-finding design is the first such study to incorporate multiple cycles of toxicities and a continuous efficacy outcome.

*Submitted manuscript.

Correspondence to: Sumithra J. Mandrekar.

Jun Yin (co-first author)

Keywords

Adaptive design; Bayesian method; Dose-finding; Joint modeling; Phase I clinical trial; Toxicity-efficacy dual endpoint

1 Introduction

Phase I clinical trials are designed to identify the recommended phase II dose (RP2D) for future trials. For cytotoxic agents, the recommended dose is generally the maximum-tolerated dose (MTD). Traditionally, grade 3 or 4 toxicity events in the first treatment cycle are defined as dose-limiting toxicity (DLT) events and used to determine MTD. Late cycle toxicity events are recorded but not used in the dose assessment. The current development of molecularly targeted agents (MTAs) poses new challenges for the study design of phase I cancer clinical trials. Unlike the cytotoxic agents that are often administered for a limited number of treatment cycles, MTAs are administered until disease progression and often have a very different toxicity profile, characterized by chronic, prolonged events or cumulative toxicity as opposed to the early onset of severe adverse events. Therefore, it becomes important to consider toxicity events after the first treatment cycle, as well as repeated and chronic occurrence of lower grade events besides just grade 3 and 4 events. The idea of using longitudinal toxicity information have been explored by Legedza and Ibrahim (2000); Braun *et al.* (2007); Yin *et al.* (2017).

MTAs also have different toxicity-efficacy relationships compared to cytotoxic agents. Numerous studies have identified that lower doses of MTAs may offer similar efficacy as higher dose. As a result, searching for the MTD may not be the optimal treatment strategy for MTAs. Incorporation of early efficacy signals if available has become important for these novel agents. Only limited methods exist for dose-finding designs that account for toxicities and efficacy as dual-endpoint in the selection of recommended phase II dose. Thall and Cook (2004) used a set of efficacy-toxicity trade-off contours to accommodate either trinary or bivariate binary outcomes that includes efficacy. Bekele and Shen (2005) incorporated the correlation between the binary toxicity and continuous activity outcome via a latent Gaussian variable. Houede *et al.* (2010) used a generalization of the Aranda-Ordaz model and a Gaussian copula to model the marginal outcome and joint distribution of dual toxicity and efficacy endpoints. Apart from those Bayesian approaches mentioned above, there are also frequentist procedures developed for dual-endpoint design. For example, Dragalin and Fedorov (2006) proposed to use either Gumbel bivariate logistic regression or Cox bivariate binary model to model the bivariate distribution of binary efficacy and toxicity endpoints; Fedorov *et al.* (2012) adopted the bivariate probit dose-response model and constructed a utility function to derive an optimal design. A common feature of these designs is that they only considered binary (or categorical) toxicity endpoint of the first treatment cycle in phase I dose-finding designs, ignoring the fact that toxicity data are high dimensional in nature, with various types, grades, attribution over multiple treatment cycles. Bekele and Thall proposed the total toxicity burden (TTB) as the arithmetic sum of different grades and types of toxicity, weighted by the severity weights elicited from clinicians (Bekele and Thall, 2004). Lee *et al.* (2012) proposed the toxicity burden score (TBS) to summarize toxicity

using a weighted sum, where the severity weights were estimated via regression using historical data. Ezzalfani *et al.* (2013) proposed another flexible toxicity endpoint, called the total toxicity profile (TTP), upon which our proposed method is based as an illustration. However, the proposed design can easily be generalized to any continuous/quasi-continuous toxicity endpoints, including TTB, TBS, and etc.

The total toxicity profile (TTP) was developed to overcome the over-simplification of toxicity data in phase I trials (Ezzalfani *et al.*, 2013). The TTP score captures multiple types and grades of toxicities occurring during the first treatment cycle. Following the notation in Ezzalfani *et al.* (2013), let w_{lh} denote the elicited weight of toxicity type l ($l \in \{1, \dots, L\}$) occurring at grade h ($h \in \{0, \dots, 4\}$). Hence, the weight vector for toxicity l is $\mathbf{w}_l = (w_{l0}, \dots, w_{l4})^T$ and the weight matrix is denoted as $\mathbf{W} = (\mathbf{w}_1, \dots, \mathbf{w}_L)^T$. For patient i , denote the maximum observed grade of toxicity type l as G_{il} . Then the TTP_i is defined as

$$TTP_i = \sqrt{\sum_{l=1}^L \sum_{h=0}^4 w_{lh}^2 1(G_{il} = h)}, \quad (1)$$

where $1(G_{il} = h)$ is an indicator function which takes value 1 if the maximum observed grade is h for toxicity type l , and 0 otherwise. The TTP is further normalized to nTTP, in order to constrain the continuous toxicity endpoint to be within 0 and 1, $nTTP_i = \frac{TTP_i}{v}$, where v is a normalization constant (for details, please refer to Ezzalfani *et al.* (2013)). This is an improvement from using the traditional DLT based endpoint in that it takes into account clinical multidimensionality of multiple types/grades of toxicities for a given toxicity profile, as well as the moderate toxicity events commonly ignored by using DLT endpoint. However, patients participating in phase I clinical trials usually receive more than one cycle of experimental regimen in the absence of DLT or disease progression. To account for this limitation, an extension to this design to incorporate nTTP scores from multiple treatment cycles was proposed by Yin *et al.* (2017).

This article proposes a three-stage dose-finding design based on both longitudinal toxicity data of nTTP scores and an efficacy endpoint. This is an extension of our previous work (Yin *et al.*, 2017), which only uses nTTP scores from multiple treatment cycles. Furthermore, the proposed design is easily extended to other continuous/quasi-continuous toxicity endpoints than nTTP. To our best knowledge, it is the first design to simultaneously account for both the multiple types/grades toxicity events over multiple treatment cycles and a continuous efficacy endpoint. In Section 2 of the article, a joint model is introduced that takes into account the correlation between the toxicity data over multiple treatment cycles and a continuous efficacy outcome. Section 3 describes a three-stage dose-finding algorithm where stage 1 of the design uses toxicity data to perform dose-escalation and to identify a set of initially allowable (safe) doses; stage 2 of the design incorporates an efficacy outcome to update the set of allowable doses and randomizes the new cohort of patients to the allowable doses with emphasis towards those with higher predicted efficacy; stage 3 uses all data from all treated patients at the end of the trial to make final recommendations. The recommended

phase II dose selection, in this article, is to achieve the lowest possible dose with acceptable efficacy. In Section 4, extensive simulations are conducted to evaluate the operating characteristics of the proposed design under various clinical relevant scenarios. Section 5 concludes the manuscript with a discussion of the proposed design, as well as some insights into future work.

2 Joint Model

We jointly model the toxicity profile, nTTP scores across multiple cycles, and a continuous efficacy outcome for each patient. The joint model, introduced by Wang *et al.* (2000), is comprised of two submodels: for longitudinal nTTP scores, a linear mixed effect model; while for continuous efficacy outcome, a linear model. Here, we transform any continuous efficacy outcome so that it ranges from 0 to 1 by using empirical distribution function. Suppose we have cumulative data for n patients. Let Y_{ij} be the nTTP score for patient i ($i = 1, 2, \dots, n$) at cycle j , where $t_{ij} = t_j = j$ represents the j^{th} ($j = 1, 2, \dots, J$) cycle of treatment, the same across all patients. We use x ($x = 1, 2, \dots, K$) to denote the dose of the agent and x_i is the dose allocated to patient i . We assume that the same dose is given to a patient in each cycle of the treatment. Let E_i be the continuous efficacy outcome for the i^{th} patient.

The linear mixed effect submodel with a random intercept for the longitudinal nTTP scores is such that

$$Y_{ij} = \beta_0 + \beta_1 x_i + \beta_2 t_j + u_i + \epsilon_{ij}, \quad (2)$$

where

$$\epsilon_{ij} \sim N(0, \sigma_\epsilon^2),$$

$$u_i \sim N(0, \sigma_u^2),$$

and the linear submodel for the efficacy outcome is given below:

$$E_i = \alpha_0 + \alpha_1 x_i + \alpha_2 x_i^2 + \gamma u_i + \epsilon_{e_i}, \quad (3)$$

where

$$\epsilon_{e_i} \sim N(0, \sigma_e^2).$$

We assume that $u_1, u_2, \dots, u_n, \epsilon_{11}, \epsilon_{12}, \dots, \epsilon_{nJ}, \epsilon_{e_1}, \epsilon_{e_2}, \dots, \epsilon_{e_n}$ are independent where u_i is the random intercept for the i^{th} patient, shared with the two submodels, ϵ_{ij} is the error for patient

i nTTP score at cycle j and ϵ_{e_i} is the error for efficacy outcome for patient i . Let θ represent the parameters to be estimated such that $\theta = (\beta_0, \beta_1, \beta_2, \alpha_1, \alpha_2, \alpha_3, \gamma, \sigma_e, \sigma_u, \sigma_e)'$.

Let us use $\pi_Y(x, \theta, t_j)$ to denote the mean of nTTP score for a randomly selected patient who undergoes the j^{th} treatment cycle with allocated dose level x given the parameters θ , so that $\pi_Y(x, \theta, t_j) = \beta_0 + \beta_1 x + \beta_2 t_j$. Therefore, $\beta_0, \beta_1, \beta_2$ relate to the mean structure of toxicity profile. In order to reflect the fact that the toxicities of most cancer agents increase with dose, we add a constraint a priori to the dose effect β_1 such that $\beta_1 > 0$. Also, let $\pi_E(x, \theta)$ represent the mean of efficacy outcome for the patient to whom dose level x is allocated given the parameters θ , so that $\pi_E(x, \theta) = \alpha_0 + \alpha_1 x + \alpha_2 x^2$. Hence, $\alpha_0, \alpha_1, \alpha_2$ maneuver a quadratic mean structure of efficacy outcome. This quadratic mean structure, $\pi_E(x, \theta)$, is capable of describing most common patterns between efficacy and dose, including a flat (the efficacy does not change with dose), increasing/decreasing (the efficacy increases/decreases as dose level goes up), plateau (the efficacy increases and reaches a plateau as dose level increases) and a parabolic (the efficacy first increases and then decreases as dose level varies from low to high) relationship. We will explore these scenarios in Section 4. σ_e, σ_e are standard deviations of the errors for nTTP score and efficacy outcome, respectively while σ_u is the standard deviation of random intercepts. Random intercepts u_i serve as the linkage between two submodels, and γ indicates the strength of the association such that the covariance between the nTTP score and efficacy outcome for a patient, given the treatment cycle, the parameters θ and the allocated dose level, is $\gamma\sigma_u^2$.

A patient will discontinue the treatment anytime they experience a DLT. Hence, patients can have different number of treatment cycles. However, efficacy outcome is assumed to be always measured at a fixed time point during the treatment (e.g., at the end of cycle 3), patients who drop out due to DLT before that time point will have missing efficacy data.

In the early stages of our design, we do not have patients' toxicity/efficacy information for all J cycles of treatment. We, therefore, introduce a simplified version of submodel (2), as below:

$$Y_{ij} = \beta_0 + \beta_1 x_i + \beta_2 t'_j + u_i + \epsilon_{ij}, \quad (4)$$

where t'_j dichotomizes t_j , a binary indicator of first cycle or beyond, such that

$$t'_j = \begin{cases} 0 & \text{if } j = 1 \\ 1 & \text{if } j = 2, \dots, J, \end{cases}$$

where all other components are the same. This, in addition, emphasizes our concern about the toxicity at the first cycle of treatment and the toxicities for the other cycles beyond as an aggregate measure.

2.1 Estimation

For parameter estimation of the joint model, we implement Bayesian methods, Markov Chain Monte Carlo (MCMC) to estimate the posterior distribution of the parameters, using JAGS (Hornik *et al.*, 2003). Non-informative prior distributions are specified since elicitation in this context is difficult, therefore, the estimation of the parameters will largely depend on data. For parameters $\beta_0, \beta_2, a_0, a_1, a_2, \gamma$, we specify independent normal priors with mean 0 and precision 0.001 (the inverse of the variance). For all other parameters, we use uniform priors from 0 to 1000. We discard the first 5,000 samples as burn-in and sample the subsequent 5,000 iterations. The posterior mean of $\pi_Y(x, \theta, t_j)$ and $\pi_E(x, \theta)$ are used to guide the dose-escalation/de-escalation which will be specified in Section 3. The core R code for implementing MCMC is provided in Appendix A.4.

3 Dose-finding Algorithm

A three-stage phase I dose-finding algorithm, whose goal is to find efficacious doses that are also safe, is proposed. Suppose N is the maximum sample size. Stage 1 only utilizes longitudinal data of nTTP scores to navigate the dose-escalation for each subsequent patient cohort of size m as well as identifies initially allowable (safe) doses in terms of toxicity when cumulative sample size reaches $\frac{N}{2}$. Stage 2 involves efficacy outcome, and by jointly modeling the toxicity and efficacy profile as specified in Section 2, it updates the set of allowable doses and randomizes patients to the allowable doses with emphasis towards those with higher predicted efficacy for each new cohort. Stage 3 concludes the algorithm when all the data from all treated patients becomes available (i.e., at the end of the trial), where we fit the joint model to the full data and find the efficacious doses that are also allowable (safe). Early termination of the trial is allowed, when there are no allowable (safe) doses in terms of toxicity but skipping of dose levels not previously tried is not allowed at any time. Below we specify how each stage works in more details.

3.1 Stage 1

Stage 1 aims to perform the dose-escalation/de-escalation and define initially allowable (safe) doses in terms of toxicity, based on longitudinal data of nTTP scores only until the sample size of patients enrolled reaches $\frac{N}{2}$. We enroll patients by cohorts of size m .

Dose 1 is assumed to be the starting dose and starting from the first cohort of patients, we use the 3 + 3 design for dose escalation until we escalate to dose 2. Once dose 2 is allocated to a new cohort and when its first cycle nTTP scores become available, we switch to the linear mixed effect submodel (4) in Section 2, fitting the cumulative longitudinal toxicity data for dose escalation. We employ the submodel (4) when we have toxicity data for more than one dose level, in order to give more accurate estimates than applying the model with only one dose level.

Suppose $\mathbb{O}$ denotes the current cumulative data and based on $\mathbb{O}$, the dose-escalation is guided by Bayesian risk evaluation. This evaluation is applied after doses 1 and 2 have been tested. We define a loss function L for dose level x and cycle 1 of the treatment such that

$$L(\pi_Y(x, \theta, t'_1), \pi_1) = |\pi_Y(x, \theta, t'_1) - \pi_1|,$$

where π_1 is the target toxicity in nTTP score in the first cycle of treatment, and $\pi_Y(x, \theta, t'_1)$ is the mean nTTP score given parameter θ , at cycle 1 of the treatment for dose level x . This loss function L was used by Yin *et al.* (2017). The dose level x that delivers the minimum $\mathbb{E}[L(\pi_Y(x, \theta, t'_1), \pi_1) | \mathbb{O}]$, namely minimizing the Bayesian risk, will be allocated to the next cohort of patients. Note that no skipping of dose levels not previously tried is allowed, so if there happens to be skipping of dose levels from minimizing the Bayesian risk, we will de-escalate to the next safer dose that does not skip any dose levels not previously tried. We define allowable (safe) doses after enrolling three cohorts of patients. The dose x will be declared an allowable (safe) dose based on safety if the following two conditions are met:

$$\mathbb{P}\{\pi_Y(x, \theta, t'_1) < c_1 | \mathbb{O}\} > p_1, \quad (5)$$

$$\mathbb{P}\{\pi_Y(x, \theta, t'_j = 1) < c_2 | \mathbb{O}\} > p_2, \quad (6)$$

where c_1, c_2 are the upper bounds of the mean nTTP score for the first and subsequent cycles of treatment, while p_1, p_2 are the corresponding probability cutoffs respectively. These parameters need to be pre-defined, and should be chosen based on both physicians' discretion and design's operating characteristics, which will be discussed in Section 5. Condition (5) concerns the toxicity at the first cycle of treatment, while condition (6) regards the toxicities for the other late cycles, with $\pi_Y(x, \theta, t'_j = 1)$ serving as an aggregate mean nTTP score for treatment cycles beyond cycle 1 at dose level x , given the parameter θ . These two probability conditions (5) and (6) act here as a stopping rule such that the trial shall be terminated early if there is no allowable (safe) dose. Otherwise, stage 1 continues until the cumulative sample size of patients enrolled reaches $\frac{N}{2}$ and at the end of stage 1, we identify a set of initially allowable doses, $\mathbb{A}$, ready to enter stage 2.

3.2 Stage 2

Assuming that efficacy data is available on patients from stage 1, we fit the joint model (3) and (4), and update the set of allowable (safe) doses, $\mathbb{A}$, using the two probability conditions (5), (6). The next cohort of patients are randomized to the allowable doses with emphasis towards those dose levels with higher predicted efficacy. The probability that dose level $a \in \mathbb{A}$ is assigned is as follows:

$$\frac{\exp\{\mathbb{E}[\pi_E(a, \theta) | \mathbb{O}]\}}{\sum_{x \in \mathbb{A}} \exp\{\mathbb{E}[\pi_E(x, \theta) | \mathbb{O}]\}},$$

where $\mathbb{E}[\pi_E(a, \theta) | \mathbb{O}]$ is the posterior mean of efficacy outcome, the predicted efficacy, for dose level $a \in \mathbb{A}$. Thus, the higher the predicted efficacy of a dose, the more likely it will be assigned to the next cohort of patients. We continue this update for the set of allowable doses, $\mathbb{A}$, and efficacy-based randomization for each new cohort until the maximum sample size N is reached. Again, early termination is allowed if there is no allowable (safe) dose at any time, i.e., $\mathbb{A} = \emptyset$

3.3 Stage 3

The purpose of Stage 3 is to define the efficacious doses that are also safe at the end of the trial and make a final recommendation of the dose level for future, phase II trial. When all data from all treated patients become available, we implement the joint modeling (2) and (3) as described in Section 2, a fully parameterized version. Again, we update the set of allowable doses $\mathbb{A}$ using the two probability conditions (5) and (6), with t'_j replaced by t_j and for the second condition (6) regarding later cycles of treatment beyond cycle 1, we use instead

$$\mathbb{P}\left\{\overline{\pi_Y(x, \theta, t_j > 1)} < c_2 | \mathbb{O}\right\} > p_2, \quad (7)$$

where $\overline{\pi_Y(x, \theta, t_j > 1)} = \frac{1}{J-1} \sum_{j=2, \dots, J} \pi_Y(x, \theta, t_j = j)$. We aggregate the toxicity information for cycles 2 through J by taking the average. Subsequently, for each allowable dose $a \in \mathbb{A}$, we compute the posterior mean of efficacy response, $\mathbb{E}[\pi_E(a, \theta) | \mathbb{O}]$. Let $l \in \mathbb{A}$ be the allowable dose that gives the largest posterior mean of efficacy, such that $l = \operatorname{argmax}_{a \in \mathbb{A}} \mathbb{E}[\pi_E(a, \theta) | \mathbb{O}]$. We define a proximity threshold δ such that any dose $a \in \mathbb{A}$ that satisfies the condition $|\mathbb{E}[\pi_E(a, \theta) | \mathbb{O}] - \mathbb{E}[\pi_E(l, \theta) | \mathbb{O}]| \leq \delta$ will be declared an efficacious dose since it is in the efficacy proximity of the dose l , that gives the largest posterior mean of efficacy. We thus define the set of efficacious doses that are also safe, $\mathbb{H}$, such that $\mathbb{H} = \{h \in \mathbb{A} : |\mathbb{E}[\pi_E(h, \theta) | \mathbb{O}] - \mathbb{E}[\pi_E(l, \theta) | \mathbb{O}]| \leq \delta\}$

We report the set $\mathbb{H}$ at the end of the trial along with the toxicity profile from different cycles of the treatment, $\mathbb{E}[\pi_Y(h, \theta, t_j) | \mathbb{O}]$, and efficacy profile, $\mathbb{E}[\pi_E(h, \theta) | \mathbb{O}]$ for any $h \in \mathbb{H}$. Any dose $h \in \mathbb{H}$ can be picked based on physician's judgment and preference but in our work, we choose the lowest (safest) dose in set $\mathbb{H}$ as the final recommendation for future, phase II trial. We explore several scenarios with different toxicity and efficacy structures, and conduct simulation studies in Section 4 to evaluate the performance of operating characteristics for the design.

4 Simulation Studies

4.1 Generation of the Toxicity Data

Let us assume that there are three independent types of toxicities related to the treatment: renal, neurological and hematological toxicities. The clinical weight matrix, elicited from the physician, is shown as follows:

$$W = \begin{pmatrix} 0 & 0.5 & 0.75 & 1 & 1.5 \\ 0 & 0.5 & 0.75 & 1 & 1.5 \\ 0 & 0 & 0 & 0.5 & 1 \end{pmatrix}.$$

DLT, in this setting, is defined as the occurrence of a grade 3 or 4 renal/neurological toxicity or a grade 4 hematological toxicity. Based on this weight matrix, we compute the TTP score for patients. The maximum TTP score that can be acquired from the matrix is 2.34, corresponding to the scenario where a patient experiences grade 4 toxicities for all three types. We thus normalize TTP by dividing the value by a normalization constant, 2.5, to obtain nTTP for each patient. The target toxicity nTTP elicited from the physician is set at 0.28. For details on the normalization constant and the target nTTP at cycle 1 of the treatment, please refer to Ezzalfani *et al.* (2013). In the simulation, however, we need to simulate the toxicity profile for each patient in order to compute an nTTP score. Please see Appendix A.1 for more details on how toxicity data was generated non-parametrically.

4.2 Generation of the Efficacy Outcome

The efficacy outcome, in our setting, is assumed to be a continuous variable from 0 to 1. We explore 5 common dose-efficacy patterns in the simulation study, as described in Section 2. We generate efficacy outcome for each patient from the beta distribution. Figure 1 displays the dose-efficacy patterns and the distribution of efficacy outcome for each dose in each pattern. It is clearly seen from dose-efficacy pattern 1 to 5 that efficacy data are generated from the beta distributions that have large variation and/or skewness. For more details, please refer to Appendix A.2.

4.3 Simulation Settings

We consider 14 scenarios in total, that takes into account 6 toxicity structures and 5 dose-efficacy patterns. For each scenario, we simulated 1,000 trials that explore 6 dose levels with maximum 6 treatment cycles, where dose level 1 is the starting dose. We enroll patients by cohorts of 3 and the maximum sample size for each trial is set at 36. We assume that efficacy outcome is measured at the end of cycle 3 of the treatment so if the patient drops out of the trial before cycle 3, his/her efficacy data will be missing. Missing information is also present for toxicity data due to DLT dropouts.

- Parameters
 - $\pi_1 = 0.28$, the target toxicity nTTP for cycle 1 of the treatment is set at 0.28.
 - $c_1 = c_2 = \pi_1$, the upper bounds for cycle 1 and the subsequent cycles toxicity are set equal to π_1 .

– $p_1 = p_2 = 0.2$, the two probability cutoffs for conditions (5) and (6) are set at 0.2.

– $\delta = 0.1$, so that all the safe doses whose posterior means of efficacy are less than or equal to 0.1 away from the largest one among the safe doses will be declared efficacious doses.

- Performance metrics

– $\mathbb{P}_{\text{recom}}$, the percentage of dose recommendation, where we recommend the lowest dose that is efficacious,

$$\mathbb{P}_{\text{recom}}(x) = \frac{\text{\# of simulated trials that recommend dose level } x}{\text{\# of simulated trials in total}}.$$

– $\mathbb{P}_{\text{alloc}}$, the percentage of dose allocation, computed by dividing the number of patients allocated to the dose by the total number of patients enrolled,

$$\mathbb{P}_{\text{alloc}}(x) = \frac{\text{\# of patients allocated to the dose level } x}{\text{\# of patients enrolled in total}}.$$

– $\mathbb{P}_{\text{effy}}$, the percentage of dose being efficacious and safe, as defined below:

$$\mathbb{P}_{\text{effy}}(x) = \frac{\text{\# of simulated trials that declare dose level } x \text{ as being efficacious and safe}}{\text{\# of simulated trials in total}}.$$

Note that $\mathbb{P}_{\text{effy}}$ is often different from $\mathbb{P}_{\text{recom}}$ since $\mathbb{P}_{\text{effy}}$ indicates the probability that any particular dose is selected as an efficacious dose that is also safe while $\mathbb{P}_{\text{recom}}$ encodes the probability that a dose is recommended as the lowest (safest) dose that is also efficacious. There may be multiple safe and efficacious doses for each trial, among which the lowest dose is recommended in the study. The simulation study is performed using R (R Core Team, 2016).

4.4 Results

The simulation results for scenario 1 to 5 are summarized in Table 1. Scenario 1 to 5 correspond to the dose-efficacy pattern 1 to 5 in Figure 1, i.e., the increasing, flat, plateau, decreasing and parabolic relationship for efficacy with dose, respectively. In addition, they have a toxicity structure where the target toxicity dose at cycle 1 of the treatment is dose 5 and the cycle effect is flat, namely, the mean nTTP (mnTTP) for each dose level is the same across cycles.

In scenario 1, the most efficacious dose among the safe doses is dose 5 whose mean of efficacy is 0.7. Seventy-seven percent of the trials declare this dose as the efficacious dose and 72% of the recommendations correspond to this dose. Dose 4 is the second best choice in this scenario if physician prefers a lower toxicity, which has 11.1% chance of the recommendations. In total, 83.1% of the recommendations go to these top 2 choices. Scenario 2 has a flat relationship in terms of dose-efficacy pattern since all doses have a

mean of efficacy equal to 0.5. About 69% of the recommendations correspond to the lowest dose, dose 1, which is the optimal one. Around 18% of simulated trials recommend dose 2, which is equally desirable as dose 1 since they have very close toxicity across all cycles, 0.046 (dose 1) vs 0.054 (dose 2). Nearly 87% of the trials, in total, make a recommendation for dose 1 or dose 2. Scenario 3 demonstrates a plateau relationship between efficacy and dose, where the efficacious doses, by its definition, are dose 3 to 5. When doses have equal efficacy, the lower doses will be preferred since they give lower toxicities. Almost 95% of the recommendations correspond to dose 3 or dose 4, which are lower doses than dose 5 yet have the same efficacy. Almost 100% of the trials recommend dose 1, the most efficacious dose, in scenario 4, where the mean of efficacy decreases as dose level varies from low to high. Scenario 5 shows a parabolic relationship for dose-efficacy pattern and 99.7% of the trials declare that dose 3, whose mean of efficacy is at the peak, is an efficacious dose. Nearly 97% of the recommendations come to the top 2 choices, dose 3 and dose 2.

Table 2 displays the simulation results for scenario 6 to 10, where the only change from scenario 1 to 5 is that target toxicity dose is dose 3 instead of dose 5, so that dose 4 to 6 are not considered safe doses. In scenario 6, dose 2 and 3, by definition, are efficacious doses since their mean of efficacy are within $\delta = 0.1$ distance. Around 70% of the recommendations correspond to the efficacious doses. Again, in a flat relationship between efficacy and dose, in scenario 7, 95.4% of the trials recommend top 2 choices, dose 1 or dose 2, which are lower doses than dose 3. Scenario 8 behaves similarly as scenario 10, since when we focus on the safe doses, dose 1 to 3, they have a similar increasing dose-efficacy pattern in both of these two scenarios. Around 96% of the recommendations go for the two best doses, dose 3 or dose 2 in both scenario 8 and 10. Scenario 9 resembles scenario 4, where 99.2% of the trials recommend the best dose, dose 1, that has the highest mean of efficacy.

In terms of the metric $\mathbb{P}_{\text{alloc}}$, all scenarios 1 to 10 allocate less than 6.2% of the patients to the doses more toxic than the target toxicity dose, which demonstrates good overdose control of our design.

The simulation results for the last four scenarios, scenario 11 to 14, are demonstrated in Table 3, where we fix a dose-efficacy pattern, the parabolic relationship. Scenario 11 demonstrates a case where all doses are toxic with mnTTP larger than the target toxicity, 0.28. None of the doses are recommended in this scenario, with 88% of the patients being allocated to the starting dose, dose 1. Since our design allows early termination if all doses are too toxic, the average number of patients enrolled is 10. Therefore, in scenario 11, most of the trials terminate early after enrolling 3 cohorts of patients. Scenario 12 corresponds to the case where only dose 1 is safe and our design recommends dose 1 for 94.6% of the simulated trials. Scenario 13 and 14 show the increasing cycle effect and the decreasing cycle effect respectively, where the mnTTP for each dose increases/decreases as patients go through later cycles. Both of these scenarios have similar results under parabolic dose-efficacy relationship: around 97% of the recommendations go for the best two doses, dose 3 or dose 2, while more than 99% of the trials declare that dose 3, at the efficacy peak, is an

efficacious dose. Apart from these studies, we did additional simulations, as shown in Appendix A.3, to test the performance of our design in other scenario settings.

5 Discussion

Conventional dose-finding designs for phase I clinical trials do not utilize efficacy data, and toxicity data from late treatment cycles in the dose-finding decision. The rapid development of cancer immunotherapy and MTAs require the consideration of both efficacy and toxicity data that are often ignored in traditional dose-finding studies. As a result, new strategies must be developed for these phase I dose-finding studies.

This article presents a novel phase I design that combines an early-stage efficacy endpoint and toxicity profiles from multiple treatment cycles during the dose-finding process. It is an extension of our previous work (Yin *et al.*, 2017) that only uses toxicity data from multiple treatment cycles. The proposed design uses a novel three-stage procedure in dose-finding. The advantage of the three-stage procedure is: (1). use the first stage to ensure the patient safety while exploring doses in the dose-finding procedure using continuous/quasi-continuous toxicity scores (e.g., nTTP, TTB, TBS) over multiple treatment cycles; (2). recruit additional patients in the second stage to explore the early-stage efficacy endpoint among safe doses; and (3). combine all data from all treated patients at the end of the study to find the lowest possible (safest) dose that is also efficacious. To our best knowledge, this is the first design to combine an early-stage efficacy endpoint and longitudinal toxicity endpoints over multiple treatment cycles in the dose-finding studies.

Simulation studies have been conducted to demonstrate that the proposed design consistently finds the safe doses with desired efficacy profiles in a wide range of scenarios. A Bayesian framework with MCMC is adopted because it naturally fits with the adaptive nature of phase I dose-finding trials. In the simulation studies, the dose variable x is defined to be the dose levels that take the values of 1, 2, ..., however, our method can be easily adapted to incorporate actual doses or some log transformations of actual doses, as the case may be.

The design also allows for patient dropouts due to DLT, therefore, missing data is present in both the longitudinal toxicities and the efficacy outcome. Around 20% – 40% of efficacy data is missing in our simulation studies depending on the scenarios. One exception is scenario 11 where all doses are too toxic and almost all efficacy data are missing since very few patients continue to cycle 3 of the treatment. In addition, our efficacy data generating distribution has quite a large amount of skewness/variation. Under these conditions, our joint modeling performs quite well, as shown by simulation results in Section 4.4.

The choices of c_1 and c_2 are picked based on the trial: if more toxicity is acceptable, then a higher upper bound of toxicity than the target toxicity can be chosen, and p_1 and p_2 can consequently be picked by simulations. In simulations, we also tried $c_1 = c_2 = 0.36$, larger than the target toxicity 0.28, and p_1 and p_2 were set at 0.8. The maximally tolerated toxicity, therefore, was 0.36. The simulation result for scenario 1 showed a higher percentage of recommendations, 42%, for dose 6, whose mnTTP is 0.36 and thus an allowable (safe) dose

in this setting. It has the largest mean efficacy of 0.9, among all doses. Another 52% of the recommendations correspond to the second best dose, dose 5, with a mean efficacy of 0.7. Around 94% of the trials, in total for scenario 1, recommend these two best doses. Across all scenarios, the design is more likely to define the target toxicity dose, with mnTPP 0.28, as the allowable (safe) dose, thus recommending this dose more frequently if it is the only efficacious dose. The selection of different weight matrices of the nTTP-based toxicity profiles and the selection of an appropriate efficacy endpoint can also have an impact on the dose-finding process. Close collaborations with physicians and medical researchers are therefore required for this design, as with any other trials. Our method assumes that the same dose is given to a patient in each cycle of the treatment, thus it is an area of future research to allow dose modification across treatment cycles. In addition, we conjectured that half of the total number of patients assigned to stage 1 would allow us a reliable estimate for efficacy parameters in stage 2 and 3. And it indeed gave us desirable performance of the operating characteristics in our simulation studies considering a wide variety of dose-response scenarios. However, it remains a future work to investigate the proportion for stage 1 sample size which could optimize previously specified utility functions. Another limitation of our design is that our dose-finding algorithm might not take full advantage of the proposed joint modeling as we did not utilize efficacy information during stage 1 of the design. Since the efficacy endpoint is evaluated at later cycles, its observations are not available until several cohorts of patients have been enrolled. For ethical considerations, we cannot wait for efficacy data to become available before treating patients. We therefore use stage 1 to accumulate efficacy responses while exploring safety of doses so that a more robust and reliable efficacy-based randomization among safe doses can be expected in stage 2 of the design. More efficient use of the proposed modeling can certainly be investigated as part of future research.

In summary, we present a new dose-finding method that accommodates an early efficacy endpoint and multiple toxicity types/grades over multiple treatment cycles in the dose-finding and dose recommendation for future studies. The simulations demonstrate that the proposed design performs well in terms of identifying the optimal doses in various scenarios. We have developed an R package **phase1RMD** to implement the design, which is available on CRAN. (<https://cran.r-project.org/web/packages/phase1RMD/index.html>)

A

A.1: Generation of Toxicity Data

In order to generate toxicity data, nTTP, for each patient, we need to define a matrix of probabilities, for each type of toxicity and each cycle of the treatment, of observing grades 0 to 4 toxicity, for K dose levels. For example, a possible such matrix, for cycle 1 of the treatment and renal toxicity, where $K = 6$, looks as below:

$$\mathbb{P}_{\text{renal}} = \begin{pmatrix} 0.823 & 0.152 & 0.022 & 0.002 & 0.001 \\ 0.791 & 0.172 & 0.032 & 0.004 & 0.001 \\ 0.758 & 0.180 & 0.043 & 0.010 & 0.009 \\ 0.685 & 0.190 & 0.068 & 0.044 & 0.013 \\ 0.662 & 0.200 & 0.078 & 0.046 & 0.014 \\ 0.605 & 0.223 & 0.082 & 0.070 & 0.020 \end{pmatrix},$$

where grades from 0 to 4 define the columns of the matrix while the dose levels from 1 to 6 define the rows. Such matrices for all three types of toxicities and all treatment cycles define a toxicity structure, where the mnTTP (mean nTTP) for each dose level and cycle can be derived. When all such matrices are known, we can compute, for each dose level and cycle, the probabilities (weights) of each of the 5^3 combinations of the TPs (toxicity profile). For each combination, we can also compute its nTTP score from the clinical weight matrix. The weighted sum of nTTP for all combinations is thus the mnTTP associated with the dose level and the cycle. The pDLT (probability of DLT) can be computed similarly.

These probability matrices are used to generate nTTP for each patient, given the dose allocated and the cycle of the treatment. For example, suppose a patient is assigned dose 1 at cycle 1 of the treatment. For the renal toxicity, we look at the first row of matrix $\mathbb{P}_{\text{renal}}$,

(0.823, 0.152, 0.022, 0.002, 0.001), which corresponds to the probabilities of observing renal toxicity grades 0 to 4 respectively at dose 1. We thus sample a renal toxicity grade for this patient, according to this probability distribution. We repeat this sampling for the other two types of toxicities and in the end, we have a combination of the TP for the patient, for example, grade 1 renal associated with grade 1 neurological and grade 3 hematological toxicities. The nTTP is thus given by the clinical weight matrix, such that

$\text{nTTP} = \sqrt{0.5^2 + 0.5^2 + 0.5^2} / 2.5 = 0.35$. We also assess if the patient experiences a DLT by its definition, and if a patient has a DLT, he/she will drop out for the subsequent cycles, if any.

A.2: Generation of Efficacy Outcome

Figure 1(b) to 1(f) show the distribution of efficacy outcome for dose-efficacy pattern 1 to 5 across each dose level. Pattern 1 (Figure 1(b)) corresponds to an increasing relationship between efficacy and dose, as reflected by the red solid line in Figure 1(a), “Dose-Efficacy Patterns”, where the mean of efficacy outcome increases as dose level goes up. Pattern 4 (Figure 1(e)), the blue dashed line in Figure 1(a), represents a decreasing relationship, opposite to the pattern 1. Pattern 2 (Figure 1(c)), a flat line, indicates a flat relationship where the mean of efficacy outcome does not change with dose. Pattern 3 (Figure 1(d)) demonstrates a situation where the mean of efficacy outcome increases and then reaches a plateau as dose level increases, corresponding to the green dashed line in Figure 1(a) and let us call this plateau relationship. The last pattern, pattern 5 (Figure 1(f)), shows a parabolic relationship, as seen from the purple dotted line in Figure 1(a) that the mean of efficacy outcome first increases and then decreases as dose level varies from low to high.

It is clearly seen from dose-efficacy pattern 1 to 5 that efficacy data are generated from the beta distributions that have large variation and/or skewness.

A.3: Additional Simulations

In this section, we considered additional scenarios. The dose-efficacy pattern 4 in Section 4 does not seem very practical in real study setting though it is theoretically interesting. Therefore, we considered two other scenarios where in scenario (A) the highest efficacy is achieved at dose 2 and in scenario (B) the highest efficacy is achieved at dose 5. The toxicity structure remains the same as the one in Table 1. We also increased the cut-off, p_1 and p_2 , for two probability conditions (5) and (6) from 0.2 to 0.8, as well as increased the value c_1 and c_2 for the maximally tolerated toxicity boundary from the target toxicity 0.28 to a higher value 0.32. Depending on how the maximally tolerated toxicity is defined, the value of p_1 and p_2 can be either close to 0 or to 1. If the target toxicity 0.28 is the maximally tolerated toxicity, a low cut-off value shall be used, for example, it was set at 0.2 in Section 4. The results are provided in Table 4.

It can be clearly seen in Table 4 that our design is still able to give a desirable performance in these two scenarios. In scenario (A), nearly 90% of the simulated trials declared the highest efficacy dose (dose 2) as an efficacious dose while in scenario (B), around 86% of the trials correctly identified the highest efficacy dose (dose 5) as an efficacious dose.

We also conducted additional simulation studies to evaluate how sensitive the performance of our design is to the different choices of priors for the parameters of interest. Non-informative prior distributions are specified since elicitation in this context is difficult, therefore, the estimation of the parameters will largely depend on data. We thus tested different choices for non-informative priors and evaluated the sensitivity of the performance of our design. We picked scenario 5 and a similar conclusion could be drawn for all other considered scenarios. In scenario 5, we specified independent normal priors with mean 0 and precision 0.001 (the inverse of the variance) for parameters $\beta_0, \beta_2, a_0, a_1, a_2, \gamma$. For all other parameters, we used uniform priors from 0 to 1000. We constructed scenario (C) and (D) where in scenario (C), parameters $\beta_0, \beta_2, a_0, a_1, a_2, \gamma$ have normal priors with mean 0 and precision 0.01 and all other parameters follow uniform prior Uniform[0,100], while in scenario (D), the precisions of normal priors become 0.0001 and the uniform priors become Uniform[0,10000]. All other settings of scenario (C) and (D) remain the same as scenario 5. The simulation results are given in Table 5.

The results are quite stable for different choices of non-informative priors as shown in Table 5. Above 99% of the trials picked the dose 3, the efficacy peak, as an efficacious dose for all three scenarios.

A.4: R Code for Implementing MCMC

In this section, we provide the core R code for implementing MCMC to draw the posterior sampling using JAGS.

```
model.file <- function()
{
```

```

beta <- c(beta_other[1], beta_dose, beta_other[2])

for(k in 1:Nsub){

  u[k] ~ dnorm(0, tau_u)

}

for(i in 1:N1){

  y[i] ~ dnorm(mu[i], tau_e)

  mu[i] <- inprod(X_y[i, ], beta) + inprod(W_y[i, ], u)

}

for(j in 1:N2){

  e[j] ~ dnorm(mu_e[j], tau_f)

  mu_e[j] <- inprod(X_e[j, ], alpha) + gamma0 * u[keeppeff.ind[j]]

}

beta_other ~ dmnorm(p1_beta_other[], p2_beta_other[, ])

beta_dose ~ dunif(p1_beta_dose, p2_beta_dose)

alpha ~ dmnorm(p1_alpha[], p2_alpha[, ])

gamma0 ~ dnorm(p1_gamma0, p2_gamma0)

tau_e ~ dunif(p1_tau_e, p2_tau_e)

tau_u ~ dunif(p1_tau_u, p2_tau_u)

tau_f ~ dunif(p1_tau_f, p2_tau_f)

}

```

In Appendix A.3, we tested the sensitivity of the performance of our design to different choices of non-informative priors, and the results are quite stable. Different starting values also gave similar results. We also examined the traceplots of all the parameters of our interests, and they mixed well. The posterior samplings also provided desirable coverage. In summary, the Bayesian modeling performs well and our joint models act as a good working model to guide the dose-escalation/recommendation process.

References

- Bekele BN and Shen Y (2005). A bayesian approach to jointly modeling toxicity and biomarker expression in a phase i/ii dose-finding trial. *Biometrics*, 61(2), 344–354.
- Bekele BN and Thall PF (2004). Dose-finding based on multiple toxicities in a soft tissue sarcoma trial. *Journal of the American Statistical Association*, 99(465), 26–35.
- Braun TM, Thall PF, Nguyen H, and de Lima M (2007). Simultaneously optimizing dose and schedule of a new cytotoxic agent. *Clinical Trials*, 4(2), 113–124. [PubMed: 17456511]
- Dragalin V and Fedorov V (2006). Adaptive designs for dose-finding based on efficacy and toxicity response. 136, 1800–1823.
- Ezzalfani M, Zohar S, Qin R, Mandrekar SJ, and Deley M-CL (2013). Dose-finding designs using a novel quasi-continuous endpoint for multiple and L'toxicities. *Statistics in Medicine*, 32(16), 2728–2746. [PubMed: 23335156]
- Fedorov V, Wu Y, and Zhang R (2012). Optimal dose and finding designs with correlated continuous and discrete responses. *Statistics in Medicine*, 31(3), 217–234. [PubMed: 22162014]
- Hornik K, Leisch F, and Zeileis A (2003). Jags: A program for analysis of bayesian graphical models using gibbs sampling. In *Proceedings of DSC*, volume 2, pages 1–1.
- Houede N, Thall PF, Nguyen H, Paoletti X, and Kramar A (2010). Utility-based optimization of combination therapy using ordinal toxicity and efficacy in phase i/ii trials. *Biometrics*, 66(2), 532–540. [PubMed: 19673865]
- Lee SM, Hershman DL, Martin P, Leonard JP, and Cheung YK (2012). Toxicity burden score: a novel approach to summarize multiple toxic effects. *Annals of Oncology*, 23(2), 537–541. [PubMed: 21536663]
- Legedza AT and Ibrahim JG (2000). Longitudinal design for phase i clinical trials using the continual reassessment method. *Controlled Clinical Trials*, 21(6), 574–588. [PubMed: 11146151]
- R Core Team (2016). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria.
- Thall PF and Cook JD (2004). Dose-finding based on efficacy and toxicity trade-offs. *Biometrics*, 60(3), 684–693. [PubMed: 15339291]
- Wang CY, Wang N, and Wang S (2000). Regression analysis when covariates are regression parameters of a random effects model for observed longitudinal measurements. *Biometrics*, 56(2), 487–495. [PubMed: 10877308]
- Yin J, Qin R, Ezzalfani M, Sargent DJ, and Mandrekar SJ (2017). A bayesian dose-finding design incorporating toxicity data from multiple treatment cycles. *Statistics in Medicine*, 36(1), 67–80. [PubMed: 27633877]

Figure 1:
Dose-efficacy patterns and the distribution of efficacy outcome for each dose in each pattern.

Table 1:

Simulation results for scenario 1 to 5: $\mathbb{P}_{\text{alloc}}$, the percentage of dose allocation, $\mathbb{P}_{\text{recom}}$, the percentage of dose recommendation, where we recommend the lowest (safest) dose that is also efficacious, and $\mathbb{P}_{\text{effy}}$, the percentage of dose being efficacious and safe. mnTTP represents the mean nTTP score while pDLT refers to the probability of DLT event. The target toxicity dose at cycle 1 of the treatment is dose 5, with flat cycle effect.

	Dose Levels						None
	1	2	3	4	5	6	
mnTTP(cycle 1)	0.046	0.054	0.108	0.183	0.280	0.359	
mnTTP(cycle 2 through 6)	0.046	0.054	0.108	0.183	0.280	0.359	
pDLT	0.008	0.011	0.064	0.195	0.330	0.446	
Scenario 1							
Mean Efficacy	0.1	0.2	0.3	0.4	0.7	0.9	
$\mathbb{P}_{\text{alloc}}$	16.4	17.3	18.2	21.1	20.9	6.2	
$\mathbb{P}_{\text{recom}}$	1.3	0.1	1.8	11.1	72.0	13.7	0.0
$\mathbb{P}_{\text{effy}}$	1.3	0.2	2.1	13.7	11.1	15.5	0.0
Scenario 2							
Mean Efficacy	0.5	0.5	0.5	0.5	0.5	0.5	
$\mathbb{P}_{\text{alloc}}$	18.2	18.3	19.0	20.7	18.2	5.5	
$\mathbb{P}_{\text{recom}}$	68.5	17.8	6.2	2.1	3.3	2.1	0.0
$\mathbb{P}_{\text{effy}}$	68.5	71.1	69.8	69.6	62.4	11.3	0.0
Scenario 3							
Mean Efficacy	0.2	0.5	0.8	0.8	0.8	0.8	
$\mathbb{P}_{\text{alloc}}$	15.0	17.6	20.0	22.9	19.2	5.4	
$\mathbb{P}_{\text{recom}}$	0.0	0.2	41.1	53.6	4.5	0.6	0.0
$\mathbb{P}_{\text{effy}}$	0.0	0.2	41.3	94.5	79.5	8.3	0.0
Scenario 4							
Mean Efficacy	0.8	0.6	0.4	0.3	0.2	0.1	
$\mathbb{P}_{\text{alloc}}$	21.7	19.7	18.0	19.0	16.7	4.9	
$\mathbb{P}_{\text{recom}}$	99.7	0.2	0.0	0.0	0.0	0.1	0.0
$\mathbb{P}_{\text{effy}}$	99.7	12.7	2.8	0.1	0.0	0.4	0.0
Scenario 5							
Mean Efficacy	0.3	0.6	0.8	0.6	0.3	0.1	
$\mathbb{P}_{\text{alloc}}$	16.5	19.6	21.0	21.7	16.7	4.7	

	Dose Levels						
	1	2	3	4	5	6	None
$\mathbb{P}_{\text{recom}}$	3.2	40.8	55.9	0.0	0.0	0.0	0.1
$\mathbb{P}_{\text{effy}}$	3.2	43.9	99.7	58.5	0.8	0.0	0.1

Table 2:

Simulation results for scenario 6 to 10: $\mathbb{P}_{\text{alloc}}$, the percentage of dose allocation, $\mathbb{P}_{\text{recom}}$, the percentage of dose recommendation, where we recommend the lowest (safest) dose that is also efficacious, and $\mathbb{P}_{\text{effy}}$, the percentage of dose being efficacious and safe. mnTTP represents the mean nTTP score while pDLT refers to the probability of DLT event. The target toxicity dose at cycle 1 of the treatment is dose 3, with flat cycle effect.

	Dose Levels						None
	1	2	3	4	5	6	
mnTTP(cycle 1)	0.108	0.183	0.280	0.359	0.409	0.433	
mnTTP(cycle 2 through 6)	0.108	0.183	0.280	0.359	0.409	0.433	
pDLT	0.064	0.195	0.330	0.446	0.513	0.558	
Scenario 6							
Mean Efficacy	0.1	0.2	0.3	0.4	0.7	0.9	
$\mathbb{P}_{\text{alloc}}$	28.4	40.5	26.6	4.3	0.2	0.0	
$\mathbb{P}_{\text{recom}}$	27.9	40.7	28.9	2.3	0.0	0.1	0.1
$\mathbb{P}_{\text{effy}}$	27.9	63.9	59.6	3.2	0.0	0.1	0.1
Scenario 7							
Mean Efficacy	0.5	0.5	0.5	0.5	0.5	0.5	
$\mathbb{P}_{\text{alloc}}$	30.3	40.6	25.1	3.8	0.2	0.0	
$\mathbb{P}_{\text{recom}}$	75.1	19.3	3.9	1.3	0.1	0.3	0.0
$\mathbb{P}_{\text{effy}}$	75.1	75.2	43.0	2.3	0.2	0.3	0.0
Scenario 8							
Mean Efficacy	0.2	0.5	0.8	0.8	0.8	0.8	
$\mathbb{P}_{\text{alloc}}$	25.9	41.6	28.1	4.2	0.2	0.0	
$\mathbb{P}_{\text{recom}}$	2.4	36.8	59.5	1.1	0.1	0.0	0.1
$\mathbb{P}_{\text{effy}}$	2.4	38.6	62.0	1.8	0.1	0.0	0.1
Scenario 9							
Mean Efficacy	0.8	0.6	0.4	0.3	0.2	0.1	
$\mathbb{P}_{\text{alloc}}$	33.3	40.0	23.0	3.5	0.2	0.0	
$\mathbb{P}_{\text{recom}}$	99.2	0.7	0.0	0.0	0.0	0.0	0.1
$\mathbb{P}_{\text{effy}}$	99.2	15.6	0.8	0.3	0.0	0.0	0.1
Scenario 10							
Mean Efficacy	0.3	0.6	0.8	0.6	0.3	0.1	
$\mathbb{P}_{\text{alloc}}$	25.8	43.1	26.7	4.0	0.3	0.1	

	Dose Levels						
	1	2	3	4	5	6	None
$\mathbb{P}_{\text{recom}}$	2.6	49.4	46.7	0.9	0.3	0.0	0.1
$\mathbb{P}_{\text{effy}}$	2.6	51.3	63.0	2.9	0.3	0.0	0.1

Table 3:

Simulation results for scenario 11 to 14: $\mathbb{P}_{\text{alloc}}$, the percentage of dose allocation, $\mathbb{P}_{\text{recom}}$, the percentage of dose recommendation, where we recommend the lowest (safest) dose that is also efficacious, and $\mathbb{P}_{\text{effy}}$, the percentage of dose being efficacious and safe. mnTTP represents the mean nTTP score while pDLT refers to the probability of DLT event. In Scenario 11, all doses are too toxic, with flat cycle effect; In Scenario 12, only dose 1 is non-toxic, with flat cycle effect; Scenario 13/14 has an increasing/decreasing cycle effect, whose target toxicity dose at cycle 1 of the treatment is dose 5. Scenario 11–14 share a parabolic efficacy structure.

	Dose Levels						
	1	2	3	4	5	6	None
Efficacy Structures							
Mean Efficacy	0.3	0.6	0.8	0.6	0.3	0.1	
Scenario 11							
mnTTP(cycle 1 through 6)	0.359	0.409	0.433	0.439	0.452	0.465	
pDLT	0.446	0.513	0.558	0.559	0.588	0.613	
$\mathbb{P}_{\text{alloc}}$	88.0	12.0	0.0	0.0	0.0	0.0	
$\mathbb{P}_{\text{recom}}$	0.0	0.0	0.0	0.0	0.0	0.0	100.0
$\mathbb{P}_{\text{effy}}$	0.0	0.0	0.0	0.0	0.0	0.0	100.0
Scenario 12							
mnTTP(cycle 1 through 6)	0.183	0.409	0.433	0.439	0.452	0.465	
pDLT	0.195	0.513	0.558	0.559	0.588	0.613	
$\mathbb{P}_{\text{alloc}}$	79.4	20.6	0.0	0.0	0.0	0.0	
$\mathbb{P}_{\text{recom}}$	94.6	0.1	0.0	0.0	0.0	0.0	5.3
$\mathbb{P}_{\text{effy}}$	94.6	0.1	0.0	0.0	0.0	0.0	5.3
Scenario 13							
mnTTP(cycle 1)	0.046	0.054	0.108	0.183	0.280	0.359	
mnTTP(cycle 2)	0.054	0.063	0.124	0.206	0.303	0.381	
mnTTP(cycle 3)	0.063	0.073	0.142	0.230	0.326	0.404	
mnTTP(cycle 4)	0.073	0.085	0.161	0.255	0.349	0.426	
mnTTP(cycle 5)	0.085	0.097	0.181	0.280	0.373	0.448	
mnTTP(cycle 6)	0.097	0.110	0.203	0.307	0.396	0.469	
$\mathbb{P}_{\text{alloc}}$	17.0	20.4	22.7	22.3	13.8	3.8	
$\mathbb{P}_{\text{recom}}$	1.6	39.7	58.5	0.1	0.0	0.0	0.1
$\mathbb{P}_{\text{effy}}$	1.6	41.3	99.6	57.6	0.0	0.0	0.1
Scenario 14							
mnTTP(cycle 1)	0.046	0.054	0.108	0.183	0.280	0.359	
mnTTP(cycle 2)	0.039	0.046	0.093	0.162	0.257	0.336	
mnTTP(cycle 3)	0.032	0.039	0.080	0.141	0.234	0.314	

	Dose Levels						None
	1	2	3	4	5	6	
mnTTP(cycle 4)	0.027	0.033	0.068	0.123	0.213	0.291	
mnTTP(cycle 5)	0.022	0.027	0.057	0.106	0.192	0.269	
mnTTP(cycle 6)	0.018	0.023	0.047	0.090	0.171	0.247	
$\mathbb{P}_{\text{alloc}}$	16.1	19.0	20.9	21.3	17.1	5.6	
$\mathbb{P}_{\text{recom}}$	2.8	39.8 ₃₀	57.1	0.1	0.1	0.0	0.1
$\mathbb{P}_{\text{effy}}$	2.8	42.5	99.4	62.3	0.8	0.0	0.1

Table 4:

Simulation results for scenario (A) and (B): $\mathbb{P}_{\text{alloc}}$, the percentage of dose allocation, $\mathbb{P}_{\text{recom}}$, the percentage of dose recommendation, where we recommend the lowest (safest) dose that is also efficacious, and $\mathbb{P}_{\text{effy}}$, the percentage of dose being efficacious and safe. mnTTP represents the mean nTTP score while pDLT refers to the probability of DLT event. The target toxicity dose at cycle 1 of the treatment is dose 5, with flat cycle effect.

	Dose Levels						None
	1	2	3	4	5	6	
mnTTP(cycle 1)	0.046	0.054	0.108	0.183	0.280	0.359	
mnTTP(cycle 2 through 6)	0.046	0.054	0.108	0.183	0.280	0.359	
pDLT	0.008	0.011	0.064	0.195	0.330	0.446	
Scenario (A)							
Mean Efficacy	0.7	0.8	0.7	0.5	0.3	0.1	
$\mathbb{P}_{\text{alloc}}$	19.9	20.7	20.7	20.1	14.8	3.8	
$\mathbb{P}_{\text{recom}}$	77.3	22.2	0.2	0.0	0.1	0.1	0.1
$\mathbb{P}_{\text{effy}}$	77.3	89.8	66.9	1.4	0.1	0.1	0.1
Scenario (B)							
Mean Efficacy	0.1	0.3	0.5	0.7	0.8	0.7	
$\mathbb{P}_{\text{alloc}}$	15.9	17.7	20.0	23.4	18.8	4.2	
$\mathbb{P}_{\text{recom}}$	0.0	0.0	4.9	48.7	43.0	3.4	0.0
$\mathbb{P}_{\text{effy}}$	0.0	0.0	4.9	53.6	86.2	8.4	0.0

Table 5:

Simulation results for scenario (C) and (D): $\mathbb{P}_{\text{alloc}}$, the percentage of dose allocation, $\mathbb{P}_{\text{recom}}$, the percentage of dose recommendation, where we recommend the lowest (safest) dose that is also efficacious, and $\mathbb{P}_{\text{effy}}$, the percentage of dose being efficacious and safe. mnTTP represents the mean nTTP score while pDLT refers to the probability of DLT event. The target toxicity dose at cycle 1 of the treatment is dose 5, with flat cycle effect.

	Dose Levels						
	1	2	3	4	5	6	None
mnTTP(cycle 1)	0.046	0.054	0.108	0.183	0.280	0.359	
mnTTP(cycle 2 through 6)	0.046	0.054	0.108	0.183	0.280	0.359	
pDLT	0.008	0.011	0.064	0.195	0.330	0.446	
Scenario (C)							
Mean Efficacy	0.3	0.6	0.8	0.6	0.3	0.1	
$\mathbb{P}_{\text{alloc}}$	16.8	21.1	22.2	22.6	14.4	29	
$\mathbb{P}_{\text{recom}}$	1.3	39.6	59.1	0.0	0.0	0.0	0.0
$\mathbb{P}_{\text{effy}}$	1.3	40.8	99.9	51.3	0.5	0.0	0.0
Scenario (D)							
Mean Efficacy	0.3	0.6	0.8	0.6	0.3	0.1	
$\mathbb{P}_{\text{alloc}}$	16.3	19.5	21.0	21.0	16.9	5.3	
$\mathbb{P}_{\text{recom}}$	2.3	43.0	54.3	0.1	0.0	0.1	0.2
$\mathbb{P}_{\text{effy}}$	2.3	45.0	99.3	62.3	1.0	0.1	0.2
Scenario 5							
Mean Efficacy	0.3	0.6	0.8	0.6	0.3	0.1	
$\mathbb{P}_{\text{alloc}}$	16.5	19.6	21.0	21.7	16.7	4.7	
$\mathbb{P}_{\text{recom}}$	3.2	40.8	55.9	0.0	0.0	0.0	0.1
$\mathbb{P}_{\text{effy}}$	3.2	43.9	99.7	58.5	0.8	0.0	0.1