Dose Finding in Early Phase I/II Cancer Clinical Trial Using Drug Combinations of Cytotoxic Agents

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Abstract

We present a two-stage dose finding phase I/II design of a combination of two drugs with continuous dose levels in early phase cancer clinical trials. The goal is to estimate dose combination regions that are tolerable and with a desired level of efficacy. In the first stage of the design, the relationship between doses and the probability of dose limiting toxicity (DLT) is modeled parametrically and the design proceeds using conditional escalation with overdose control. At the end of stage I, the maximum tolerated dose (MTD) curve is estimated as a function of Bayes estimates of the model parameters. In the second stage of the design, we investigate some parametric models to link the probability of treatment efficacy with dose combinations along the MTD curve. We propose a Bayesian adaptive design for conducting the phase II trial with the goal of determining dose combination regions along the MTD curve with a desired level of efficacy. The methodology is evaluated by presenting the operating characteristics under different scenarios for the true probability of treatment efficacy as a function of dose combinations on the MTD curve and trial sample size.

Key Words: Cancer Phase I trials; Phase I/II trials; Maximum tolerated dose; Escalation with overdose control; Drug combination; Dose limiting toxicity; Continuous dose; Treatment Efficacy; Bayesian adaptive design.

1. Introduction

The primary objective of cancer phase I/II clinical trials is to determine a tolerable dose level that maximizes treatment efficacy. For treatments where response evaluation takes few cycles of therapy, it is standard practice to perform a two-stage design where a maximum tolerable dose (MTD) of a new drug or combinations of drugs is first determined, then this recommended phase II dose is studied in stage 2 and evaluated for treatment efficacy, possibly using a different population of cancer patients from stage 1. The two-stage design is routinely used in early phase cancer trials investigating a single agent or combinations of 2 or more drugs except that in stage 2, a single dose level is investigated. It is well known that combining several drugs in cancer treatment can help reduce tumor resistance to chemotherapy by targeting different signaling pathways simultaneously and improve tumor response when using additive or synergistic drugs [1]. To this end, dose combination phase I trials where the dose levels of at least two agents

are allowed to vary have been studied extensively in the last decade [2-15]. Some of these methods are designed to identify a single MTD combination whereas others can yield several or even an infinite number of MTDs. Recommending a single MTD combination for efficacy study may result in a failed phase II trial since other MTDs may present higher treatment efficacy. Methods that pre-specify a small number of dose combinations can miss dose combinations with similar acceptable DLT level and possibly with higher probability of response. This could happen for two reasons. First, the discrete set of dose combinations is selected by the investigator based on prior experience with single agents. Therefore, when these agents are combined, the selected set may not include intermediate dose combinations with probability of DLT close to the target probability of DLT and target probability of treatment response. Second, even if this discrete set includes dose combinations with probability of DLT close to the target, their probability of response may be very different and these approaches may recommend a dose with lower probability of response.

In this report, we propose a two-stage design using dose combinations of two drugs with continuous dose levels. In the first stage, a phase I trial is carried out and an estimated MTD curve is proposed using escalation with overdose approach (EWOC) [13, 14] . An alternative approach is to use the continual reassessment method (CRM) as described in [15]. In the second stage, we describe a Bayesian adaptive design to carry out a phase II trial searching for dose combinations along the estimated MTD curve from stage 1 that yield the highest probability of treatment efficacy. We evaluate the performance of the method using parametric models and extensive simulations with sample sizes that are typically used in single agent phase II trials.

2. Model

In this section, we describe the models and algorithms used to carry out a two-stage design for identifying tolerable and efficacious dose combinations of cytotoxic agents. Stage 1 is a review of the models and algorithms described in Tighiouart et al.[13, 14].

2.1 Stage 1

Consider the dose-toxicity model of the form

$$\text{Prob}(Z = 1 \mid x, y) = F(\mu + \beta x + \gamma y + \eta xy), \tag{2.1}$$

where Z is the indicator of DLT, $Z = 1$ if a patient given the dose combination (x,y) exhibits DLT within one cycle of therapy, and $Z = 0$ otherwise, $x \in [X_{\min}, X_{\max}]$ is the dose level of agent A, $y \in [Y_{\min}, Y_{\max}]$ is the dose level of agent B, and F is a known cumulative distribution function. Suppose that the doses of agents A and B are continuous and standardized to be in the interval [0, 1].
We will assume that that the probability of DLT increases with the dose of any one of the agents when the other one is held constant. A necessary and sufficient condition for this property to hold is to assume $\beta > 0$ and $\gamma > 0$ and the interaction term η is nonnegative. The MTD is defined as any dose combination (x^*, y^*) such that

$$\text{Prob}(Z = 1 \mid x^*, y^*) = \theta. \tag{2.2}$$

The target probability of DLT θ is set relatively high when the DLT is a reversible or non-fatal condition, and low when it is life threatening. We reparameterize model (2.1) in terms of parameters clinicians can easily interpret. One way is to use ρ_{10}, the probability of DLT when the levels of drugs A and B are 1 and 0, respectively, ρ_{01}, the probability of DLT when the levels of drugs A and B are 0 and 1, respectively, and ρ_{00}, the probability of DLT when the levels of drugs A and B are both 0. It can then be shown that the MTD is

$$C = \left\{ (x^*, y^*) : y^* = \frac{\left(F^{-1}(\theta) - F^{-1}(\rho_{00})\right) - \left(F^{-1}(\rho_{10}) - F^{-1}(\rho_{00})\right)x^*}{\left(F^{-1}(\rho_{01}) - F^{-1}(\rho_{00})\right) + \eta x^*} \right\}. \tag{2.3}$$

Let $D_n = \{(x_i, y_i, z_i),\ i = 1, \ldots, n\}$ be the data after enrolling n patients in the trial. The likelihood function is

$$\begin{aligned} L(\rho_{00}, \rho_{01}, \rho_{10}, \eta \mid D_n) = \prod_{i=1}^{n} & \left(G(\rho_{00}, \rho_{01}, \rho_{10}, \eta; x_i, y_i)\right)^{z_i} \\ & \times \left(1 - G(\rho_{00}, \rho_{01}, \rho_{10}, \eta; x_i, y_i)\right)^{1-z_i}, \end{aligned} \tag{2.4}$$

where

$$\begin{aligned} & G(\rho_{00}, \rho_{01}, \rho_{10}, \eta; x_i, y_i) \\ & = F\left(F^{-1}(\rho_{00}) + \left(F^{-1}(\rho_{10}) - F^{-1}(\rho_{00})\right)x_i + \left(F^{-1}(\rho_{01}) - F^{-1}(\rho_{00})\right)y_i + \eta x_i y_i\right). \end{aligned} \tag{2.5}$$

2.1.1 Prior and Posterior Distributions

Under model reparameterization 1, (2.4) implies that $0 < \rho_{00} < \theta$ since $\beta > 0$. We consider the priors $\rho_0/\theta \sim$ beta(a_1, b_1), $\Gamma_{A|0} \sim$ beta(a_2, b_2), $\Gamma_{B|0} \sim$ beta(a_3, b_3), $\eta \sim$ gamma(a, b) with mean $E(\eta) = a / b$ and variance $Var(\eta) = a / b^2$. Vague priors for these parameters are achieved by taking $a_j = b_j = 1$, $j = 1, 2, 3$. A vague prior for η is then achieved by setting $E(\eta) = 8\left(F^{-1}(\theta) - F^{-1}(E(\rho_{00}))\right) \Big/ E(\Gamma_{A|0})E(\Gamma_{B|0})$. A large variance is selected for η, see [16] for the rationale behind this choice. Using Bayes rule, the posterior distribution of the model parameters is proportional to the product of the likelihood and prior distribution

$$\begin{aligned} \pi(\rho_{00}, \Gamma_{A|0}, \Gamma_{B|0}, \eta \mid D_n) \propto \prod_{i=1}^{n} & \left(F(\rho_{00}, \Gamma_{A|0}, \Gamma_{B|0}, \eta; x_i, y_i)\right)^{z_i} \\ & \times \left(1 - F(\rho_{00}, \Gamma_{A|0}, \Gamma_{B|0}, \eta; x_i, y_i)\right)^{1-z_i} \rho_{00}^{\,a_1 - 1}\left(1 - \rho_{00}\right)^{b_1 - 1} \\ & \times \left(\Gamma_{A|0}\right)^{a_2 - 1}\left(1 - \Gamma_{A|0}\right)^{b_2 - 1}\left(\Gamma_{B|0}\right)^{a_3 - 1}\left(1 - \Gamma_{B|0}\right)^{a_3 - 1}\eta^{a-1}e^{-b\eta}. \end{aligned} \tag{2.6}$$

Features of this posterior distribution are estimated using WinBUGS[17] and JAGS.

2.1.2 Trial Design

We review a dose allocation algorithm described in [13] using EWOC principle where at each stage of the trial, the posterior probability of overdosing a future patient is bounded by a feasibility bound α. An alternative algorithm enrolling cohorts of two patients simultaneously receiving different dose combinations can be found in [14].

1. The first patient receives dose $(x_1, y_1) = (0, 0)$ and suppose the patient has no DLT, $z_1 = 0$.
2. Fix $x_1 = 0$, and calculate the posterior distribution of the MTD of agent B, given that the level of agent A is $x_1 = 0$, $\pi(\Gamma_{B|A=0} \mid D_1)$. The dose for patient 2 is (x_2, y_2) where $x_2 = x_1$ and y_2 is the α-th percentile of this posterior distribution.
3. Fix y_2, and calculate the posterior distribution of the MTD of agent A, given that the level of agent B is y_2, $\pi(\Gamma_{A|B=y2} \mid D_1)$. The dose for patient 3 is (x_3, y_3) where x_3 is the α-th percentile of this posterior distribution and $y_3 = y_2$.

In general, when we move from dose (x_i, y_i) to (x_{i+1}, y_{i+1}), either $x_i = x_{i+1}$ or $y_i = y_{i+1}$. Specifically, if i is even, then $x_{i+1} = \Pi^{-1}_{\Gamma_{A|B=y_i}}(\alpha \mid D_i)$ and $y_{i+1} = y_i$. If i is odd, then $x_{i+1} = x_i$ and $y_{i+1} = \Pi^{-1}_{\Gamma_{B|A=x_i}}(\alpha \mid D_i)$. Here, $\Pi^{-1}_{\Gamma_{A|B=y_i}}(\alpha \mid D_i)$ is the inverse cdf of the posterior distribution $\pi(\Gamma_{A|B=y_i} \mid D_i)$.

4. Repeat step 3 by fixing either dose x_i or y_i, depending on whether i is even or odd, until n patients are enrolled to the trial subject to the following stopping rule.

Stopping rule: We stop enrollment to the trial if $P(P(\text{DLT}|(x,y) = (0,0)) \geq \theta + \delta_1 \mid \text{data}) > \delta_2$, i.e. if the posterior probability that the probability of DLT at the minimum available dose combination in the trial exceeds the target probability of DLT is high. δ_1 and δ_2 are design parameters chosen to achieve desirable model operating characteristics.

At the end of the trial, we estimate the MTD curve using Bayes estimates of the parameters defining this curve. For example, an estimate of the MTD curve is obtained using (2.7) as

$$\hat{C} = \left\{ (x^*, y^*) : y^* = \frac{\left(F^{-1}(\theta) - F^{-1}(\hat{\rho}_{00})\right) - \left(F^{-1}(\hat{\rho}_{10}) - F^{-1}(\hat{\rho}_{00})\right) x^*}{\left(F^{-1}(\hat{\rho}_{01}) - F^{-1}(\hat{\rho}_{00})\right) + \hat{\eta} x^*} \right\}, \qquad (2.7)$$

where $\hat{\rho}_{00}, \hat{\rho}_{01}, \hat{\rho}_{10}, \hat{\eta}$ are the posterior medians given the data D_n.

Design operating characteristics of the method were studied extensively in [13, 14]. Figure 1 shows part of the simulation results under one scenario as reported in [13]. Suppose that the dashed line in this figure represents an estimated MTD curve from a phase I trial. In stage 2, we describe a phase II trial aimed at searching for dose combinations along this curve that yield a maximum probability of efficacy.

2.2 Stage 2

2.2.1 Model

Let C_{est} be the estimated MTD curve obtained from a phase I study using one of the methods described in [13, 14]. Let δ be the indicator of treatment response such as tumor shrinkage, $\delta = 1$ if we have a positive response after a pre-defined number of treatment

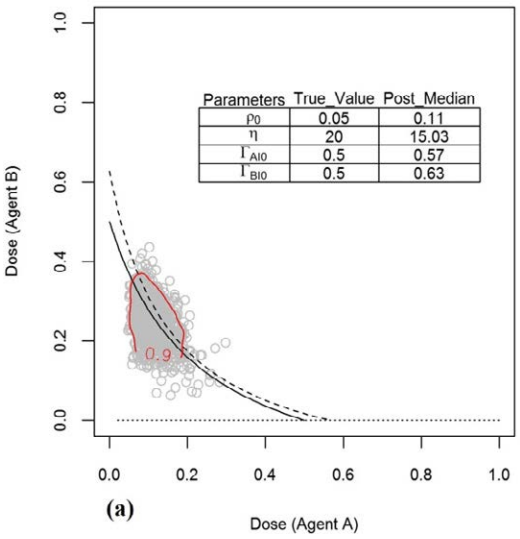


Figure 1. Summary statistics from m =1000 simulated trials under scenario 1. (a) shows the true and estimated MTD curve. The grey diamonds represent the last dose combination from each simulated trial along with a 90% confidence region.

cycles, and $\delta = 0$ otherwise. Let p_1 be the target probability of response, i.e., the minimum probability of response for the treatment to be worth pursuing in a large phase III trial. We propose to carry out a phase II study to identify dose combinations $\boldsymbol{x}$ in C_{est} such that $P(\delta = 1 \mid \text{dose} = \boldsymbol{x}) > p_1$. Let x be the dose of drug A such that $(x, y) \in C_{est}$ and suppose that x is standardized to be in the interval [0, 1]. In the sequel, x denotes both the standardized dose and the corresponding dose combination on C_{est}. We model the probability of treatment response given dose combination x in C_{est} as

$$P(\delta = 1 \mid x, \boldsymbol{\rho}) = F(f(x; \boldsymbol{\rho})), \tag{2.8}$$

where F is a known link function and $f(x; \boldsymbol{\rho})$ is an unknown function. Note that x_2 is uniquely determined by x_1 and the MTD curve. Let $D_m = \{(\delta_i, x_i), i=1,\ldots,m\}$ be the data after enrolling m patients in the trial, where δ_i is the response of the ith patient treated with dose combination x_i and $\pi(\boldsymbol{\rho})$ be a prior density on the parameter $\boldsymbol{\rho}$. The posterior distribution is

$$\pi(\boldsymbol{\rho} \mid D_m) \propto \prod_{i=1}^{m} \left[F(f(x_i; \boldsymbol{\rho}))\right]^{\delta_i} \left[1 - F(f(x_i; \boldsymbol{\rho}))\right]^{1-\delta_1} \pi(\boldsymbol{\rho}). \tag{2.9}$$

Let p_x be the probability of treatment efficacy at dose combination x and denote by p_0 the probability of efficacy of a poor treatment. We describe an algorithm to conduct a phase II trial in order to test the hypothesis

H_0: $p_x \leq p_0$ for all x versus H_1: $p_x > p_0$ for some dose combination x.

2.2.2 Algorithm

1. Treat n_1 patients at dose combinations $x_1,\ldots,x_{n1}$ equally spaced along the MTD curve.
2. Obtain a Bayes estimate $\hat{\boldsymbol{\rho}}$ of $\boldsymbol{\rho}$ given the data D_{n1} using (2.9).
3. Generate n_2 dose combinations from the standardized density $F(f(x;\hat{\boldsymbol{\rho}}))$ and assign them to the next n_2 patients.
4. Repeat steps 2 and 3 until a total of n patients have been enrolled to the trial subject to pre-specified stopping rules.

This algorithm can be viewed as an extension of a Bayesian adaptive design to select a superior arm among a finite number of arms [18] to selecting a superior arm from an infinite number of arms.

Decision rule:
We accept the alternative hypothesis if

$$Max_x \left[P(F(f(x;\rho)) > p_0 \mid D_n \right] > \delta_u, \tag{2.10}$$

where δ_u is a design parameter. In this report, stopping rules for futility or early efficacy were not implemented.

3. Simulation Studies

3.1 Simulation Set-up and Scenarios

We evaluate design operating characteristics by assuming a logistic link function $F(u) = (1 + exp(-u))^{-1}$ and a quadratic function $f(x) = a\,(x - h)^2 + k$ in (2.8). This is a simple form of $f(\cdot)$ yet flexible enough to accommodate cases of constant probability of efficacy along the MTD curve, high probability of efficacy around the middle of the MTD curve and high probability of efficacy at the edges of the MTD curve. We explored sample sizes of 40 and 50, $p_0 = 0.3, 0.5, 0.7$, argmax $f(x) = 0.0, 0.2, 0.5, 0.8, 0.1$, and target effect size of 0.2. Vague priors are achieved by assuming that a, h, k are independent a priori with $a \sim N(0, 10^8)$, $h \sim U(0, 1)$, $k \sim U(-6.3, 3.7)$. The initial number of patients enrolled to the trial was set to $n_1 = 10$ and $n_2 = 5$ was used in the adaptive phase of the design. The design parameter for the decision rule in (2.10) was taken as $\delta_u = 0.8$. In each scenario, we simulated $m = 2000$ trial replicates the true model using the true model to generate the binary responses.

3.2 Design Operating Characteristics

For each scenario, we report an estimated "Bayesian power" and a "type I error probability" by estimating the probability of accepting the alternative hypothesis (under a particular alternative) using the equation

$$P(H_1) \approx \frac{1}{m}\sum_{i=1}^{m} I\left(Max_x P_i\left(F(f(x;\boldsymbol{\rho})) > p_0 \mid D_{n,i} \right) > \delta_u \right), \tag{3.1}$$

where

$$P_i\left(F(f(x;\boldsymbol{\rho})) > p_0 \mid D_{n,i} \right) \approx \frac{1}{M}\sum_{j=1}^{M} I\left(F(f(x;\boldsymbol{\rho}_{j,i})) > p_0 \right), \tag{3.2}$$

and $\boldsymbol{\rho}_{1,i},\ldots,\boldsymbol{\rho}_{M,i}$ is an MCMC sample from the posterior distribution $\pi(\boldsymbol{\rho} \mid D_{n,i})$. We also report the estimated efficacy curve by replacing $\boldsymbol{\rho}$ in (2.8) by the average posterior medians across all simulated trials

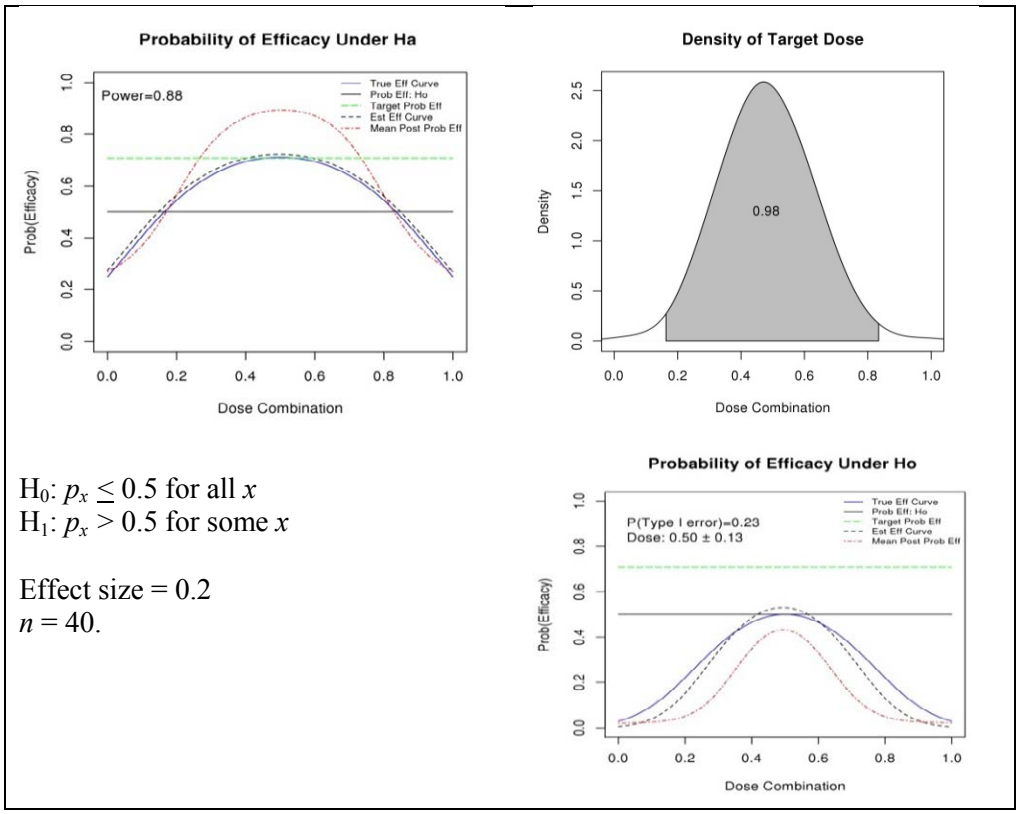
$$F(f(x;\bar{\boldsymbol{\rho}})) \tag{3.3}$$

where $\bar{\boldsymbol{\rho}} = (\bar{a},\bar{h},\bar{k})$, $\bar{a} = m^{-1}\sum_{i=1}^{m}\hat{a}_i$ and $\hat{a}_i$ is the posterior median from the *i*-th trial. The statistics $\bar{h},\bar{k}$ are similarly defined. Finally, we also report the mean posterior probability of efficacy curve

$$\frac{1}{m}\sum_{i=1}^{m} P_i\left(F(f(x;\boldsymbol{\rho})) > p_0 \mid D_{n,i}\right). \tag{3.4}$$

3.3 Results

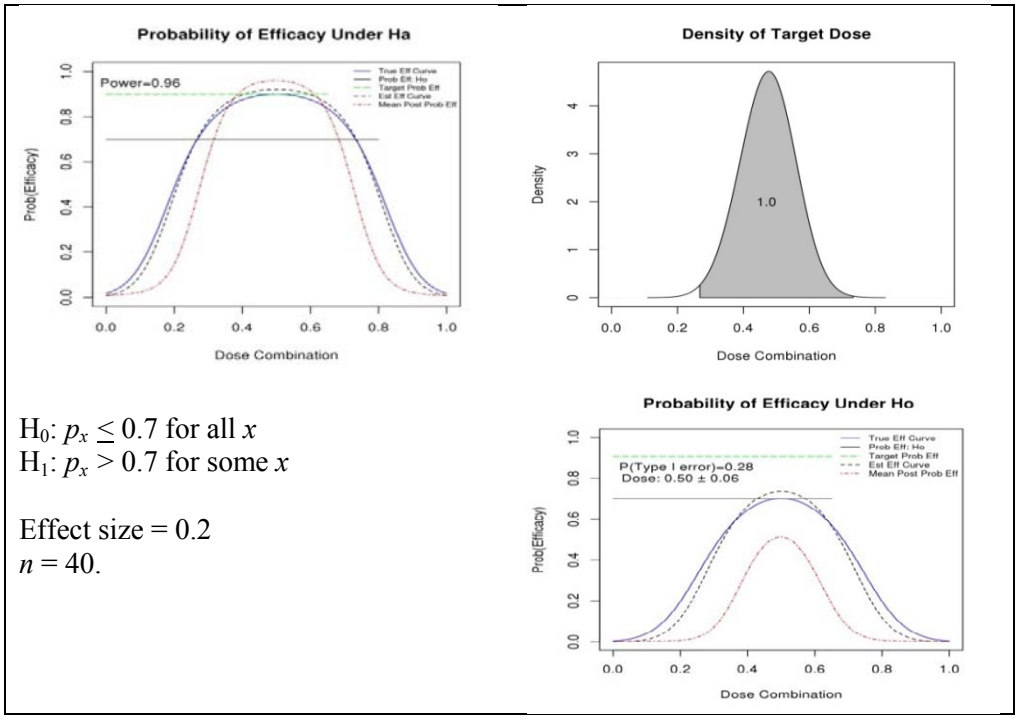
We present the results of five scenarios in Figures 2−6. Figure 2 is a case where the true probability of efficacy shown by the blue curve is highest at the standardized dose combination $x = 0.5$ and is higher than the probability of a poor treatment in the interval [0.18, 0.82]. The effect size is 0.2 and this is achieved at a single dose combination $x = 0.5$ corresponding to the intersection of the blue curve and the green horizontal line. The true probability of response decreases as we move away from the middle of the MTD curve. The dashed black curve is the estimated efficacy curve as defined in (3.3) and is very close to the true efficacy curve. The mean posterior probability of efficacy defined in (3.4) and shown in red is higher in a neighborhood of $x = 0.5$ as expected. The probability of accepting the alternative under this scenario as defined in (3.1) is 0.88. This can be interpreted as the "Bayesian power" of the test under this particular alternative hypothesis. The top right of Figure 2 gives the estimated density of the dose combinations that satisfy the decision rule (2.10). This shows that the probability of selecting a dose combination that has a probability of treatment response of more than p_0 is 0.98. The mode of this density is $x = 0.5$. The bottom right of Figure 1 is a case where the probability of treatment response does not exceed $p_0 = 0.5$ for all dose combinations, see the blue curve. In this case, the mean posterior probability of efficacy is low with a maximum value of 0.42 achieved at $x = 0.5$ as expected. The probability of accepting the alternative under this scenario is 0.23 and can be interpreted as the "Bayesian type I error probability" under this particular scenario. The scenario in Figure 3 is similar to the previous one except for the probability of a poor treatment response $p_0 = 0.7$. The power of the test is 0.96 and the probability of a type I error is 0.28. The target dose is selected with probability 1. Figure 4 is a scenario where the probability of treatment response is very low on one part of the estimated MTD curve and is more than $p_0 = 0.5$ for dose combination in [0.06, 0.35] with the target probability of response $p_1 = 0.7$ achieved at dose combination $x = 0.2$. Power in this case is 0.86 and the dose combination with probability of efficacy above $p_0 = 0.5$ is selected 93% of the time. The bottom right of Figure 4 shows that the probability of a type I error under that scenario is 0.21. Figure 5 is a similar situation except that the probability of a poor treatment response, $p_0 = 0.3$. In this case, we increased the sample size to $n = 50$ in order to achieve a power of 0.84



H_0: $p_x \leq 0.5$ for all x
H_1: $p_x > 0.5$ for some x

Effect size = 0.2
$n = 40$.

Figure 2. Power (top left), type I error probability (bottom right), and distribution of selected dose combination with desired probability of efficacy.



H_0: $p_x \leq 0.7$ for all x
H_1: $p_x > 0.7$ for some x

Effect size = 0.2
$n = 40$.

Figure 3. Power (top left), type I error probability (bottom right), and distribution of selected dose combination with desired probability of efficacy.

and a type I error probability of 0.14. The last scenario shown in Figure 6 is a rare situation where the probability of treatment response is lowest in the middle of the estimated MTD curve and increases as we approach the edges of the MTD curve. This may happen if the effect of either drug is attenuated by the effect of the other drug, a situation that can arise when dealing with two antagonistic drugs. In this case, power is 0.87 and the target dose combination is selected with probability 0.48 + 0.49 = 0.97. The bottom right of Figure 6 shows that the type I error is 0.15. We note that the true probability of efficacy curve at the top right of Figure 6 exceeds the target $p_1 = 0.7$ in the set $[0, 0.07] \cup [0.93,1]$. If we consider the case where this curve achieves the target $p_1 = 0.7$ at the two dose combinations 0 and 1 only, then the power of the test is decreased significantly and the trial will require a much larger sample size. Therefore, it is important to discuss the plausible scenarios that may occur in practice with the clinician to elucidate the design operating characteristics. Based on these preliminary results, we conclude that phase II trials searching for dose combinations along the MTD curve that yield high probability of treatment response are feasible with reasonable sample sizes. We are currently assessing the performance of this design under model misspecification and implementing stopping rules for early treatment efficacy or futility and rejecting dose combination regions with low probability of treatment efficacy during the trial.

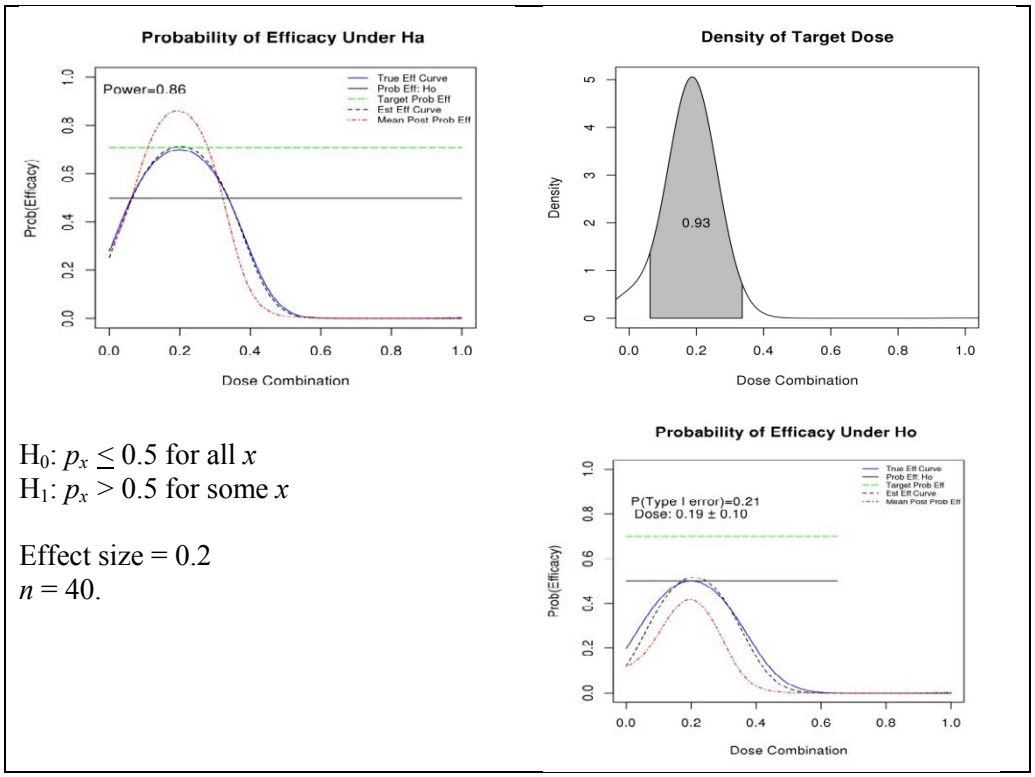
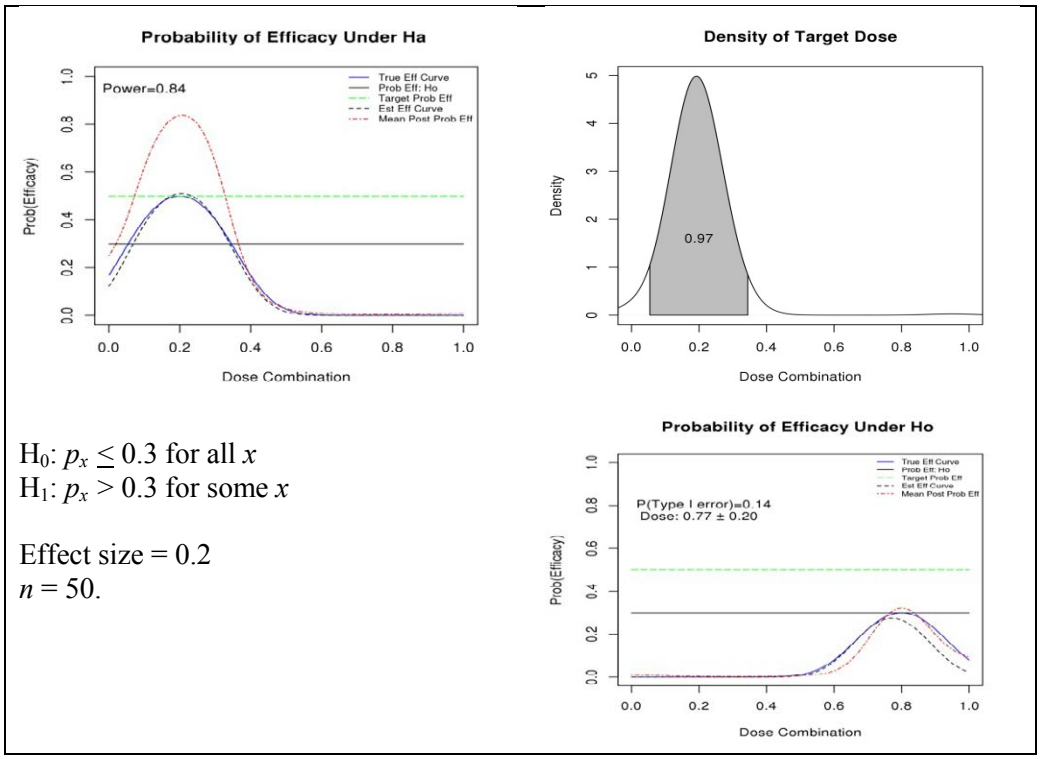


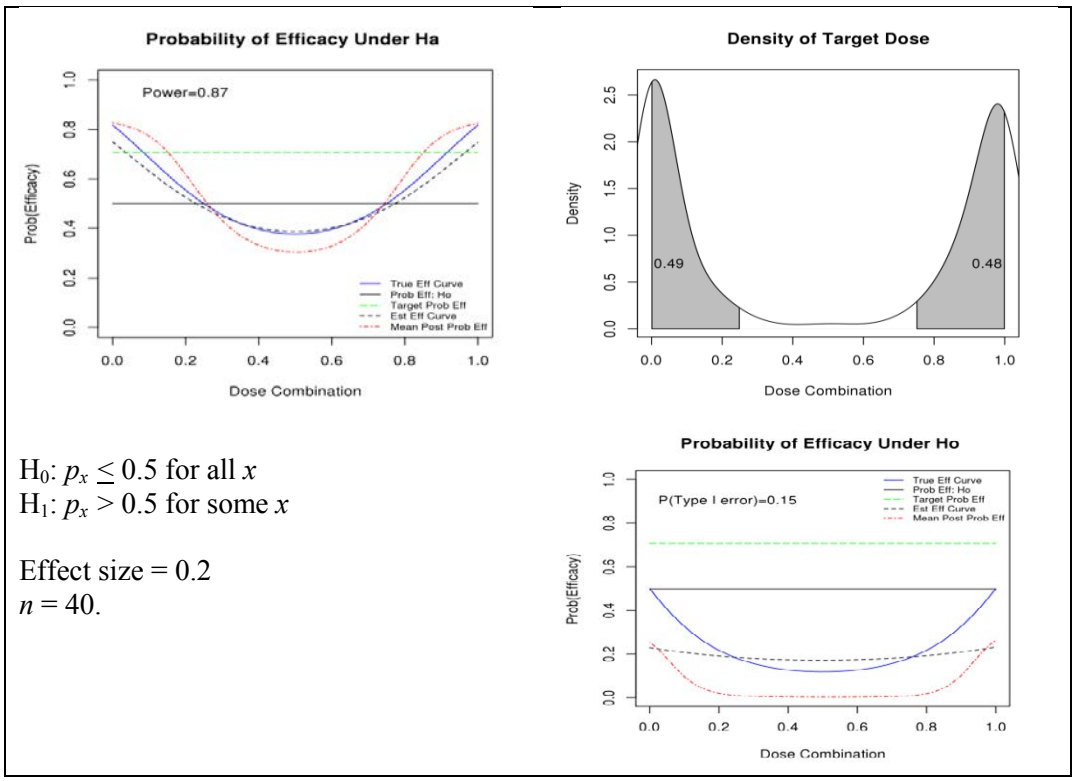
Figure 4. Power (top left), type I error probability (bottom right), and distribution of selected dose combination with desired probability of efficacy.



H_0: $p_x \leq 0.3$ for all x
H_1: $p_x > 0.3$ for some x

Effect size = 0.2
$n = 50$.

Figure 5. Power (top left), type I error probability (bottom right), and distribution of selected dose combination with desired probability of efficacy.



H_0: $p_x \leq 0.5$ for all x
H_1: $p_x > 0.5$ for some x

Effect size = 0.2
$n = 40$.

Figure 6. Power (top left), type I error probability (bottom right), and distribution of selected dose combination with desired probability of efficacy.

4. Discussion

We described a two-stage Bayesian adaptive design for cancer phase I clinical trials using two drugs with continuous dose levels. The goal is to (1) estimate the MTD curve in the two-dimensional Cartesian plane and (2) search for dose combination regions along the MTD curve that yield a desired probability of treatment response. Design of the phase I trial and estimation of the MTD curve in stage 1 can be carried out using either EWOC [14, 16] or CRM [15]. In each case, we showed that a sample size of 40 patients yield good operating characteristics under a large number of scenarios with vague prior knowledge about the toxicity profiles of each agent. In stage 2, we modeled treatment efficacy as a binary indicator of treatment response using a quadratic form of the dose combination-treatment response relationship. This is a reasonable assumption since it accommodates cases of constant probability of efficacy along the MTD curve, high probability of efficacy around the middle of the MTD curve, high probability of efficacy at the edges of the MTD curve, and makes the model parsimonious. In this stage, a Bayesian adaptive design is proposed to conduct a phase II trial with the goal of identifying dose combination regions that yield a desired probability of treatment response. Initially, a number of patients are treated with dose combinations equally spaced along the estimated MTD curve from stage 1 and after resolving their treatment response status, the estimated probability of efficacy curve is updated. A small number of patients are then allocated to dose combinations generated from this updated efficacy curve. The trial continues until we reach the final sample size. This design can be viewed as an extension of the Bayesian adaptive design comparing a finite number of arms [18] to comparing an infinite number of arms.

We studied the properties of this design under 5 scenarios for the true probability of efficacy as a function of dose combinations and we found that the method yields reasonable power and type I error probability using sample size between 40 and 50. Based on these scenarios and proposed models, we conclude that this two-stage design is feasible with a total sample size of 90 to 100. We are currently studying the performance of stage 2 under model misspecification and implementing stopping rules for futility, early efficacy, and dropping dose combination regions with statistical evidence of low probability of treatment efficacy during the trial.

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References

1. Frey E, III., Karon M, Levin RH, Freireich EJ, Taylor RJ, Hananian J, Selawry O, Holland JF, Hoogstraten B, Wolman IJ, Abir E, Sawitsky A, Lee S, Mills SD, Burgert EO, Spurr CL, Patterson RB, Ebaugh FG, James GWI, Moon JH. The Effectiveness of

Combinations of Antileukemic Agents in Inducing and Maintaining Remission in Children with Acute Leukemia. *Blood* 1965; **26**: 642-656.
2. Thall PF, Millikan RE, Mueller P, Lee SJ. Dose-finding with two agents in phase I oncology trials. *Biometrics* 2003; **59**: 487-496.
3. Wang K, Ivanova A. Two-dimensional dose finding in discrete dose space. *Biometrics* 2005; **61**: 217-222.
4. Yin GS, Yuan Y. A Latent Contingency Table Approach to Dose Finding for Combinations of Two Agents. *Biometrics* 2009; **65**: 866-875.
5. Yin GS, Yuan Y. Bayesian dose finding in oncology for drug combinations by copula regression. *Journal of the Royal Statistical Society Series C-Applied Statistics* 2009; **58**: 211-224.
6. Braun TM, Wang SF. A Hierarchical Bayesian Design for Phase I Trials of Novel Combinations of Cancer Therapeutic Agents. *Biometrics* 2010; **66**: 805-812.
7. Wages NA, Conaway MR, O'Quigley J. Continual Reassessment Method for Partial Ordering. *Biometrics* 2011; **67**: 1555-1563.
8. Wages NA, Conaway MR, O'Quigley J. Dose-finding design for multi-drug combinations. *Clinical Trials* 2011; **8**: 380-389.
9. Sweeting MJ, Mander AP. Escalation strategies for combination therapy Phase I trials. *Pharmaceutical Statistics* 2012; **11**: 258-266.
10. Shi Y, Yin G. Escalation with overdose control for phase I drug-combination trials. *Stat Med* 2013: in press.
11. Riviere MK, Yuan Y, Dubois F, Zohar S. A Bayesian dose-finding design for drug combination clinical trials based on the logistic model. *Pharm Stat* 2014; **13**: 247-257.
12. Mander AP, Sweeting MJ. A product of independent beta probabilities dose escalation design for dual-agent phase I trials. *Stat Med* 2015; **34**: 1261-1276.
13. Tighiouart M, Piantadosi S, Rogatko A. Dose finding with drug combinations in cancer phase I clinical trials using conditional escalation with overdose control. *Stat Med* 2014; **33**: 3815-3829.
14. Tighiouart M, Piantadosi S, Rogatko A. Dose finding for drug combination in early cancer phase I trials using conditional escalation with overdose control. In JSM Proceedings, Biopharmaceutical section, Alexandria, VA: American Statistical Association. 2014.
15. Tighiouart M, Li Q. Dose Finding for Drug Combination in Early Cancer Phase I Trials using Conditional Continual Reassessment Method. In JSM Proceedings, Biopharmaceutical section, Alexandria, VA: American Statistical Association. 2015.
16. Tighiouart M, Piantadosi S, Rogatko A. Dose finding with drug combinations in cancer phase I clinical trials using conditional escalation with overdose control. *Stat Med* 2014; **33**: 3815-3829.
17. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS - A Bayesian modelling framework: Concepts, structure, and extensibility. *Statistics and Computing* 2000; **10**: 325-337.
18. Berry SM, Carlin BP, Lee JJ, Muller P. *Bayesian Adaptive Methods for Clinical Trials*. Chapan & Hall: Boca Raton, Florida, 2011.