

Dose escalation trial designs based on a molecularly targeted endpoint[‡]

Sally Hunsberger^{1,*}, Lawrence V. Rubinstein¹, Janet Dancey² and Edward L. Korn¹

¹*Biometrics Research Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, U.S.A.*

²*Investigational Drug Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, U.S.A.*

SUMMARY

Traditional phase I dose-finding studies for chemotoxic agents base dose escalation on toxicity, with escalation continuing until unacceptable toxicity is observed. Recent development of molecularly targeted agents that have little or no toxicity in the therapeutic dose range has raised questions over the best study designs for phase I studies. Two types of designs are proposed and evaluated in this paper. In these designs, escalation is based on a binary response that indicates whether or not the agent has had the desired effect on the molecular target. One design is developed to ensure that if the true target response rate is low there will be a high probability of escalating and if the true target response rate is high there will be a low probability of escalating. The other design is developed to continue to escalate as long as the true response rate is increasing and to stop escalating when the response rate plateaus or decreases. A limited simulation study is performed and the designs are compared with respect to the dose level at the end of escalation and the number of patients treated on study. Published in 2005 by John Wiley & Sons, Ltd.

KEY WORDS: phase I; toxicity; clinical trial

1. INTRODUCTION

The usual clinical development of chemotherapeutic agents for treatment of cancer begins with phase I studies. Phase I studies are typically designed to find the dose to be recommended for further testing by finding the highest dose that has acceptable toxicity. The assumptions underlying phase I designs are that (1) as the dose increases the clinical benefit increases, (2) as the dose increases toxicity increases and (3) there is a dose that has acceptable toxicity and provides clinical benefit. Recently, molecularly targeted agents are being developed where the

*Correspondence to: Sally Hunsberger, Biostatistics Research Branch, National Cancer Institute, 6130 Executive Blvd, Rm 8120, Bethesda, MD 20892, U.S.A.

†E-mail: sallyh@ctep.nci.nih.gov

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hypothesized mechanism of action may lead to a violation of these assumptions. With these new agents it is hypothesized that (a) there may be a plateau on the dose–efficacy curve so that higher doses may not improve clinical benefit (or may only marginally improve clinical benefit) and (b) toxicity does not necessarily increase with increased doses (or may occur beyond doses that are yielding sufficient clinical benefit).

In this paper we consider several phase I designs for molecularly targeted agents. After a brief review in Section 2, of phase I study designs that have previously been used or proposed, we present several new designs for molecularly targeted agents in Section 3. In Section 4, we present simulations to evaluate the properties of the new designs. We end with a discussion in Section 5.

2. BACKGROUND

In phase I studies where the goal is to find the maximum tolerated dose (MTD) of a cytotoxic agent, the standard ‘3 + 3’ design accrues patients in cohorts of three and escalates until a dose limiting toxicity (DLT) is observed (DLTs are very specifically defined). If one DLT is observed among the initial three patients, three more patients are accrued to that dose level. If ≥ 2 DLTs are observed (among up to six patients) escalation stops and the MTD has been exceeded. The MTD is the highest dose where no more than one DLT is observed. The MTD is the dose that is recommended for further evaluation. There are variants of this design that escalate more quickly through non-toxic dose levels [1]. This method involves no parametric model assumptions on the shape of the dose–toxicity curve. The decision to escalate or not is solely based on toxicity results from the current dose level. Others have used model-based approaches. Storer [2] proposed defining the MTD by using a logistic regression model with the toxicity data and then estimating the MTD that is associated with a targeted maximum DLT rate of 20–30 per cent. Patients were escalated in single patient cohorts until a toxicity was observed and then two or three patients were added to a dose level. Escalation or de-escalation decisions were based on the number of toxicities. Accrual of patients ended when a fixed sample size was reached. All patients were used in the logistic regression estimate of the MTD. O’Quigley *et al.* [3] extended the idea of Storer by using the dose–toxicity model to guide the dose escalation as well as to define the MTD (this is referred to as the continual reassessment method (CRM)). Rubinstein and Simon [4] give a thorough discussion of phase I clinical trial designs for cytotoxic agents.

Molecularly targeted agents may require phase I study designs that are different from designs for cytotoxic agents. Friedman *et al.* [5] performed a phase I study using a molecularly targeted agent O⁶-benzylguanine where escalation was based on depletion of the target enzyme O⁶-alkylguanine-DNA alkyltransferase (AGT) activity rather than toxicity. Up to 13 patients were treated at a dose level. If at any point AGT levels were detectable in three or more patients escalation occurred. Dose escalation ended when undetectable AGT levels in 11 or more out of 13 patients occurred. The probability of undetectable AGT levels in $\geq \frac{11}{13}$ patients was 0.000001 if the true undetectable AGT proportion was 20 per cent. The probability of observing $\geq \frac{11}{13}$ patients without AGT was 0.87 when the true undetectable AGT proportion was 90 per cent.

Others have used the combination of toxicity and a molecular target response as the endpoint in phase I studies. Designs for escalation studies that combine toxicity and response can be

found in References [6–10]. Our interest is in the situation where escalation is based solely on response to a molecularly targeted agent assuming that significant toxicity will not occur. If a molecularly targeted agent produces significant toxic side effects we assume escalation would be based on toxicity alone with a standard design.

3. PROPOSED DESIGNS FOR MOLECULARLY TARGETED AGENTS

We propose designs for molecularly targeted agents that are based on the assumption that there is a binary (positive/negative) response measured in each patient after treatment with the agent. The response indicates whether or not the agent has had the desired effect on the target. For example, the response might be based on the level of a molecular target, or the change in the level of a target that suggests clinical promise. The usefulness of the designs depend upon the validity of the assays to measure the response (molecular target) and patients having the molecular target. With these designs it is imperative that the target effect confers clinical benefit or in combination with another agent will confer clinical benefit. We assume that if a response is measured on a continuous scale the response can be converted to a binary indicator of success. For example, a blood level of an active metabolite of the agent above an amount required for pre-clinical activity might be taken as a positive response. We do not address escalation based on continuous endpoints in this paper.

The dose–response curve for molecularly targeted agents is expected to increase and then remain constant as the dose increases. However, in practice the response rate may not remain exactly constant as the dose increases, but could continually increase by very small amounts. Therefore, we define the plateau to be doses that correspond to response rates within 10 per cent (on an absolute scale) of the maximum (or limiting) response rate. The ‘optimum biological dose’ could be defined as the lowest dose that yields the highest possible true response rate. For the designs proposed in this paper the goal is *not* to find the optimal biological dose since such a dose may not exist or may require large numbers of patients to detect. The goal of the proposed designs is to find a biologically ‘adequate’ dose while using few patients, since at this stage of the development of an agent it is important to move quickly from dose finding to evaluating efficacy. An adequate dose is defined as either a dose that yields a specific (high) response rate or a dose in the plateau.

We propose two types of designs to accommodate the two concepts of an adequate dose. In the first type, the design is developed to ensure that if the true target response rate is low (indicating lack of clinical benefit) there will be a high probability of escalating further and if the true target response rate is high (indicating possibility of clinical benefit) there will be a low probability of escalating further. In the second type of design, we target doses in the plateau. Therefore, the design is developed to continue to escalate as long as the true response rate is increasing and to stop escalating when the response rate plateaus or decreases. In all of the designs it is assumed that dose levels have already been prespecified.

The first type of design mimics the standard 3 + 3 dose escalation designs discussed in Section 2. We present two sets of dose escalation rules. In the first case the design was based on distinguishing between response rates of $p_0 = 0.3$ and $p_1 = 0.8$. That is, we wish to continue to escalate if the true response rate at a dose level is close to 0.3 but to stop escalating if the true response rate is close to 0.8. We refer to this design as Proportion [4/6].

3.1. Proportion [4/6]

- *1. Escalate in cohorts of size three while $\leq 1/3$ responses are observed.
2. Expand dose level to six when $\geq 2/3$ responses are observed.
3. Continue escalation as in steps 1 and 2 if $\leq 3/6$ responses are observed.
4. Dose recommended for future clinical testing: dose level that achieves $\geq 4/6$ responses or maximum dose level tested.

*If the starting dose level achieves $\geq 4/6$ responses then use the following de-escalation rules.

- 1. De-escalate in cohorts of size three.
- 2. When $\leq 1/3$ responses are observed, treat an additional three patients at the next higher dose level unless it is the starting dose.
- 3. Dose recommended for future clinical testing: lowest dose with $\geq 4/6$ responses.

De-escalation in this design occurs if the first dose meets the activity criteria since the goal is to recommend for further testing the lowest dose that has sufficient activity. Early escalation to higher doses before a dose level is completed is allowed when it is clear the response criteria for stopping will not be met, for example, 0/2 or 2/5 responses. This is in contrast to the standard toxicity based designs, where all information at a dose level must be collected before escalation is allowed.

The next design distinguishes between $p_0 = 0.4$ and $p_1 = 0.9$. We will refer to this design as Proportion [5/6].

3.2. Proportion [5/6]

Modify the following steps from Proportion [4/6] as follows:

3. Continue escalation as in steps 1 and 2 if $\leq 4/6$ responses are observed.
4. Dose for further testing: dose level that achieves $\geq 5/6$ responses.
- 3. Dose for further testing: lowest dose with $\geq 5/6$ responses.

Table I gives some of the properties of Proportions [4/6] and [5/6]. In both designs the probability of escalating when the true rate is equal to p_0 is large, 0.94 and 0.96. The probability of escalating when the true rate equals p_1 is low, 0.15 and 0.11.

For the Proportion designs a maximum dose level could be specified. Since the Proportion designs are designed to escalate until there is a high probability of meeting the desired response rate, a maximum dose level protects against the trial never ending in situations where the response rate has reached a plateau below the desired rate. If the maximum dose level is reached then the lowest dose among the expanded cohorts that achieve the highest response rate is taken into further testing.

Table I. Probability of escalating for proportion designs.

Design	30 per cent	40 per cent	50 per cent	60 per cent	70 per cent	80 per cent	90 per cent
Proportion [4/6]	0.94*	0.85	0.70	0.52	0.32	0.15	0.04
Proportion [5/6]	0.99	0.96	0.89	0.77	0.58	0.34	0.11

*Bolded probabilities correspond to design parameters.

Another way to design a study to achieve a specified target response rate would be to use the CRM. The paper does not pursue evaluating the CRM since it is more complicated to use and our desire was to develop simple phase I designs.

In the second type of designs the desire is to stop escalating if the target response rate appears to remain constant. Unlike the Proportion designs, the dose escalation may stop despite the fact that the observed response rate is low. In these designs the escalation decision is based on the estimated slope of the regression line using dose level as the independent variable and the response rate at each dose level as the dependent variable. Only the highest three or four dose levels are used to calculate the slope. Escalation stops when the estimated slope is ≤ 0 (as long as at least one response has been observed). The dose with the highest response rate is the dose recommended for use in future clinical trials. If there is a tie in the highest response rate among one or more dose levels the highest dose level is chosen.

We investigate three different designs using different cohort sizes (3 or 6) at each dose level and different numbers of dose levels (3 or 4) in the calculation of the slope. We consider the following combinations of cohort sizes and consecutive dose levels to calculate the slope: three patients per cohort with the highest four dose levels used to calculate the slope (denoted as Slope 3P/4L), six patients per cohort with the four highest dose levels used to calculate the slope (Slope 6P/4L), and six patients per cohort with the three highest dose levels used to calculate the slope (Slope 6P/3L). Note that in the first two designs a minimum of four dose levels will be used with a minimum of 12 and 24 patients. In the last design a minimum of three dose levels will be used with a minimum of 18 patients.

In the slope designs we impose the constraint that there must be at least one observed response for the design to stop. Otherwise, a situation with no responses in three or four consecutive dose levels would estimate a slope of zero and the stopping criteria would be met. It is possible to have one response at the first or second dose level, no responses at the other dose levels, and the design would stop escalation. Either situation is not ideal (i.e. responses 1,0,0,0 or 0,1,0,0) but, in the end, perhaps the correct decision would be made. The investigator would look at the data and could conclude that the dosing was started too far below the active doses, the dose steps were too close together, the assay was not working well, or the response definition was not applicable to the clinical situation. The choices would then be to continue, start a new study beginning at a much higher dose, choose larger dose steps, check the assay, or decide the target is not appropriate for use in determining a dose.

Each of the designs (Proportion [4/6] and [5/6], Slope 3P/4L, 6P/4L and 6P/3L) can be modified to accelerate escalation by using single-patient cohorts until a response is seen. Once a response is observed the designs revert to the procedures described above: for the Proportion designs the cohort where the response is observed is expanded to three or potentially six. If the first expanded dose meets the stopping criteria de-escalation occurs as in steps -1 to -3 . For the slope designs the dose level where the response is observed is expanded to three (3P) or six (6P) patients, and patients are accrued to two (3L) or three (4L) more levels. In all of these designs we assume that there is little or no toxicity associated with the agent being studied. If dose limiting toxicity is observed the criteria to escalate is immediately changed to be based on DLT and the escalation rules described in Section 2 are used.

4. SIMULATIONS

We performed a limited simulation study to examine the properties of the dose escalation designs under four different true response patterns. (One might be able to calculate the exact statistical properties of the proportion designs as Lin and Shih [11] have done with the 'A + B' design, but note the proportion design is not exactly the same as the 'A + B' designs discussed in their paper.) For each of the six proposed trial designs, 10 000 simulated trials were generated for each of the four true response patterns.

The first response pattern had a 0.2 probability of a positive response at the first dose step, and increased by 0.1 at every succeeding dose level up to a plateau response at 0.5 (note: in all the simulations the plateau response is a constant value). This response pattern is denoted as 0.2–0.5 by 0.1. With this pattern of response we can examine how the Proportion designs perform when a plateau occurs at a low probability of response and does not reach the intended targeted response rate.

The second and third response patterns had a 0.2 probability of a positive response at the first dose step with a plateau response at 0.9. The second response pattern increased by a probability of 0.05 at every dose level and the third pattern increased by 0.1 (these response patterns are denoted as 0.2–0.9 by 0.05 and 0.2–0.9 by 0.1, respectively). The second and third patterns allow us to examine the effect of choosing dose steps that move toward a desirable dose level at slower and faster rates. In particular there is interest in whether escalation stops too early because of small steps.

Finally, the fourth pattern of response had a 0.3 probability of a positive response at the first dose step and then increased in probability by 0.2 at each successive dose step until 0.9 (0.3–0.9 by 0.2). This pattern allows us to examine how the designs perform for an ideal dose-level ladder where the dose levels are chosen relatively well and the plateau response occurs at a high probability. Figure 1 plots the dose–response curves.

The simulations did not incorporate a maximum number of dose levels so that situations would be observed where the designs perform poorly in terms of using a large number of dose levels. In the Proportion design, early escalation was not utilized because in many situations patients will be accrued in the cohort before the response is available for the earlier treated patients in the cohort.

Two outcomes that are important when evaluating results from the simulations are the dose level at which the design stops and the number of patients used in the study. For each of the dose–response curves, 'adequate' (defined as doses that yield response rates within 10 per cent of the maximum) doses are those in the plateau. Given a design reaches the plateau the best design stops close to the first dose in the plateau and uses the fewest patients. Tables II–V include, (1) the percentage of simulated trials that stopped at a dose level that corresponded to a response rate in the plateau, (2) the percentage of simulations that stopped in the plateau or at a dose level with a response probability within 0.1 probability of the response rate of the plateau (3) the percentage of simulations that stopped within 0.1 probability below the plateau response rate or one dose level above (Tables I and III) or two dose levels above (Table II) the beginning of the plateau, (4) the percentiles of the final dose levels, (5) the percentiles of the number of patients treated and, (6) percentiles of the number of patients treated below the plateau. For point (3) the upper cut-off corresponded to the same number of dose steps above the plateau as dose steps below plateau that corresponded to being 0.1 probability away from the plateau response rate. Note: in Table V the per cent of studies

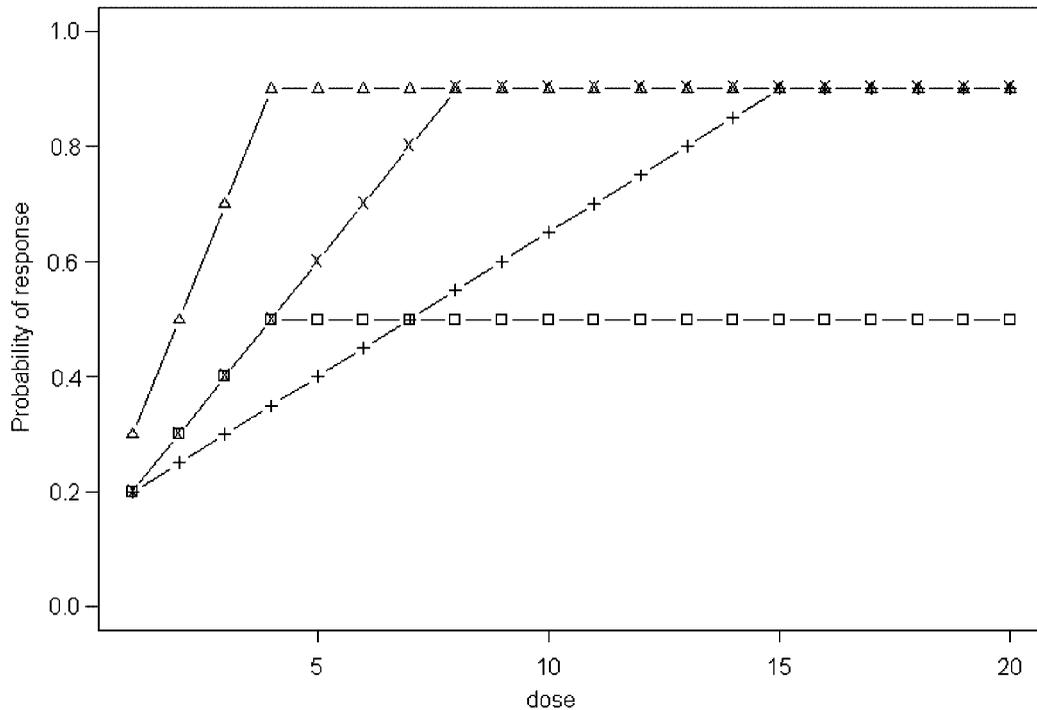


Figure 1. Dose–response curves used in the simulations. 0.2–0.5 by 0.1 = ‘□’, 0.2–0.9 by 0.05 = ‘+’, 0.2–0.9 by 0.1 = ‘x’, 0.3–0.9 by 0.2 = ‘Δ’. Note, several symbols are overlaid due to identical response probabilities, especially at the plateau response probability of 0.9.

that reached within 0.1 probability of the plateau is the same as the per cent that reached the plateau since the response rate increases by 0.2 for each dose step. The per cent that is within 0.1 probability and less than one dose step higher is the per cent of studies that select the beginning of the plateau as the final dose.

The columns of Tables II–V reflect the design that was used with the label ‘acc’ indicating the accelerated designs of one patient per dose level until a response was observed and ‘std’ indicating acceleration was not used. The rows reflect the criteria to evaluate the simulations that were previously described. The four tables reflect the four response patterns that were studied.

In all four response patterns, the accelerated designs perform better than the standard designs. The percentage of studies that escalate to the plateau is always at least as high as the standard design and fewer patients are treated. Since the accelerated designs only put a single patient at lower doses, fewer patients are treated below the plateau. In what follows, all references to designs will be to the accelerated versions.

The Proportion designs tends to stop escalation before the plateau dose levels when the plateau response rate is 0.9 (as can be seen in Tables III–V). This is not surprising since Proportion [4/6] is designed to stop with high probability when the response rate is 0.8. The Proportion [5/6] performs better than [4/6] since it is designed to stop when the response rate

Table II. Trial design properties for pattern of response 0.2–0.5 by 0.1.

	Proportion				Slope						
	[4/6]		[5/6]		3P/4L		6P/3L		6P/4L		
	Std	Acc	Std	Acc	Std	Acc	Std	Acc	Std	Acc	
Per cent dose $\geq 4^*$	79	81	95	95	75	89	79	92	59	88	
Per cent dose ≥ 3	93	94	99	95	85	94	89	96	70	91	
Per cent $3 \leq \text{dose} \leq 5$	55	52	24	23	32	31	32	19	65	56	
Percentiles of final dose level	75	7	7	15	15	6	7	7	9	5	7
	50	5	5	9	9	6	6	6	6	4	5
	25	4	4	6	6	3	5	5	6	2	4
Percentiles of # patients	75	27	24	63	60	21	21	48	43	30	31
	50	18	16	39	34	18	16	42	37	24	26
	25	15	12	24	19	15	14	36	31	18	21
Percentiles of patients treated < dose 4	75	12	10	12	10	9	7	18	13	18	13
	50	9	8	12	8	9	5	18	8	18	8
	25	9	5	9	3	9	3	18	3	18	3

*The plateau starts at 4.

Table III. Trial design properties for pattern of response 0.2–0.9 by 0.05.

	Proportion				Slope						
	[4/6]		[5/6]		3P/4L		6P/3L		6P/4L		
	Std	Acc	Std	Acc	Std	Acc	Std	Acc	Std	Acc	
Per cent dose $\geq 15^*$	0	0	1	1	1	4	2	8	0	0	
Per cent dose ≥ 13	0	0	9	9	2	9	4	16	0	2	
Per cent $13 \leq \text{dose} \leq 17$	0	0	9	9	2	7	3	13	0	2	
Percentiles of final dose level	75	8	9	11	11	6	9	7	10	4	8
	50	7	7	9	9	5	6	5	7	3	5
	25	5	5	8	8	3	5	3	6	2	4
Percentiles of # patients	75	33	28	48	42	21	23	48	53	30	31
	50	27	21	39	33	18	17	36	41	24	26
	25	21	15	30	24	12	14	30	32	18	20
Percentiles of patients treated < dose 15	75	33	28	48	42	21	22	48	51	30	31
	50	27	21	39	33	18	17	36	40	24	26
	25	21	15	30	24	12	14	30	32	18	20

*Plateau starts at 15.

is 0.9 but it still stops early. In Table II both Proportion designs continue to escalate beyond the beginning of the plateau since the plateau response rate is 0.5. Proportion [5/6] performs worse in this regard than Proportion [4/6]. Overall, Proportion [5/6] seems to perform better than Proportion [4/6] in most situations.

Table IV. Trial design properties for pattern of response 0.2–0.9 by 0.1.

	Proportion				Slope						
	[4/6]		[5/6]		3P/4L		6P/3L		6P/4L		
	Std	Acc	Std	Acc	Std	Acc	Std	Acc	Std	Acc	
Per cent dose $\geq 8^*$	1	2	13	13	44	54	57	75	7	35	
Per cent dose ≥ 7	9	11	37	13	50	62	63	81	12	49	
Per cent $7 \leq \text{dose} \leq 9$	9	11	37	38	16	18	15	17	11	37	
Percentiles of final dose level	75	6	6	7	7	10	11	11	11	5	8
	50	5	5	6	6	7	9	9	10	4	6
	25	4	4	5	5	5	5	5	8	2	5
Percentiles of # patients	75	24	19	30	27	33	30	66	62	36	38
	50	18	15	27	21	21	22	60	52	24	30
	25	15	12	21	16	15	15	36	41	18	25
Percentiles of patients treated < dose 8	75	24	19	30	26	21	18	42	37	36	31
	50	18	15	24	21	21	15	42	32	24	26
	25	15	12	21	16	15	13	36	27	18	21

*Plateau starts at 8.

Table V. Trial design properties for pattern of response 0.3–0.9 by 0.2.

	Proportion				Slope						
	[4/6]		[5/6]		3P/4L		6P/3L		6P/4L		
	Std	Acc	Std	Acc	Std	Acc	Std	Acc	Std	Acc	
Per cent dose $\geq 4^*$	21	23	50	51	96	97	97	99	86	97	
Per cent dose = 4	20	22	44	45	0	0	0	0	16	12	
Percentiles of final dose level	75	3	3	4	4	10	10	9	9	6	7
	50	3	3	4	4	7	7	7	7	5	5
	25	2	2	3	3	6	6	6	6	4	5
Percentiles of # patients	75	15	14	18	18	30	27	54	49	36	36
	50	12	11	15	14	24	21	42	42	36	31
	25	9	10	12	11	21	17	42	37	30	26
Percentiles of patients treated < dose 4	75	12	12	15	13	9	9	18	18	18	18
	50	12	10	12	10	9	7	18	13	18	13
	25	9	9	12	9	9	5	18	8	18	8

*Plateau starts at 4.

For the slope designs, 6P/4L tends to stop escalating quickly in all tables. In fact, it appears that the location of the plateau and the increase in the response rates between dose levels has very little impact on whether the design escalates, since percentiles of the final dose are similar in all four tables. Slope 3P/4L and 6P/3L tend to perform very similarly in terms of

per cent of studies reaching the plateau and median final dose level, but 3P/4L uses far fewer total patients and treats fewer patients below active doses. Therefore, Slope 3P/4L seems to perform best among the slope designs in the simulations studied here.

Comparing Proportion [5/6] with Slope 3P/4L, Slope 3P/4L performs slightly better than Proportions [5/6]: In Tables IV and V, Slope 3P/4L reaches the plateau much more often and treats fewer patients at inactive doses than Proportions [5/6]. In Table II the per cent reaching the plateau is similar between the two designs with Slope 3P/4L stopping closer to the plateau than Proportions [5/6]. In Table III neither design works well, with the median final dose level being 9 vs 6 (corresponding response rates at these dose levels are 0.6 and 0.45).

5. DISCUSSION

At the beginning of this investigation, it was not clear that it would be feasible to base a dose escalation on a molecularly targeted endpoint without requiring large numbers of patients treated at each dose level. Keeping the number of patients treated in a phase I trial low is important because one wants to quickly progress to trials that evaluate the efficacy of the agent. Our recommended design, Slope 3P/4L, appears to perform adequately with only three patients treated at each dose level when there are not too many dose levels before the response plateau. An adequate design with these small numbers of patients is possible because our goal for the slope design is to reach a dose that gives a response within 10 per cent of the maximum (in the plateau), rather than to find the 'optimum biological dose'. The choice of dose steps is important: based on our limited simulations none of the designs considered work well when there are many dose levels required to reach the plateau. This suggests that if the agent is not expected to cause toxicities, aggressive dose escalation steps may be desirable with these designs.

The use of the proposed designs assumes that there is a molecularly targeted endpoint which is associated with clinical benefit and for which accurate measurement is feasible. There can be many challenges in developing such an endpoint [12–15], and such challenges have probably led to their infrequent use [16]. Thus, even with a molecularly targeted agent, it may be appropriate to use a standard toxicity-driven trial design that escalates to a maximum dose that is tolerable or feasible to administer [17]. However, when an appropriate molecularly targeted endpoint is available, the proposed designs may facilitate the testing of agents and the achievement of clinical benefit at much lower doses than would be obtained from a standard toxicity-driven design.

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