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Adaptive Designs for Identifying Optimal Biological Dose for Molecularly Targeted Agents

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Abstract

Background—Traditionally, the purpose of a dose-finding design in cancer is to find the maximum tolerated dose based solely on toxicity. However, for molecularly targeted agents, little toxicity may arise within the therapeutic dose range and the dose-response curves may not be monotonic. This challenges the principle that more is better, which is widely accepted for conventional chemotherapy.

Methods—We propose three adaptive dose-finding designs for trials evaluating molecularly targeted agents, for which the dose-response curves are unimodal or plateaued. The goal of these designs is to find the optimal biological dose, which is defined as the lowest dose with the highest rate of efficacy while safe. The first proposed design is parametric and assumes a logistic dose-efficacy curve for dose finding; the second design is nonparametric and uses the isotonic regression to identify the optimal biological dose; and the third design has the spirit of a “semiparametric” approach by assuming a logistic model only locally around the current dose.

Results—We conducted extensive simulation studies to investigate the operating characteristics of the proposed designs. Simulation studies show that the nonparametric and semiparametric designs have good operating characteristics for finding the optimal biological dose.

Limitations—The proposed designs assume a binary endpoint. Extension of the proposed designs to ordinal and time-to-event endpoints worth further investigation.

Conclusion—Among the three proposed designs, the nonparametric and semiparametric designs yield consistently good operating characteristics and thus are recommended for practical use. The software to implement these two designs is available for free download at <http://odin.mdacc.tmc.edu/~yyuan/>.

Keywords

dose-finding; optimal biological dose; Bayesian adaptive design; isotonic regression; molecularly targeted agent

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1 Introduction

Traditionally, the primary goal of a phase I cancer clinical trial for a cytotoxic drug is to identify the maximum tolerated dose (MTD) of the new agent, based on the assumption that both efficacy and toxicity increase monotonically with the dose. The recent development of novel molecularly targeted agents has challenged this paradigm as the monotonic assumption of dose-toxicity and dose-efficacy relationships may not hold. Molecularly targeted agents are developed to modulate specific aberrant pathways in cancer cells while sparing normal tissue. As a result, the toxicities are often expected to be minimal within the therapeutic dose range and the dose-efficacy curves may not follow monotonic patterns [1, 2, 3, 4]. For example, Postel-Vinay et al.[5] investigated the dose-efficacy relationship of monotherapy based on 135 patients enrolled in phase I trials at the Royal Marsden Hospital from 5 January 2005 to 6 June 2006. The patients were classified into three cohorts A, B and C according to the dose received as a percentage of the MTD (0-33%, 34-65%, >66%). The efficacy endpoint was the non-progression rate, i.e., complete/partial response or stable disease for at least 3 months. The monotherapy demonstrated a nonmonotonic dose-efficacy relationship: the non-progression rate for the patients in cohorts A, B and C were 21%, 50% and 31% after receiving the treatments. That is, the median dose rather than the highest dose (i.e., cohort C) leads to the highest efficacy.

The primary goal of a dose-finding design for molecularly targeted agents is to find the optimal biological dose, which can be defined in different ways according to the goal of the clinical trial. In this article, we define the optimal biological dose as the lowest dose that has the highest efficacy rate while simultaneously safeguarding patients, i.e., the dose at the beginning of the plateau of the dose-efficacy curve. This definition has been used by some existing trial designs [6, 7]. Due to the nonmonotonic dose-efficacy relationship, the optimal biological dose is not always the highest dose and may appear in the middle of the investigational dose range. This challenges the principle that more is better, which is widely accepted for conventional chemotherapy [8]. In practice, the dose-efficacy curves for molecularly targeted agents are often expected to be unimodal (or umbrella-shaped[9]) or to plateau within the therapeutic dose range. Although more complicated multimodal dose-efficacy curves are possible, they rarely occur within the therapeutic dose range.

In contrast to the rich body of literature on phase I dose-finding trial designs for cytotoxic agents, research on phase I trial designs for molecularly targeted agents is limited [10, 11]. Under the assumption of minimal toxicity, Hunsberger et al. [6] proposed the slope-sign design to find the biological adequate dose for molecularly targeted agents. The goal of the slope-sign design is to find a biologically “adequate” dose, defined as either a dose that yields a specific (high) response rate or a dose in the plateau, while using few patients. The slope-sign design directs the dose finding based on the sign of the estimate of the slope of the dose-efficacy curve using the efficacy data collected from a certain number of adjacent dose levels. If the sign of the estimate of the slope is positive, the dose level is escalated; otherwise, the trial is terminated and the dose level with the highest efficacy response rate is recommended as the biological adequate dose. This slope-sign design is simple, and requires small sample size because it terminates the trial once the estimate of the slope is negative.

In this article, we propose three new dose-finding designs to search for the optimal biological dose of molecularly targeted agents. Our first design models the entire dose-efficacy curve with a Bayesian logistic regression and adaptively assigns patients based on the model estimates. To improve the robustness of the design, the second design fits the dose-efficacy curve with an isotonic regression without making any parametric assumption as to the shape of the curve. The third proposed design has the spirit of a “semiparametric” approach by assuming a logistic model only locally around the current dose.

The rest of this article is organized as follows. In Section 2 we propose three new designs. In Section 3 we carry out comprehensive simulation studies to evaluate the performance of the proposed designs. Based on the simulation studies, we provide concluding comments and recommendations in Section 4.

2 Dose-finding methods

2.1 Toxicity monitoring

Compared to conventional cytotoxic agents, toxicity is often of less concern for molecularly targeted agents and the dose finding is mainly driven by efficacy. However, it is still important to monitor toxicity during the dose finding to ensure patients’ safety.

Let $(d_1, \dots, d_J)$ denote a set of J pre-specified increasing doses for the molecularly targeted agent under investigation and q_j denote the toxicity probability of dose level j . Assuming that x_j out of n_j patients experienced toxicity at dose level j , we model the toxicity of each dose level independently using a beta-binomial model

$$\begin{aligned} x_j &\sim \text{binom}(n_j, q_j) \\ q_j &\sim \text{beta}(a, b) \end{aligned}$$

where $\text{binom}(\cdot)$ and $\text{beta}(\cdot)$ denote binomial and beta distributions, respectively, and a and b are hyperparameters.

Let ϕ denote the target toxicity upper bound, the safety of dose level j can be monitored by the posterior probability $\Pr(q_j > \phi | n_j, x_j)$. Specifically, we define the admissible set $\mathcal{A}$ as a set of doses satisfying the following safety rule:

$$\mathcal{A} = \left\{ j : \widetilde{Pr}(q_j > \phi | n_j, x_j) < C_T, j=1, \dots, J \right\} \quad (1)$$

where $\widetilde{Pr}(q_j > \phi | n_j, x_j)$ is the isotonic transformed posterior probability $\Pr(q_j > \phi | n_j, x_j)$ based on the pool adjacent violators algorithm (PAVA) [13, 14], and C_T is a pre-specified toxicity threshold. The isotonic transformation is used to impose dose-toxicity monotonicity and borrow information across dose levels. During the dose finding, we restrict dose assignment and selection within the admissible set $\mathcal{A}$, thereby protecting patients from overly toxic doses. Before treating any patient in the trial, all investigational doses should be in $\mathcal{A}$ and open for testing. This can be done by choosing the values of hyperparameters a

and b such that $Beta(\varphi; a, b) = 1 - C_T + \delta$, where δ is a small positive number, e.g., $\delta = 0.05$. That is, *a priori*, all doses just satisfy the safety rule given in (1).

2.2 Logistic design

We assume that efficacy is recorded as a binary outcome. Let p_j denote the probability of efficacy at dose level j . Because the dose-efficacy curve for a molecularly targeted agent is often non-monotonic, an intuitive method for fitting this curve is the logistic regression with a quadratic term, which can be written as

$$\log(p_j / (1 - p_j)) = \alpha + \beta d_j + \gamma d_j^2, \quad j=1, \dots, J.$$

Assume that at dose level j , y_j out of n_j patients experienced efficacy, the likelihood for the observed data $\mathcal{D} = \{y_j, n_j; j=1, \dots, J\}$ is given by

$$L(\mathcal{D} | \alpha, \beta, \gamma) \propto \prod_{j=1}^J \left(\frac{e^{\alpha + \beta d_j + \gamma d_j^2}}{1 + e^{\alpha + \beta d_j + \gamma d_j^2}} \right)^{y_j} \left(\frac{1}{1 + e^{\alpha + \beta d_j + \gamma d_j^2}} \right)^{n_j - y_j};$$

and the posterior of unknown regression parameters α , β and γ is

$f(\alpha, \beta, \gamma | \mathcal{D}) \propto f(\alpha, \beta, \gamma) L(\mathcal{D} | \alpha, \beta, \gamma)$ where $f(\alpha, \beta, \gamma)$ is the prior distribution of α , β and γ .

Similar as Gelman et al [12], we specify a Cauchy prior distribution with center 0 and scale 10 for α , i.e., $Cauchy(0, 10)$; and two independent Cauchy priors $Cauchy(0, 2.5)$ for β and γ , respectively. The posterior distribution can be easily sampled based on the Markov chain Monte Carlo (MCMC) method and used for guiding dose escalation and de-escalation.

The proposed Bayesian logistic model-based dose-finding method can be summarized as follows:

1. The first cohort of patients is treated at the lowest dose d_1 , or at the physician-specified dose.
2. At the current dose level j , based on the toxicity outcomes, applying safety rule (1) to find the admissible set $\mathcal{A}$.
3. Identify the dose level j^* which has the highest posterior estimate of efficacy probability within $\mathcal{A}$. If $j^* > j$, the dose level is escalated to $j+1$; if $j^* < j$, the dose level is de-escalated to $j-1$; otherwise, the dose level remains at j .
4. Once the maximum sample size is reached, the dose that has the highest estimate of efficacy probability within $\mathcal{A}$ is selected as the optimal biological dose.

This parametric design is straightforward and easy to implement, but may be sensitive to model misspecifications. In the subsection that follows, we propose a nonparametric approach based on the isotonic regression.

2.3 Isotonic design

Within conventional phase I trial designs for cytotoxic agents, various isotonic designs have been proposed to find the MTD without making any parametric assumption beyond the monotonicity on the dose-toxicity curve. However, the existing isotonic designs cannot be directly used to find the optimal biological dose because in order to conduct isotonic regression, these designs require that the dose-response order constraint is known (e.g., monotonicity), which may not be satisfied for molecularly targeted agents.

Specifically, for the molecularly targeted agents with unimodal or plateaued dose-efficacy curves, our goal is to find the optimal biological dose, the dose level j^* such that

$$p_1 \leq \cdots \leq p_{j^*} \geq \cdots \geq p_J. \quad (2)$$

In other words, before we identify the optimal biological dose, the order constraint (2) is actually unknown. To overcome this difficulty, we take the approach of double-sided isotonic regression [15]. In this approach, we first enumerate all J possible locations of j^* , $j^* = 1, \dots, J$. Given each of the locations, say $j^* = k$, the isotonic estimates $\{\hat{p}_j^{(k)}; j=1, \dots, J\}$ can be obtained by fitting two separate standard isotonic regressions: one for $p_1, \dots, p_{j^*}$ with the constraint $p_1 \leq \cdots \leq p_{j^*}$ and the other one for $p_{j^*+1}, \dots, p_J$ with the constraint $p_{j^*+1} \geq \cdots \geq p_J$. Each of these two isotonic regressions can be done using the PAVA algorithm [13, 14], which yields isotonic estimates by replacing any adjacent observations violated the monotonicity assumption with their (weighted) average.

After applying this procedure to each of J possible locations of j^* , we obtain J sets of possible isotonic estimates $\{\hat{p}_j^{(k)}\}, k=1, \dots, J$. We select as the final isotonic estimates $\{\hat{p}_j\} = \{\hat{p}_j^{(k^*)}\}$, the set of isotonic estimates with the smallest sum of the square error, i.e.,

$$k^* = \underset{k \in (1, \dots, J)}{\operatorname{argmin}} \sum_{j=1}^J \left(\hat{p}_j^{(k)} - \frac{y_k}{n_k} \right)^2$$

Our isotonic design can be described as follows:

1. Treat the first cohort of patients at the lowest dose d_1 , or at the physician-specified dose.
2. At the current dose level j , based on the toxicity outcomes, applying safety rule (1) to find the admissible set $\mathcal{A}$.
3. Identify the dose level j^* that has the highest isotonic estimate of efficacy probability among the tried doses within $\mathcal{A}$. Where there are ties, we select j^* as the lowest dose level among the ties. Let j^f denote the highest dose level tried thus far. If $j^* > j$, we escalate the dose level to $j+1$; if $j^* < j$, we de-escalate the dose level to $j-1$; if $j^* = j = j^f$, we escalate the dose level to $j+1$ given that $j+1$ is in $\mathcal{A}$, otherwise we retain the dose level j .

4. Once the maximum sample size is reached, we select the lowest dose that has the highest estimate of efficacy probability within $\mathcal{A}$ as the optimal biological dose.

One limitation of the isotonic regression is that it cannot estimate the efficacy probabilities for the untried doses at which no patients have been treated. Therefore, during the trial conduct, when the dose with the highest estimate of efficacy is the highest tried dose (i.e., $j^* = j = j^J$), there is no information to determine whether we have achieved the maximum point of the dose-efficacy curve or not. To overcome this limitation, in the above dose-finding algorithm, when $j^* = j = j^J$ we automatically escalate the dose level to further explore the dose-efficacy curve and search the maximum point, given that the next higher dose level is safe (i.e., within the admissible set $\mathcal{A}$).

2.4 Local logistic design

We have proposed the L-logistic design. In the L-logistic design, we fit a local Bayesian linear logistic model based on the local data $\mathcal{D}_j = \{y_k, n_k; k = j - l + 1, \dots, j\}$ collected from the current dose level j up to the previous $l - 1$ dose levels as,

$$\log(p_k / (1 - p_k)) = \alpha + \beta d_k, \quad k = j - l + 1, \dots, j.$$

$$\alpha \sim \text{Cauchy}(0, 10), \quad \beta \sim \text{Cauchy}(0, 2.5),$$

where $2 \leq l \leq J$. We take the weakly informative Cauchy prior distribution for α and β , as described in Section 2.1. We recommend $l = 2$ because we find that increasing the value of l yields similar or even worse operating characteristics in our simulation studies. One may question how reliable the estimation of the parameters for the local logistic model is based on data observed from 2 doses. We note that for the purpose of dose finding, our goal here is not to obtain precise estimates of the model parameters, but to capture the local trend (e.g., increasing or decreasing) of the dose-response curve for directing dose escalation/deescalation. As long as the estimates correctly identify the trend of the curve (i.e., the sign of the slope), they lead to appropriate dose escalation and deescalation. Simulation studies in Section 3 show that the L-logistic design based on two local doses yields good operating characteristics, suggesting that the estimation using local data is adequately stable to identify the local trend of the dose-response curve.

To direct the dose escalation/de-escalation in a trial, we calculate the posterior probability $Pr(\beta > 0 | \mathcal{D}_j)$ based on the local logistic model. Let C_{E1} and C_{E2} be pre-specified efficacy cutoffs and $C_{E1} > C_{E2}$. If $Pr(\beta > 0 | \mathcal{D}_j) > C_{E1}$ (i.e., the current trend of the dose-efficacy curve is increasing), we escalate the dose because the next higher dose level is expected to have higher efficacy. In contrast, if $Pr(\beta > 0 | \mathcal{D}_j) < C_{E2}$, which indicates a decreasing dose-efficacy curve, we de-escalate the dose because the lower dose level is expected to have higher efficacy. Otherwise, we stay at the current dose to accumulate more data. The values of C_{E1} and C_{E2} can be calibrated by simulation to obtain good operating characteristics. Typically, C_{E1} should be larger than C_{E2} by a certain reasonable margin, such as 10% to

20%. By using the posterior probability $Pr(\beta > 0 | \mathcal{D}_j)$ as the criterion of dose escalation, we automatically account for the uncertainty associated with parameter estimation.

The dose-finding algorithm for the proposed L-logistic design is described as follows:

1. Starting from the lowest I dose levels, treat one cohort of patients at each dose levels.
2. At the current dose level j , based on the toxicity outcomes, applying safety rule (1) to find the admissible set $\mathcal{A}$.
3. Based on the efficacy outcomes from the current and previous $I-1$ dose levels, calculate the posterior probability $Pr(\beta > 0 | \mathcal{D}_j)$. If $Pr(\beta > 0 | \mathcal{D}_j) > C_{E1}$, the dose level is escalated to $j+1$ when $j+1$ is in $\mathcal{A}$ and otherwise retain at j ; if $Pr(\beta > 0 | \mathcal{D}_j) < C_{E2}$, the dose level is de-escalated to $j-1$; otherwise, i.e., $C_{E2} \leq Pr(\beta > 0 | \mathcal{D}_j) \leq C_{E1}$, the dose level j is retained.
4. Once the maximum sample size is reached, based on all the observed data, we carry out a double-sided isotonic regression and select the lowest dose that has the highest estimate of the efficacy probability as the optimal biological dose.

One potential problem of the above dose-finding algorithm is that the dose movement may bounce back and forth between dose levels j and $j+1$ when the dose level j is the maximum point of the dose-efficacy curve. To avoid this problem, before conducting any dose escalation, we will determine whether $Pr(\beta > 0 | \mathcal{D}_{j+1}) < C_{E2}$ whenever the dose level $j+1$ has been used to treat any patients. If $Pr(\beta > 0 | \mathcal{D}_{j+1}) < C_{E2}$, indicating that the dose level j is the maximum point of the curve, we will retain the current dose level. The values of C_{E1} and C_{E2} are calibrated according to the desirable operating characteristics.

3 Simulation studies

We investigated the operating characteristics of the proposed designs through simulation studies under eight efficacy and toxicity scenarios, as listed in Table 1. We considered five dose levels and started the trials at the lowest dose level. We assumed a target toxicity upper bound of $\phi = 0.3$, a toxicity threshold of $C_T = 0.8$ and a maximum sample size of 30 in cohorts of size 3. Under each scenario, we simulated 5,000 trials. For the L-logistic design, we specified efficacy cutoffs $C_{E1} = 0.4$ and $C_{E2} = 0.3$ according to the calibration study. We used two adjacent doses (i.e., $I = 2$) to fit the local logistic model in the proposed L-logistic design. We examined other choices for the number of adjacent doses and found very similar performance levels (results not shown). We compared our designs with the slope-sign design and a traditional design. In the slope-sign design, three adjacent dose levels were used to estimate the slope. For fair comparison and to ensure that the slope-sign design targets the same dose (i.e., the optimal biological dose) as the proposed designs, in the slope-sign design, we used the method described in Section 2.1 for safety monitoring and let efficacy guide the dose escalation. Under the traditional approach, we first conducted the dose escalation using the conventional “3+3” design, and once the MTD is identified, we then

randomized the remaining patients between the MTD and the dose one level lower than the MTD.

Table 1 shows the simulation results, including the dose selection probability, the average percentage of patients treated at each dose level, the average percentages of patients experienced efficacy and toxicity, and the averaged sample size under the slope-sign, traditional, logistic, isotonic and L-logistic designs. In practice, besides the optimal biological dose, the other doses with high efficacy and low toxicity are often interested to investigators as well. Therefore, we also reported the selection percentage of the optimal biological dose region, which is defined as the two doses that have the highest response rates within the admissible set $\mathcal{A}$.

In scenario 1, the dose-efficacy curve is unimodal and the fourth dose level is the optimal biological dose with the highest efficacy rate and acceptable toxicity rate. The traditional design yield the lowest optimal biological dose selection percentage of 21.6%, The logistic and isotonic designs outperformed the slope-sign design and the traditional design with a selection percentage of 31.1% and 45.6% respectively. The L-logistic design performed best and selected the optimal biological dose 54.4% percent of the time, respectively. The three proposed designs also yielded the highest selection percentages of the optimal biological dose region, ranging from 69% to 79%. In addition, the proposed designs assigned higher percentages of patients to the optimal biological dose than the other two designs. Specifically, the percentages of patients allocated at the optimal biological dose under the logistic, isotonic and L-logistic designs were 6.6%, 12.2% and 13.9% higher than that under the slope-sign design and 6.9%, 12.5% and 14.2% higher than that under the traditional design. The slope-sign design had the smallest sample size and used less than half the number of patients than the other designs. In terms of toxicity, the slope-sign and traditional designs yielded lower percentages of toxicity than the proposed designs. This is partly due to the fact that the proposed designs assigned more patients to the optimal biological dose, which has a relatively high toxicity rate of 30%.

In scenario 2, the optimal biological dose was located at dose level 2 whereas the MTD was located at dose level 5. As the traditional design focuses on evaluating the doses around the MTD, it selected dose 4 as the optimal biological dose with a percentage of 40.0% whereas only 24.4% of selecting dose 2 as the optimal biological dose. All the other designs performed significantly better than the traditional design. Specifically, the isotonic and L-logistic designs outperformed other designs and selected dose level 2 with the percentages of 78.6% and 77.0%, respectively. The slope-sign and proposed designs yielded similar toxicity rates (about 6%) that are substantially lower than that of the traditional design (i.e., 12.6%).

Scenarios 3 to 4 also considered unimodal patterns, with different toxicity profiles. Across these two scenarios, the logistic design demonstrated a large variation: it yielded the highest optimal biological dose selection (51.8%) in scenario 4 but the lowest selection percentage (36.4%) in scenario 3, suggesting the sensitivity of this parametric approach. The proposed isotonic and L-logistic designs performed consistently and outperformed the slope-sign design and the traditional design across these two scenarios. The percentages of toxicity under these two designs were slightly higher than that of the slope-sign design. The slope-

sign design had the advantage of using less than half of the number of patients than other designs.

Scenarios 5 examined the performance of the designs when the dose-efficacy curve was monotonic. We can see that the proposed designs outperformed the other two designs with higher selection percentages of the optimal biological dose and higher efficacy rates. The slope-sign design was safer with a lower percentage of toxicity. Scenarios 6 to 8 simulated the cases in which efficacy initially increased with dose and then plateaued. In these cases, the target optimal biological dose was the lowest safety dose yielding the highest efficacy rate. Both the optimal biological dose and the MTD was located at dose level 2 in scenario 6. The slope-sign design performed worst and other designs yielded similar percentage of optimal biological dose selection in this scenario. In scenarios 7 and 8, all doses were safe and the optimal biological dose was located at dose levels 4 and 2, respectively. The isotonic and L-logistic designs outperformed the slope-sign design.

In summary, the proposed designs outperformed the slope-sign design and the traditional design in terms of selecting the target doses and allocating patients to the efficacious doses. The slope-sign design has the advantages of using smaller sample sizes and being safer, and provides a good design option when the sample size is of concern for the trial. Among the three proposed designs, the isotonic and L-logistic designs yielded consistently good operating characteristics, and are recommended for practical use. We do not recommend the parametric logistic design because of its sensitivity for the dose-efficacy and dose-toxicity curves.

In the proposed logistic and L-logistic designs, we adopted the weakly informative prior recommended by Gelman et al [12] for regression parameters β and γ . To assess the sensitivity to this prior, we examined the operating characteristics of the proposed methods under a tighter prior $\beta, \gamma \sim \text{Cauchy}(0, 1.25)$ and a more vague prior $\beta, \gamma \sim \text{Cauchy}(0, 5)$. Table 2 showed the results where the true efficacy rate was (0.4, 0.6, 0.8, 0.7, 0.55) and we assumed minimal toxicity with the dose level range. We can see that the results are rather stable across different priors, suggesting that our designs are not sensitive to the prior distribution.

4 Discussion

In this article, we have proposed three dose-finding trial designs, namely, the logistic, isotonic and L-logistic designs to determine the optimal biologic dose for molecularly targeted agents. The logistic design is purely parametrical; the isotonic design is based on the nonparametric isotonic regression; and the L-logistic assumes a logistic dose-response model only locally around the current dose. Simulation studies show that the isotonic and L-logistic designs have good operating characteristics for finding the optimal biological dose.

The proposed designs are appropriate for trials in which the efficacy outcome is binary and observable shortly after the initiation of the treatment. They cannot be applied directly to cases in which the efficacy outcome requires a long follow-up time to be assessed. To address this delayed outcome issue, a possible strategy is to treat the delayed efficacy

outcome as a missing data problem and using missing data methodology to handle it, future research in this direction is warranted.

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Table 1

The dose selection percentage, average percentage of patients treated at each dose level, average percentage of efficacy and toxicity, average percentage of promising dose selection and average sample size under the slope-sign, traditional, logistic, isotonic and L-logistic designs.

Design	Dose level					% of efficacy	% of toxicity	% of OBD region	# of sample
	1	2	3	4	5				
Scenario 1									
Slope-sign	True efficacy	0.2	0.4	0.6	0.8	0.55			
	True toxicity	0.08	0.12	0.2	0.3	0.4			
	Selection (%)	3.4	23.6	36.5	30.3	6.2			
Traditional	Patient(%)	26.3	26.3	26.3	14.1	7.0	47.4	17.8	66.8
	Selection (%)	22.8	27.4	27.0	21.6	1.1			12.0
	Patient(%)	32.4	26.1	21.8	13.8	5.9	44.4	16.5	48.6
Logistic	Selection (%)	12.8	11.4	39.9	31.1	4.7			
	Patients (%)	22.0	18.3	32.0	20.7	7.3	51.7	19.7	71.0
	Selection (%)	12.5	15.8	23.4	45.6	2.7			30.0
Isotonic	Patients (%)	21.0	22.0	21.0	26.3	9.7	52.0	20.3	69.0
	Selection (%)	6.8	10.0	24.9	54.4	3.9			30.0
	Patients (%)	16.7	19.3	20.3	28.0	15.7	54.3	22.3	79.3
Scenario 2									
Slope-sign	True efficacy	0.6	0.8	0.5	0.4	0.2			
	True toxicity	0.01	0.05	0.10	0.15	0.3			
	Selection (%)	13.3	59.1	23.9	3.5	0.2			
Traditional	Patient(%)	31.2	31.2	31.2	6.0	0.4	62.5	6.4	72.4
	Selection (%)	4.3	24.4	25.9	40.0	5.4			9.8
	Patient(%)	14.9	18.2	22.4	27.0	17.5	49.0	12.6	28.7
Logistic	Selection (%)	25.3	64.4	9.4	0.4	0.5			30.0
	Patients (%)	32.9	45.1	19.3	2.6	0.2	66.4	5.0	89.7
	Selection (%)	14.0	78.6	5.4	2.0	0.0			30.0
Isotonic	Patients (%)	21.8	58.4	15.0	4.1	0.7	68.6	5.6	92.6
	Selection (%)	11.4	77.0	9.1	2.5	0.0			30.0
	Patients (%)	14.9	49.3	22.4	9.8	3.8	64.4	6.2	88.4

Design	Dose level					% of efficacy	% of toxicity	% of OBD region	# of sample
	1	2	3	4	5				
Scenario 3									
Slope-sign	True efficacy	0.2	0.4	0.6	0.8	0.55			
	True toxicity	0.06	0.08	0.14	0.2	0.3			
	Selection (%)	5.7	16.5	29.4	38.7	9.7			
Traditional	Patient(%)	25.4	25.4	25.4	14.9	8.9	13.3	68.1	12.4
	Selection (%)	12.6	18.1	22.7	43.6	2.9			
	Patient(%)	23.2	21.4	21.4	21.0	12.9	50.0	66.3	30.0
Logistic	Selection (%)	12.3	9.2	35.4	36.4	6.7			
	Patients (%)	21.3	17.0	30.3	22.7	8.3	14.0	71.8	30.0
	Selection (%)	12.0	13.7	16.8	52.7	4.7			
Isotonic	Patients (%)	20.3	20.7	18.7	29.0	11.0	14.7	69.5	30.0
	Selection (%)	4.1	7.7	18.6	62.8	6.8			
	Patients (%)	14.3	18.0	18.3	30.0	19.3	55.7	81.4	30.0
Scenario 4									
Slope-sign	True efficacy	0.2	0.4	0.6	0.8	0.55			
	True toxicity	0.05	0.1	0.25	0.5	0.6			
	Selection (%)	4.1	22.9	48.1	23.0	1.9			
Traditional	Patient(%)	26.8	26.8	26.8	15.0	4.7	22.1	71.0	11.7
	Selection (%)	18.8	41.7	30.4	9.0	0.1			
	Patient(%)	30.5	33.9	25.3	8.9	1.4	20.5	72.1	30.0
Logistic	Selection (%)	12.5	21.1	51.8	12.2	2.3			
	Patients (%)	21.7	21.7	36.0	15.3	5.3	50.0	72.9	30.0
	Selection (%)	12.4	25.4	49.5	12.1	0.6			
Isotonic	Patients (%)	20.7	25.0	27.7	19.3	7.7	50.3	74.9	30.0
	Selection (%)	5.8	21.4	50.0	21.7	1.1			
	Patients (%)	15.3	23.3	29.7	21	10.7	52.7	71.4	30.0
Scenario 5									
Slope-sign	True efficacy	0.05	0.25	0.45	0.65	0.8			
	True toxicity	0.05	0.1	0.15	0.2	0.5			
	Selection (%)	2.1	20.0	19.7	35.0	23.2			

Design		Dose level					% of efficacy	% of toxicity	% of OBD region	# of sample
		1	2	3	4	5				
Traditional	Patient (%)	25.0	25.0	25.0	15.1	9.8	35.6	16.0	54.7	12.6
	Selection (%)	13.7	20.2	27.4	31.7	7.0				
Logistic	Patient (%)	24.8	22.3	23.8	20.5	8.7	37.6	15.5	59.0	30.0
	Selection (%)	6.1	12.3	30.6	44.5	6.4				
Isotonic	Patients (%)	15.3	18.7	28.7	24.7	12.7	44.3	18.3	75.1	30.0
	Selection (%)	6.1	14.3	19.9	53.3	6.4				
L-logistic	Patients (%)	15.0	21.3	20.7	26.0	17.0	45.7	20.0	73.2	30.0
	Selection (%)	3.5	5.6	16.1	64.6	10.2				
<i>Scenario 6</i>	Patients (%)	13.3	16.3	19.3	28.7	22.3	50.0	22.2	80.7	30.0
	True efficacy	0.1	0.3	0.5	0.5	0.5				
	True toxicity	0.1	0.2	0.4	0.5	0.6				
Slope-sign	Selection (%)	7.8	36.7	38.8	12.2	4.5				
	Patient (%)	28.3	28.3	28.3	11.9	3.0	33.3	29.1	44.5	11.0
Traditional	Selection (%)	44.5	41.9	12.3	1.2	0.2				
	Patient (%)	52.2	30.1	13.6	3.5	0.6	23.1	23.5	86.4	30.0
Logistic	Selection (%)	19.0	42.2	31.1	6.4	1.3				
	Patient (%)	23.7	30.6	32.0	11.3	2.5	34.2	28.7	61.2	30.0
Isotonic	Selection (%)	18.3	42.3	31.0	7.9	0.5				
	Patients (%)	23.0	32.1	27.5	12.8	4.7	34.2	29.3	60.6	30.0
L-Logistic	Selection (%)	18.1	39.3	27.7	12.4	2.5				
	Patient (%)	23.4	28.4	24.9	15.9	7.4	35.3	30.2	57.4	30.0
<i>Scenario 7</i>										
	True efficacy	0.1	0.3	0.45	0.6	0.6				
	True toxicity	0.01	0.03	0.05	0.1	0.2				
Slope-sign	Selection (%)	3.1	14.7	25.8	31.3	25.1				
	Patient(%)	25.0	25.0	25.0	15.6	9.4	35.7	5.9	56.4	12.5
Traditional	Selection (%)	1.6	4.8	21.2	42.7	29.7				
	Patient(%)	12.0	13.7	17.8	31.1	25.4	47.3	9.6	72.4	30.0
Logistic	Selection (%)	0.8	1.1	13.3	44.8	40.0				

Design		Dose level					% of efficacy	% of toxicity	% of OBD region	# of sample
		1	2	3	4	5				
Isotonic	Patients (%)	10.7	11.7	17.9	29.3	30.4	48.4	10.5	84.8	30.0
	Selection (%)	0.7	6.7	14.6	45.5	32.5				
L-logistic	Patients (%)	10.9	13.3	18.4	29.6	27.7	47.4	9.9	78.0	30.0
	Selection (%)	0.6	4.9	20.1	40.4	34.0				
Scenario 8	Patients (%)	10.5	11.6	14.0	23.5	40.4	49.3	11.7	74.4	30.0
	True efficacy	0.2	0.4	0.4	0.4	0.4				
	True toxicity	0.05	0.07	0.12	0.23	0.3				
	Selection (%)	14.3	24.8	39.3	15.0	6.6				
Slope-sign	Patient (%)	28.4	28.4	28.4	11.8	3.0	33.5	10.8	64.1	11.0
	Selection (%)	9.3	26.2	27.2	25.1	12.3				
Traditional	Patient (%)	20.0	21.6	23.8	21.9	12.6	35.8	14.2	53.3	30.0
	Selection (%)	11.1	17.0	38.0	22.2	11.7				
Logistic	Patients (%)	14.8	20.6	28.8	22.3	13.6	36.9	15.0	55.0	30.0
	Selection (%)	6.3	34.4	26.4	23.8	9.1				
Isotonic	Patients (%)	14.9	21.9	28.4	22.3	12.5	37.5	14.7	60.8	30.0
	Selection (%)	7.7	35.9	21.4	23.8	11.2				
L-logistic	Patients (%)	13.0	16.4	23.5	24.7	22.5	38.0	15.2	57.3	30.0

Table 2

Prior sensitivity analysis for the logistic and L-logistic designs.

Design		Dose level					% of efficacy
		1	2	3	4	5	
True efficacy		0.4	0.6	0.8	0.7	0.55	
$\beta, \gamma \sim \text{Cauchy}(0, 1.25)$							
Logistic	Selection (%)	17.5	5.8	61.4	11.1	4.2	
	Patients (%)	27.0	15.3	41.3	13.4	3.0	63.7
L-logistic	Selection (%)	4.1	13.5	48.1	27.9	6.4	
	Patients (%)	15.3	18.3	25.3	24.3	16.8	63.3
$\alpha, \gamma \sim \text{Cauchy}(0, 2.5)$							
Logistic	Selection (%)	12.9	10.4	60.7	11.5	4.5	
	Patients (%)	22.7	17.3	42.7	14.0	3.3	65.1
L-logistic	Selection (%)	4.6	11.7	51.1	26.8	5.9	
	Patients (%)	14.0	17.3	27.3	24.3	16.7	64.3
$\beta, \gamma \sim \text{Cauchy}(0, 5)$							
Logistic	Selection (%)	13.7	11.7	59.4	10.7	4.5	
	Patients (%)	25	18.3	40.7	12.7	3.3	64.1
L-logistic	Selection (%)	5.6	11.0	51.5	26.9	5.0	
	Patients (%)	16.0	19.3	30.3	22.3	12.1	64.3