REVIEW

Dose Escalation Methods in Phase I Cancer Clinical Trials

Christophe Le Tourneau, J. Jack Lee, Lillian L. Siu

Phase I clinical trials are an essential step in the development of anticancer drugs. The main goal of these studies is to establish the recommended dose and/or schedule of new drugs or drug combinations for phase II trials. The guiding principle for dose escalation in phase I trials is to avoid exposing too many patients to subtherapeutic doses while preserving safety and maintaining rapid accrual. Here we review dose escalation methods for phase I trials, including the rule-based and model-based dose escalation methods that have been developed to evaluate new anticancer agents. Toxicity has traditionally been the primary endpoint for phase I trials involving cytotoxic agents. However, with the emergence of molecularly targeted anticancer agents, potential alternative endpoints to delineate optimal biological activity, such as plasma drug concentration and target inhibition in tumor or surrogate tissues, have been proposed along with new trial designs. We also describe specific methods for drug combinations as well as methods that use a time-to-event endpoint or both toxicity and efficacy as endpoints. Finally, we present the advantages and drawbacks of the various dose escalation methods and discuss specific applications of the methods in developmental oncotherapeutics.

J Natl Cancer Inst 2009;101:708–720

Phase I trials represent the first application of a new drug or drug combination to humans and as such are the foundation of a successful clinical drug development process. Because the early clinical development of a novel agent may unduly influence its ultimate fate, a careful and thoughtful approach to the design of phase I trials is essential. Phase I clinical trials in oncology are typically small, single-arm, open-label, sequential studies that include patients with a good performance status whose cancers have progressed despite standard treatments. A principal goal of such trials is to establish the recommended dose and/or schedule of an experimental drug or drug combination for efficacy testing in phase II trials. A phase I trial design has many components, including starting dose, dose increment, dose escalation method, number of patients per dose level, specification of dose-limiting toxicity, target toxicity level, definition of the maximum tolerated dose (MTD) and recommended dose for phase II trials, patient selection, and number of participating centers (*see* definitions of basic concepts in Table 1). Although all of these components are relevant for the design of a phase I trial, this review will focus on selecting the dose escalation method that will yield an optimal balance of safety, efficiency, and ethical conduct.

The guiding principle for dose escalation in phase I trials is to avoid unnecessary exposure of patients to subtherapeutic doses of an agent (ie, to treat as many patients as possible within the therapeutic dose range) while preserving safety and maintaining rapid accrual. Dose escalation methods for phase I cancer clinical trials fall into two broad classes: the rule-based designs, which include the traditional 3+3 design and its variations, and the model-based designs. The rule-based designs assign patients to dose levels according to prespecified rules based on actual observations of target events (eg, the dose-limiting toxicity) from the clinical data. Typically, the MTD or recommended dose for phase II trials is determined by the prespecified rules as well. On the other hand, the model-based designs assign patients to dose levels and define the recommended dose for phase II trials based on the estimation of the target toxicity level by a model depicting the dose–toxicity relationship. However, because of safety concerns, most model-based designs are modified such that specific restrictions are set as safeguards for elements such as dose increments to avoid overshooting of the MTD and thus exposing patients to undue harm. All of these methods were developed in the era of cytotoxic drugs, during which time it was assumed that both efficacy and toxicity increase with dose. These relationships are typically represented by dose–toxicity and dose–efficacy curves in which toxicity and efficacy increase monotonically with increasing dose (Table 1 and Figure 1). Consequently, these methods have used toxicity as the primary endpoint. For molecularly targeted agents, the dose–efficacy and dose–toxicity curves may differ from those for cytotoxic agents, and efficacy may occur at doses that do not induce clinically significant toxicity (1–4). Thus, for trials involving these agents, the occurrence of drug-related biological effects has been suggested as an alternate primary endpoint besides toxicity (1–4).

Here we review the different dose escalation methods for phase I cancer clinical trials of single agents and drug combinations and discuss their pros and cons. Recent reviews (2,5) of phase I clinical trials including this update reveal that new dose escalation designs have been incorporated into phase I trials infrequently, and we

Affiliations of authors: Division of Medical Oncology and Hematology, Princess Margaret Hospital, University Health Network, University of Toronto, Toronto, ON, Canada (CLT, LLS); Department of Biostatistics, The University of Texas M. D. Anderson Cancer Center, Houston, TX (JJL).

Correspondence to: Lillian L. Siu, MD, FRCPC, Division of Medical Oncology and Hematology, Princess Margaret Hospital, University Health Network, University of Toronto, 610 University Ave, Ste 5-718, Toronto, ON, Canada M5G 2M9 (e-mail: lillian.siu@uhn.on.ca)

See "Funding" and "Notes" following "References."

DOI: 10.1093/jnci/djp079

Table 1. Glossary of terms

Term	Definition
Cohort	Group of patients treated at a dose level.
Starting dose	The dose chosen to treat the first cohort of patients in a phase I trial.
Dose increment (decrement)	The percent increase (or decrease) between dose levels.
Dose-limiting toxicity (DLT)	Toxic effects that are presumably related to the drugs that are considered unacceptable (because of their severity and/or irreversibility) and that limit further dose escalation. DLTs are defined before beginning the trial and are protocol specific. They are typically defined based on toxic effects seen in the first cycle and specified using a standardized grading criteria, for example, Common Terminology Criteria for Adverse Events.
Dose–efficacy curve	The dose–efficacy curve reflects the relationship between dose and probability of efficacy for an anticancer agent. A logistic function is commonly assumed to describe the dose–efficacy curve for cytotoxic agents and is characterized by a parameter, θ, which represents the slope of the dose–efficacy curve. Small values of θ indicate that the probability of efficacy increases very slowly with increasing dose levels, whereas large values of θ indicate a sharp increase in efficacy with increasing dose levels (*see* Figure 1).
Dose–toxicity curve	The dose–toxicity curve reflects the relationship between dose and probability of toxicity for an anticancer agent. A logistic function is commonly assumed to describe the dose–toxicity curve for cytotoxic agents and is characterized by a parameter, θ, which represents the slope of the dose–toxicity curve. Small values of θ indicate that the probability of toxicity increases very slowly with increasing dose levels, whereas large values of θ indicate a sharp increase in toxicity with increasing dose levels (*see* Figure 1).
Target toxicity level	The maximum probability of DLT that is considered acceptable in the trial. The target toxicity level in phase I trials is typically between 20% and 33%.
Maximum tolerated dose (MTD)	Phase I trials conducted in the United States: the highest dose level at which $\leq$33% of patients experience DLT. Phase I trials conducted in Europe and Japan: the lowest dose level at which $\geq$33% of patients experience DLT (a misnomer in the sense that the MTD is actually not a tolerable dose). Phase I trials that use model-based methods: the dose that produces the target toxicity level.
Optimal biological dose (OBD)	Dose associated with a prespecified most desirable effect on a biomarker among all doses studied (eg, inhibition of a key target in tumor or surrogate tissue or achievement of a prespecified immunologic parameter).
Recommended phase II dose	Phase I trials with a toxicity endpoint that are conducted in the United States: the MTD. Phase I trials with a toxicity endpoint that are conducted in Europe and Japan: one dose level below the MTD. Phase I trials in which the endpoint is a prespecified biological endpoint: the OBD.
Pharmacokinetics	Pharmacologic effects of the body on the drug (ie, the time course of drug absorption, distribution, metabolism, and excretion).
Pharmacodynamics	Pharmacologic effects of the drug on the body (eg, nadir neutrophil or platelet count, nonhematologic toxicity, molecular correlates, imaging endpoints).
Therapeutic index	The dosage or range of dosages of a drug that is required to produce a given level of damage to critical normal tissues (toxicity) divided by the dosage or range of dosages that yields a defined level of antitumor effect (efficacy) (*see* Figure 1).

explore the reasons for this disconnect. Finally, we recommend ways to assign dose escalation methods to evaluate new drugs or drug combinations. These recommendations are based on preclinical information, existing knowledge of agents that target the same or similar molecular pathways, and the availability of resources to execute such methods.

Rule-Based Designs

The main characteristic of rule-based designs is that they do not stipulate any prior assumption of the dose–toxicity curve. These designs comprise the so-called "up-and-down" designs because they allow dose escalation and de-escalation. The first up-and-down design was introduced in the late 1940s by Dixon and Mood (6), and Storer (7) described implementation of this design in clinical practice half a century later. The general principle of this design is to escalate or de-escalate the dose with diminishing fractions of the preceding dose depending on the absence or presence of severe toxicity in the previous cohort of treated patients (Figure 2, A). The simple up-and-down design converges to a dose that corresponds to a probability of severe toxicity of approximately 50%, which is higher than the 33% threshold commonly accepted in most phase I cancer clinical trials. Although variations of this up-and-down design have been developed in an attempt to increase patient safety and to use toxicity data collected in real time (8,9), these designs have not been used much in clinical practice because they risk exposing patients to unacceptable levels of toxicity. The first rule-based design to be used widely in clinical practice was the traditional 3+3 design. Variations of the traditional 3+3 design that have been put into clinical use include the accelerated titration designs and the pharmacologically guided dose escalation (PGDE) method.

Traditional 3+3 Design

The traditional 3+3 design remains the prevailing method for conducting phase I cancer clinical trials (7). It requires no modeling of

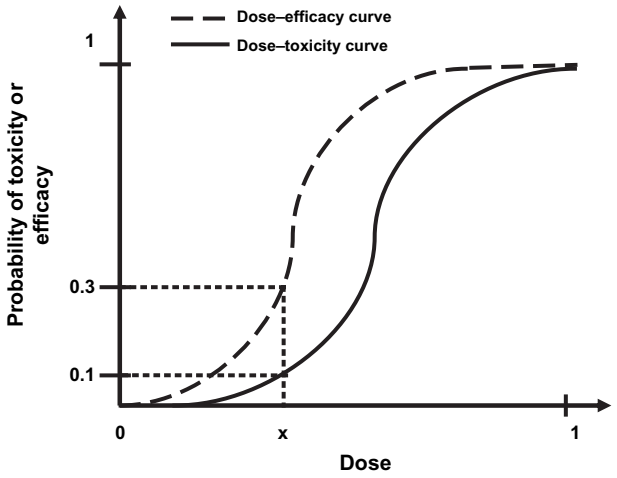

Figure 1. Typical dose–toxicity and dose–efficacy curves for cytotoxic agents. This example illustrates that at dose *x*, the probability of efficacy is 30% and the probability of toxicity is 10%; hence, the therapeutic index of the drug at dose *x* is 10% divided by 30% = 1/3.

the dose–toxicity curve beyond the classical assumption for cytotoxic drugs that toxicity increases with dose. This rule-based design proceeds with cohorts of three patients; the first cohort is treated at a starting dose that is considered to be safe based on extrapolation from animal toxicological data, and the subsequent cohorts are treated at increasing dose levels that have been fixed in advance (Figure 2, B). Historically, dose escalation has followed a modified Fibonacci sequence in which the dose increments become smaller as the dose increases (eg, the dose first increases by 100% of the preceding dose, and thereafter by 67%, 50%, 40%, and 30%–35% of the preceding doses). In most cases, the prespecified dose levels do not fit the exact Fibonacci sequence as described in the 12th century (5). If none of the three patients in a cohort experiences a dose-limiting toxicity, another three patients will be treated at the next higher dose level. However, if one of the first three patients experiences a dose-limiting toxicity, three more patients will be treated at the same dose level. The dose escalation continues until at least two patients among a cohort of three to six patients experience dose-limiting toxicities (ie, ≥33% of patients with a dose-limiting toxicity at that dose level). The recommended dose for phase II trials is conventionally defined as the dose level just below this toxic dose level.

Alternative rules besides "3+3" have been proposed, including the "2+4," "3+3+3," and "3+1+1" (also referred as "best of five") rules (10). In the "2+4" design, an additional cohort of four patients is added if one dose-limiting toxicity is observed in a first cohort of two patients. The stopping rule is the same as in the traditional 3+3 design. In the "3+3+3" design, a third cohort of three patients is added if two of six patients in the first two cohorts experience a dose-limiting toxicity at a certain dose level. The trial terminates if at least three of nine patients experience a dose-limiting toxicity. The "best of five" design is more aggressive than the traditional 3+3 design in that one additional patient is added if one or even two dose-limiting toxicities are observed among the first three patients. Another patient is added if two dose-limiting toxicities are observed among the four treated patients. Dose escalation is allowed if dose-limiting toxicities are observed among none of three, one of four, or two of five patients, but the trial will terminate if three or more dose-limiting toxicities are observed.

The main advantages of the traditional 3+3 design are that it is simple to implement and safe (Table 2). In addition, the accrual of three patients per dose level provides additional information about pharmacokinetic interpatient variability. However, a disadvantage of this design is that it involves an excessive number of escalation steps, which results in a large proportion of patients who are treated at low (ie, potentially subtherapeutic) doses while few patients actually receive doses at or near the recommended dose for phase II trials. This latter point is illustrated in Table 3, which presents the dose escalation method used as well as the number of dose levels in recent first-in-human single-agent phase I trials for anticancer agents that were eventually (1992–2008) approved by the US Food and Drug Administration (FDA) for the treatment of solid tumors. Among 21 trials that used the traditional 3+3 design, more than half involved six or more dose levels.

Accelerated Titration Designs

Accelerated titration designs combine features from variations of the traditional 3+3 design and the model-based design. Because the patient assignment to doses is based on prespecified rules, we classify accelerated titration designs as rule-based designs. Through simulations based on a stochastic model fit to data from 20 actual phase I trials of nine different drugs, Simon et al. (36) described one control design and three accelerated titration designs. The control design, design 1, is a standard 3+3 design with a 40% dose increment between successive cohorts of patients. Although the three accelerated titration designs, designs 2, 3, and 4, were created based on a statistical model as described (36), the assignment of patients to dose levels follows specific rules according to the observed toxicities at each dose level. Designs 2 and 3 allow 40% and 100% dose escalations, respectively, between single-patient cohorts until a dose-limiting toxicity or two moderate toxicities are observed during cycle 1, at which point dose escalation reverts to the more conservative one used in design 1. In design 4, the 100% dose escalation between single-patient cohorts in the accelerated phase reverts to design 1 when one dose-limiting toxicity or two moderate toxicities are observed during any cycle (not just during cycle 1). Intrapatient dose escalation is allowed during the accelerated phase of designs 2, 3, and 4 (Figure 2, C). In all three accelerated titration designs, the standard 3+3 design is used after the accelerated phase as a stopping rule, and then the described model is recommended to estimate the MTD with all toxicity data collected during the trial. In addition, the model recommended for use included a parameter for cumulative toxicity as well as a parameter for interpatient variability, such that the accelerated titration designs would provide information in these aspects. In practice, investigators often determine the MTD based on the conventional 3+3 escalation rule without fitting trial data to the model at the end of the trial. Consequently, the original model-based accelerated titration designs have been adapted primarily as rule-based designs in clinical practice.

The accelerated phase in accelerated titration designs—in which only one patient is included per dose level—along with the possibility of intrapatient dose escalation theoretically reduce the number of patients who are treated at subtherapeutic doses

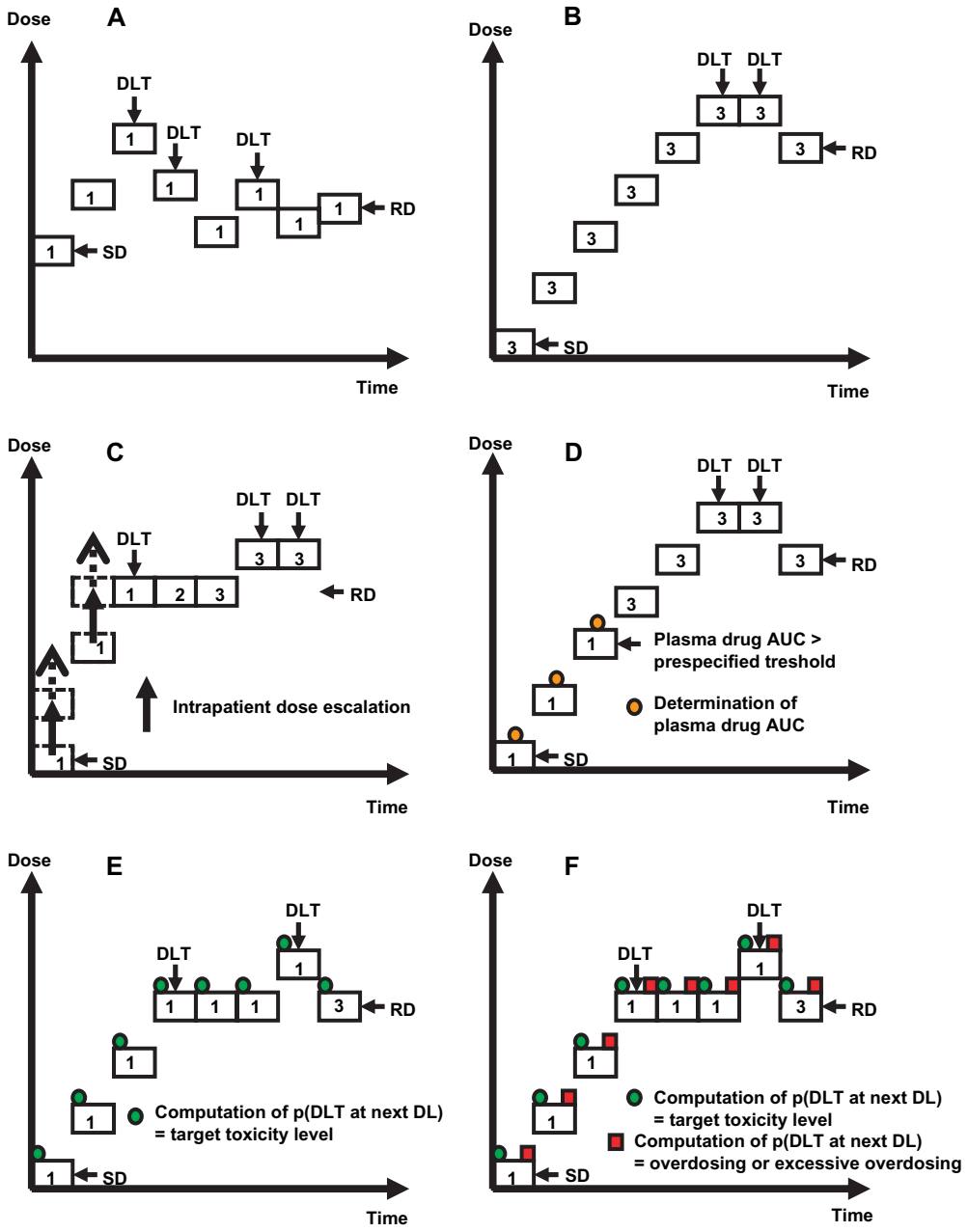

Figure 2. Graphical depiction of dose escalation methods for phase I cancer clinical trials. Each **box** represents a cohort comprising the indicated number of patients treated at a given dose level. **A**) Simple up-and-down design. **B**) Traditional 3+3 design. **C**) Accelerated titration design. **Dashed arrows** represent intrapatient dose escalation. **D**) Pharmacologically guided dose escalation. **E**) Modified continual reassessment method. **F**) Escalation with overdose control. "Overdosing or excessive overdosing" refers to doses that exceed the MTD. DLT = dose-limiting toxicity; SD = starting dose; RD = recommended dose; DL = dose level; AUC = area under the curve for drug concentration as a function of time; p(DLT at next DL) = probability of dose-limiting toxicity at the next dose level.

(Table 2). Permitting intrapatient dose escalation in accelerated titration designs is appealing because it gives some patients the opportunity to be treated at higher and presumably more effective doses. For example, in the first-in-human phase I trial of ixabepilone, which used an accelerated titration design with intrapatient dose escalation, all patients received the drug at the eventually established recommended dose for phase II trials (35). On the other hand, unless the model recommended in the original publication (36) using parameters for cumulative toxicity and interpatient variability is applied and fits the data well, one drawback of intrapatient dose escalation is that it may mask the cumulative effects of treatment or, at the very least, would make them harder to differentiate from chronic or delayed toxic effects. However, regardless of the trial design used, chronic, delayed, or cumulative toxic effects are generally not well captured by most phase I trials because most patients with advanced cancers do not remain on study for extended periods of time. Furthermore, it can be difficult to present and interpret results of trials that allow intrapatient dose escalations because a single patient may contribute data for several dose levels.

Table 2. Theoretical main advantages and drawbacks of dose escalation methods for phase I cancer clinical trials*

Dose escalation method	Advantages	Drawbacks
Rule-based designs		
Traditional 3+3 design	Easy to implement and safe	Many patients treated at subtherapeutic doses Slow dose escalation
	Provide some data on PK interpatient variability	Uncertainty about the RP2D Only the result from the current dose is used for determining the dose of next cohort of patients. Information on other doses is ignored.
Accelerated titration designs	More rapid dose escalation	If model fitting is not performed (as is often the case in clinical practice): Intrapatient dose escalation may mask cumulative or delayed toxicities
	May expose a greater proportion of patients at higher doses	Difficult interpretation of the results when intrapatient dose escalation is allowed
	Data from all patients, cumulative toxicity, and interpatient variability can be fit to a model to establish the RP2D	Uncertainty about the RP2D
Pharmacologically guided dose escalation	More rapid dose escalation	Need to obtain real-time PK results
	Provide some data on PK interpatient variability	Interpatient variability may hamper dose escalation
Model-based designs		
Modified continual reassessment method, escalation with overdose control, time-to-event continual reassessment method, EffTox, TriCRM	Target toxicity level is explicitly defined	Need to have a prior guess of the RP2D
	More rapid dose escalation	
	Use all available information from all patients	Computations after each patient or cohort of patients
	Estimate of the RP2D with a confidence interval	
	Take into account late-onset toxicities (time-to-event continual reassessment method)	Need real-time biostatistical support for dose escalation decisions (may also be an advantage)
	Take into account both toxicity and efficacy (EffTox + TriCRM)	

* PK = pharmacokinetic; RP2D = recommended phase II dose; EffTox = efficacy and toxicity method; TriCRM = an adaptative continual reassessment method that considers three potential trial outcomes: no efficacy and no toxicity, efficacy only, and toxicity only.

Pharmacologically Guided Dose Escalation

The PGDE method is another variation of the traditional 3+3 design that has not been widely used in clinical practice. This approach assumes that dose-limiting toxicities can be predicted by plasma drug concentrations and that animal models can accurately reflect this relationship in humans (37). The PGDE method has two stages. A prespecified plasma exposure defined by the area under the curve for drug concentration as a function of time (AUC) is extrapolated from preclinical data. Then, pharmacokinetic data are obtained for each patient in real time to determine the subsequent dose level. As long as the prespecified plasma exposure is not reached, dose escalation proceeds with one patient per dose level and typically at 100% dose increments (stage 1, Figure 2, D). When the target AUC is reached or if dose-limiting toxicities occur, dose escalation switches to the traditional 3+3 design with smaller (usually around 40%) dose increments (stage 2).

The PGDE method has not been widely adopted due to practical obstacles, including: 1) logistic difficulties in obtaining real-time pharmacokinetic results, which are required to determine the safety of the subsequent dose escalation; 2) problems in extrapolating preclinical pharmacokinetic data to phase I studies with different treatment schedules; and 3) risk of exposing the next patient to a highly toxic dose if the AUC obtained in the preceding patient was atypically low due to interpatient variability in drug metabolism. In clinical practice, the PGDE method has reliably defined the recommended dose for phase II trials for some cytotoxic agents such as certain anthracyclines and platinum compounds but has been found to be inappropriate for other classes of cytotoxic agents such as the antifolates, which display a high interpatient pharmacokinetic heterogeneity (38).

Other Rule-Based Designs

Several other rule-based designs have been proposed, including the isotonic regression model (39), the biased coin design (9) and its variations (40,41), and the "rolling six" design (42). The rolling six design was originally proposed as a way to shorten the timeline of pediatric phase I trials by reducing the number of times a study is suspended to accrual (42). This method allows accrual of two to six patients concurrently onto a dose level based on the numbers of patients who are currently enrolled and evaluable, who experience a dose-limiting toxicity and who remain at risk of developing a dose-limiting toxicity. Because pediatric trials are typically conducted only after completion of adult phase I trials, this design is intended to shorten the study duration in situations in which there is prior information about the dose range to be evaluated.

Ji et al. (43) developed a rule-based design in which subsequent patients are assigned to doses according to the toxicity outcome at the current dose by calculating the toxicity probability interval under the beta-binomial model. The authors also developed a freely available macro in Microsoft Office Excel software that can be downloaded to facilitate the study conduct. Simulations have shown that the performance of this dose-finding design is better than the traditional 3+3 design and comparable to some model-based designs

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