Two-Stage Design For Phase I/II Cancer Clinical Trials Using Drug Combinations of Cytotoxic Agents

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Abstract

We present a two-stage phase I/II design of a combination of two drugs in cancer clinical trials. The goal is to estimate safe dose combination regions with a desired level of efficacy. In stage I, conditional escalation with overdose control is used to allocate dose combinations to successive cohorts of patients and the maximum tolerated dose curve is estimated as a function of Bayes estimates of the model parameters. In stage II, we propose a Bayesian adaptive design for conducting the phase II trial to determine dose combination regions along the MTD curve with a desired level of efficacy. The methodology is evaluated by some simulations and application to a real trial.

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

Early phase I/II cancer clinical trials are relatively small trials designed to identify safe and promising dose levels of cytotoxic or biologic agents for use in large phase III trials. When response evaluation such as tumor shrinkage or disease progression takes few cycles of therapy to assess, 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 MTD is tested in stage 2 and evaluated for treatment efficacy, possibly using a different population of cancer patients from stage 1. It is well known that combining several cytotoxic and molecular targeted drugs in cancer treatment help reduce tumor resistance by targeting different signaling pathways simultaneously and improve tumor response when using additive or synergistic drugs [1]. As a result, dose combination phase I trials where the dose levels of two or more agents are allowed to vary have been studied extensively in the last decade [2-17]. Some of these methods are designed to identify a single MTD combination whereas others can yield several or even an infinite number of MTDs. In theory, methods that recommend a set of MTDs that can be carried forward to phase II studies may be preferable to using a single MTD since they are less likely to miss tolerable dose combinations that are efficacious. However, practical considerations such as logistics in conducting the trial, limitation of the number

of patients, and approval from sponsors of the trial may limit the use of exploration of several MTDs in a phase II trial.

In this paper, 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] . In the second stage, we describe a Bayesian adaptive design to carry out a phase II trial to identify 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 cubic spline functions for the logit of the probability of efficacy and derive the operating characteristics of the design. The methodology is further applied to a prospective phase I/II trial combining Cisplatin and Cabazitaxel (CisCab) in patient with advanced prostate cancer.

2. Stage 1

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, 16].

2.1 Model

Consider the dose-toxicity model of the form

$$\text{Prob}(T=1\,|\,x,y)=F(\eta_0+\eta_1 x+\eta_2 y+\eta_3 xy), \tag{2.1}$$

where T is the indicator of DLT, $T = 1$ if a patient given the dose combination (x,y) exhibits DLT within one cycle of therapy, and $T = 0$ 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] and the interaction term $\eta_3 > 0$.

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 $\eta_1 > 0$ and $\eta_2 > 0$. The MTD is defined as any dose combination (x^*, y^*) such that

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

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

$$C=\left\{(x^*,y^*): y^*=\frac{\left(F^{-1}(\theta)-F^{-1}(\rho_{00})\right)-\left(F^{-1}(\rho_{10})-F^{-1}(\rho_{00})\right)x^*}{\left(F^{-1}(\rho_{01})-F^{-1}(\rho_{00})\right)+\eta_3 x^*}\right\}. \tag{2.3}$$

Following the work of Tighiouart et al. [16], we assume that ρ_{01}, ρ_{10}, η_3 are independent *a priori* with $\rho_{01} \sim$ beta(a_1, b_1), $\rho_{10} \sim$ beta(a_2, b_2), and conditional on (ρ_{01}, ρ_{10}), $\rho_{00}/\min(\rho_{01}, \rho_{10}) \sim$ beta(a_3, b_3). The prior distribution of the interaction parameter η_3 is gamma with mean a / b and variance a / b^2. If $D_n = \{(x_i,y_i,T_i), i = 1, \ldots, n\}$ be the data after enrolling n patients in the trial, the posterior distribution of the model parameters is

$$\begin{aligned}\pi(\rho_{00},\rho_{01},\rho_{10},\eta_3 \mid D_n) \propto \prod_{i=1}^{n}&\left(G(\rho_{00},\rho_{01},\rho_{10},\eta_3;x_i,y_i)\right)^{T_i}\\ &\times\left(1-G(\rho_{00},\rho_{01},\rho_{10},\eta_3;x_i,y_i)\right)^{1-T_i}\\ &\times\pi(\rho_{01})\pi(\rho_{10})\pi(\rho_{00}\mid\rho_{01},\rho_{10})\pi(\eta_3),\end{aligned} \tag{2.4}$$

where

$$\begin{aligned}&G(\rho_{00},\rho_{01},\rho_{10},\eta;x_i,y_i)\\ &=F\left(F^{-1}(\rho_{00})+\left(F^{-1}(\rho_{10})-F^{-1}(\rho_{00})\right)x_i+\left(F^{-1}(\rho_{01})-F^{-1}(\rho_{00})\right)y_i+\eta_3 x_i y_i\right).\end{aligned} \tag{2.5}$$

Features of this posterior distribution are estimated using WinBUGS[18] and JAGS.

2.2 Trial Design

Dose escalation/de-escalation proceeds by treating cohorts of two patients simultaneously. It is based on the escalation with overdose control (EWOC) principle where at each stage of the trial, the posterior probability of overdosing a future patient is bounded by a feasibility bound α, see e.g. [19-21]. An alternative algorithm enrolling cohorts of two patients simultaneously receiving different dose combinations can be found in [14]. For a given cohort, one subject receives a new dose of agent A for a given dose of agent B that was previously assigned and the other patient receives a new dose of agent B for a given dose of agent A that was previously assigned. The algorithm is described in Tighiouart et al.[16] and is reviewed here for convenience.

1. The first two patients receive the same dose combination dose $(x_1, y_1) = (x_2, y_2) = (0, 0)$ and let $D_2 = \{(x_1, y_1, T_1), (x_2, y_2, T_2)\}$.
2. In the second cohort, patients 3 and 4 receive doses (x_3, y_3) and (x_4, y_4), respectively, where $y_3 = y_1$, $x_4 = x_2$, x_3 is the α-th percentile of $\pi(\Gamma_{A|B=y1} \mid D_2)$ and y_4 is the α-th percentile of $\pi(\Gamma_{B|A=x2} \mid D_2)$.
3. In the i-th cohort of two patients, if i is even, then patient $2i-1$ receives dose (x_{2i-1}, y_{2i-3}), patient $2i$ receives dose (x_{2i-2}, y_{2i}), where $x_{2i-1} = \Pi^{-1}_{\Gamma_{A|B=y_{2i-3}}}(\alpha \mid D_{2i-2}), y_{2i} = \Pi^{-1}_{\Gamma_{B|A=x_{2i-2}}}(\alpha \mid D_{2i-2})$. If i is odd, then patient $2i-1$ receives dose (x_{2i-3}, y_{2i-1}), patient $2i$ receives dose (x_{2i}, y_{2i-2}), where $y_{2i-1} = \Pi^{-1}_{\Gamma_{B|A=x_{2i-3}}}(\alpha \mid D_{2i-2}), x_{2i} = \Pi^{-1}_{\Gamma_{A|B=y_{2i-2}}}(\alpha \mid D_{2i-2})$.
4. Repeat step 3 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 using (2.3) as

$$\hat{C} = \left\{ (x^*, y^*) : y^* = \frac{\left(F^{-1}(\theta) - F^{-1}(\hat{\rho}_{00})\right) - \left(F^{-1}(\hat{\rho}_{10}) - F^{-1}(\hat{\rho}_{00})\right) x^*}{\left(F^{-1}(\hat{\rho}_{01}) - F^{-1}(\hat{\rho}_{00})\right) + \hat{\eta}_3 x^*} \right\}, \tag{2.6}$$

where $\hat{\rho}_{00}, \hat{\rho}_{01}, \hat{\rho}_{10}, \hat{\eta}_3$ are the posterior medians given the data D_n.

Tighiouart et al. [16] studied the performance of this design under a large number of scenarios for the location of the true MTD curve. In this manuscript, we present the operating characteristics of stage 1 in the context of the CisCab trial in Section 4.

3. Stage 2

Let C_{est} be the estimated MTD curve obtained from Stage 1. Let E be the indicator of treatment response such as tumor shrinkage, $E = 1$ if we have a positive response after a pre-defined number of treatment cycles, and $E = 0$ otherwise. Let p_0 be the probability of efficacy of the standard of care treatment. We propose to carry out a phase II study to identify dose combinations (x, y) in C_{est} such that $\text{P}(E = 1|(x, y)) > p_0$.

3.1 Model

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

$$P(E = 1 \mid x, \boldsymbol{\psi}) = F(f(x; \boldsymbol{\psi})), \tag{3.1}$$

where F is a known link function and $f(x; \boldsymbol{\psi})$ is an unknown function. Note that x_2 is uniquely determined by x_1 and the MTD curve. A flexible way to model the probability of efficacy along the MTD curve is the cubic spline function

$$f(x; \boldsymbol{\psi}) = \beta_0 + \beta_1 x + \beta_2 x^2 + \sum_{j=3}^{k} \beta_j (x - \kappa_j)_+^3,$$

where $\boldsymbol{\psi} = (\boldsymbol{\beta}, \boldsymbol{\kappa})$, $\boldsymbol{\beta} = (\beta_0, ..., \beta_5)$, $\boldsymbol{\kappa} = (\kappa_3, ..., \kappa_k)$ with $\kappa_3 = 0$. Let $D_m = \{(x_i, E_i), i=1,\ldots,m\}$ be the data after enrolling m patients in the trial, where E_i is the response of the ith patient treated with dose combination x_i and $\pi(\boldsymbol{\psi})$ be a prior density on the parameter $\boldsymbol{\psi}$. The posterior distribution is

$$\pi(\boldsymbol{\psi} \mid D_m) \propto \prod_{i=1}^{m} \left[F(f(x_i;\boldsymbol{\psi}))\right]^{E_i} \left[1-F(f(x_i;\boldsymbol{\psi}))\right]^{1-E_i} \pi(\boldsymbol{\psi}). \quad (3.2)$$

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.

3.2 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 $\hat{\boldsymbol{\psi}}$ of $\boldsymbol{\psi}$ given the data D_{n1} using (2.9).
3. Generate n_2 dose combinations from the standardized density $F(f(x;\hat{\boldsymbol{\psi}}))$ and assign them to the next cohort of 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 futility or early efficacy 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 [22] to selecting a superior arm from an infinite number of arms.

Decision rule:

At the end of the trial, we accept the alternative hypothesis if

$$Max_x \left[P(F(f(x;\boldsymbol{\psi})) > p_0 \mid D_n\right] > \delta_u, \quad (3.3)$$

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

3.3 Simulation Studies

We evaluate the operating characteristics of this design by assuming a logistic link function $F(u) = (1 + \exp(u))^{-1}$ and $f(x; \boldsymbol{\psi})$ is a cubic spline with two knots in (0; 1). This is a very exible class of efficacy curves and accommodates 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 one or both edges of the MTD curve. Vague priors are placed on the model parameters by assuming that $\boldsymbol{\beta} \sim \boldsymbol{N}(\mathbf{0}, \sigma^2 \boldsymbol{I}_6)$ with $\sigma^2 = 10^4$ and $(\kappa_4, \kappa_5) \sim$ Unif $\{(u,v) : 0 \leq u < v \leq 1\}$. It can be shown that the induced prior mean and variance on the probability of efficacy are $E_{\text{prior}}(F(f(x; \boldsymbol{\psi}))) \approx 0.5$ and $Var_{\text{prior}}(F(f(x; \boldsymbol{\psi}))) \approx 0.5$ for all dose combinations x in [0, 1]. 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 and the total trial sample size is 40. The design parameter for the decision rule in (3.3) was taken as $\delta_u = 0.8$. In each scenario, we simulated $M = 2000$ trial replicates.

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

$$P(H_1) \approx \frac{1}{m}\sum_{i=1}^{m} I\left(Max_x P_i\left(F(f(x;\boldsymbol{\psi})) > p_0 \mid D_{n,i}\right) > \delta_u\right), \tag{3.4}$$

where

$$P_i\left(F(f(x;\boldsymbol{\psi})) > p_0 \mid D_{n,i}\right) \approx \frac{1}{M}\sum_{j=1}^{M} I\left(F(f(x;\boldsymbol{\psi}_{j,i})) > p_0\right), \tag{3.5}$$

and $\boldsymbol{\psi}_{1,i},\ldots,\boldsymbol{\psi}_{M,i}$ is an MCMC sample from the posterior distribution $\pi(\boldsymbol{\psi} \mid D_{n,i})$. We also report the estimated efficacy curve by replacing $\boldsymbol{\psi}$ in (3.1) by the average posterior medians across all simulated trials

$$F(f(x;\bar{\boldsymbol{\psi}})) \tag{3.6}$$

Finally, we also report the mean posterior probability of efficacy curve

$$\frac{1}{m}\sum_{i=1}^{m} P_i\left(F(f(x;\boldsymbol{\psi})) > p_0 \mid D_{n,i}\right). \tag{3.7}$$

3.4 Results

We present the results of three scenarios in Figures 1−3. Figure 1 is a case where the true probability of efficacy shown by the blue curve is highest around the standardized dose combination $x = 0.4$ and is higher than the probability of a poor treatment in the interval [0.75,1]. The effect size is 0.2 and this is achieved at a single dose combination $x = 0.4$ 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 (3.6) and is very close to the true efficacy curve. The mean posterior probability of efficacy defined in (3.7) and shown in red is higher in a neighborhood of $x = 0.4$ as expected. The probability of accepting the alternative under this scenario as defined in (3.4) is 0.92. 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 (3.3). This shows that the probability of selecting a dose combination that has a probability of treatment response of more than p_0 is 0.97. The mode of this density is around $x = 0.4$. The bottom right of Figure 1 is a case where the probability of treatment response does not exceed $p_0 = 0.4$ 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 $x = 0.6$ as expected. The probability of accepting the alternative under this scenario is 0.20 and can be interpreted as the "Bayesian type I error probability" under this particular scenario. The scenario in Figure 2 is similar to the previous one except for the probability of a poor treatment response $p_0 = 0.2$. The power of the test is 0.86 and the probability of a type I error is 0.11. The target dose is selected with probability 0.97. Figure 3 is a scenario where the probability of treatment response is low on one part of the estimated MTD curve and is more than $p_0 = 0.6$ for dose combination in [0.45, 1.0] with the target probability of response $p_1 = 0.8$

achieved at dose combination x = 0.8. Power in this case is 0.90 and the dose combination with probability of efficacy above $p_0 = 0.6$ is selected 97% of the time.

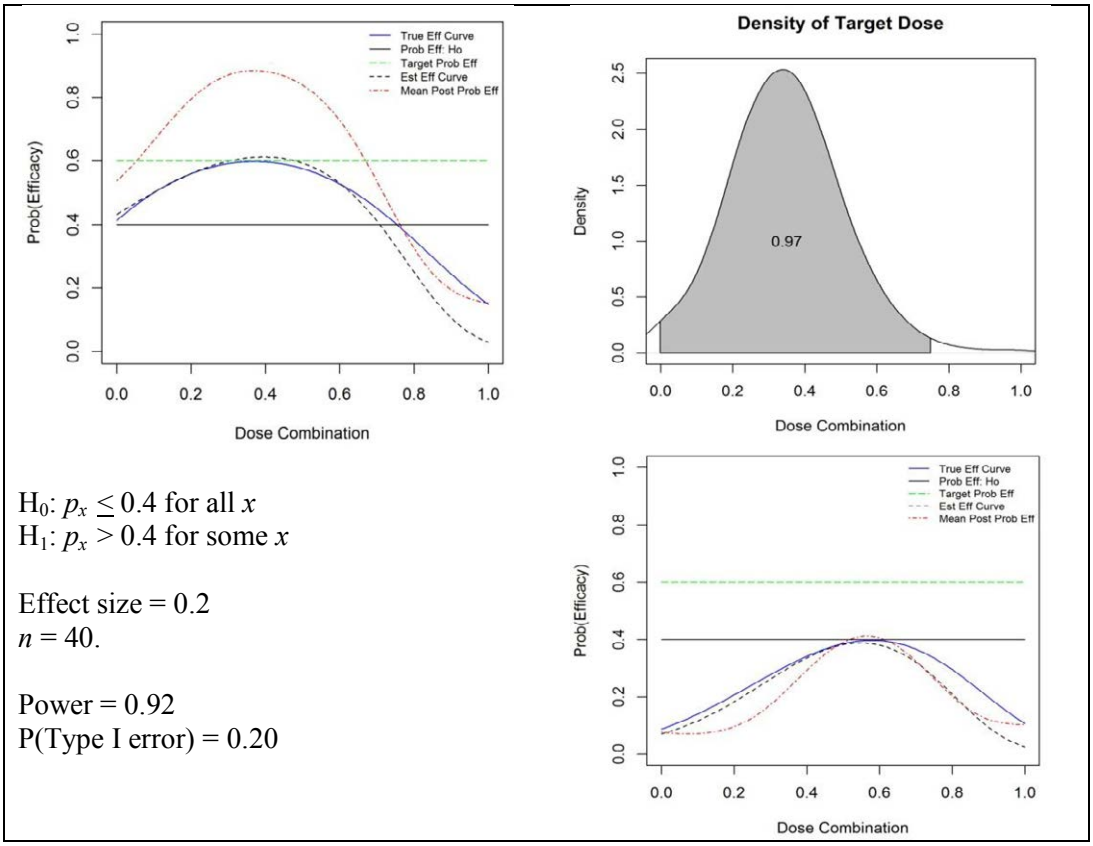


Figure 1. Power (top left), type I error probability (bottom right), and distribution of selected dose combination with desired probability of efficacy.

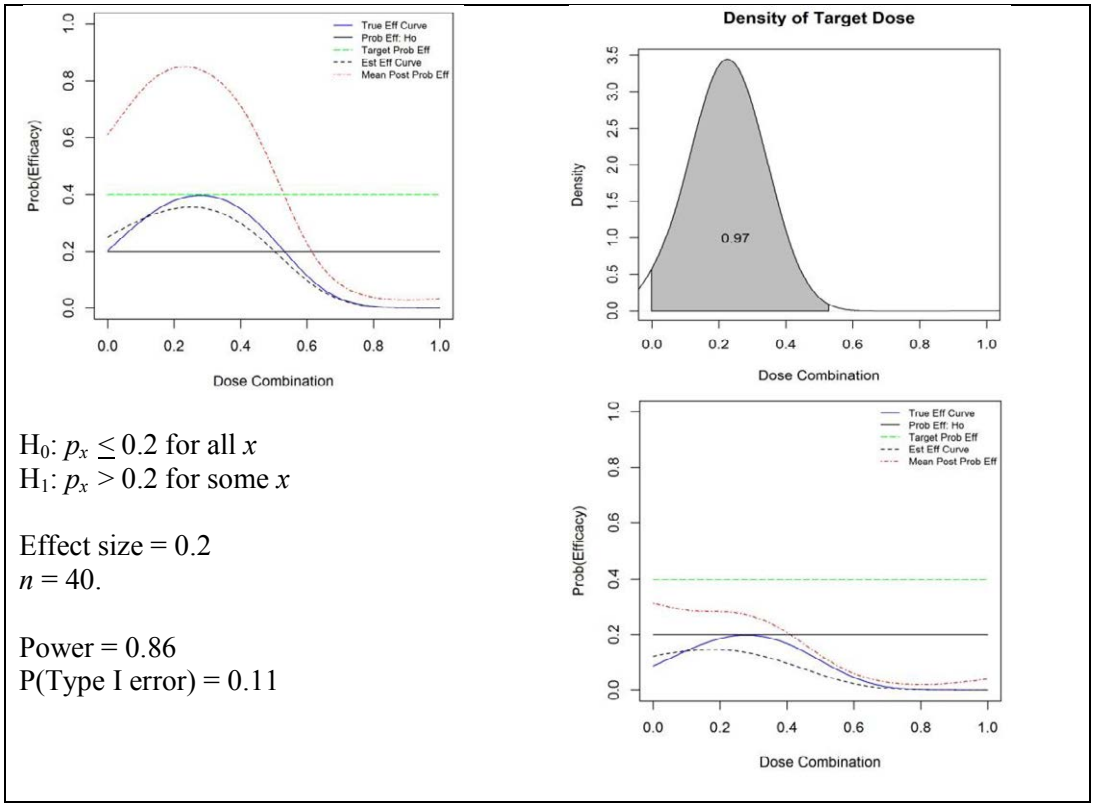
Based on these preliminary results, we conclude that phase II trials searching for dose combinations along the MTD curve that yield high probability of treatment response are feasible with reasonable sample sizes.

4. Application to the CisCab Trial

We propose to apply the above methodology to design a phase I/II trial of the combination cisplatin and cabazitaxel in patients with prostate cancer with visceral metastasis. A recently published phase I trial of this combination by Lockhart et al. [23] identified the MTD of cabazitaxel/cisplatin as 15/75 mg/m^2. This trial used a "3+3" design exploring 3 pre-specified dose levels 15/75, 20/75, 25/75. In part 1 of the trial, 9 patients we evaluated for safety and no DLT was observed at 15/75 mg/m^2. In part 2 of the study, 15 patients were treated at 15/75 mg/m^2 and 2 DLTs were observed. Based on these results and other preliminary efficacy data, we hypothesize that there exists a series of active dose combinations which are tolerable and active in prostate cancer. Cabazitaxel dose levels will be selected in the interval [10, 25] and cisplatin dose levels were selected in the interval [50, 100] administered intravenously. For stage 1, we plan to enroll 30 patients and estimate the MTD curve and in phase II, 30 patients will be enrolled to

identify dose combinations along the MTD curve with maximum clinical benefit rate. The probability of poor clinical benefit is 0.15 and we expect that a tolerable dose combination achieves a clinical benefit rate of 0.4.

We derived the operating characteristics for stage 1 using a target probability of DLT of $\theta = 0.33$ and a logistic link function in (2.1). Informative priors were used for the model parameters $\rho_{01}, \rho_{10} \sim$ beta(1.4, 5.6), and $\rho_{00} / \min(\rho_{01}, \rho_{10}) \sim$ beta(0.8, 7.2) and a vague prior for η_3 was used as in [16] so that $E(\text{P(DLT}|(15; 75))) \approx 0.33$.



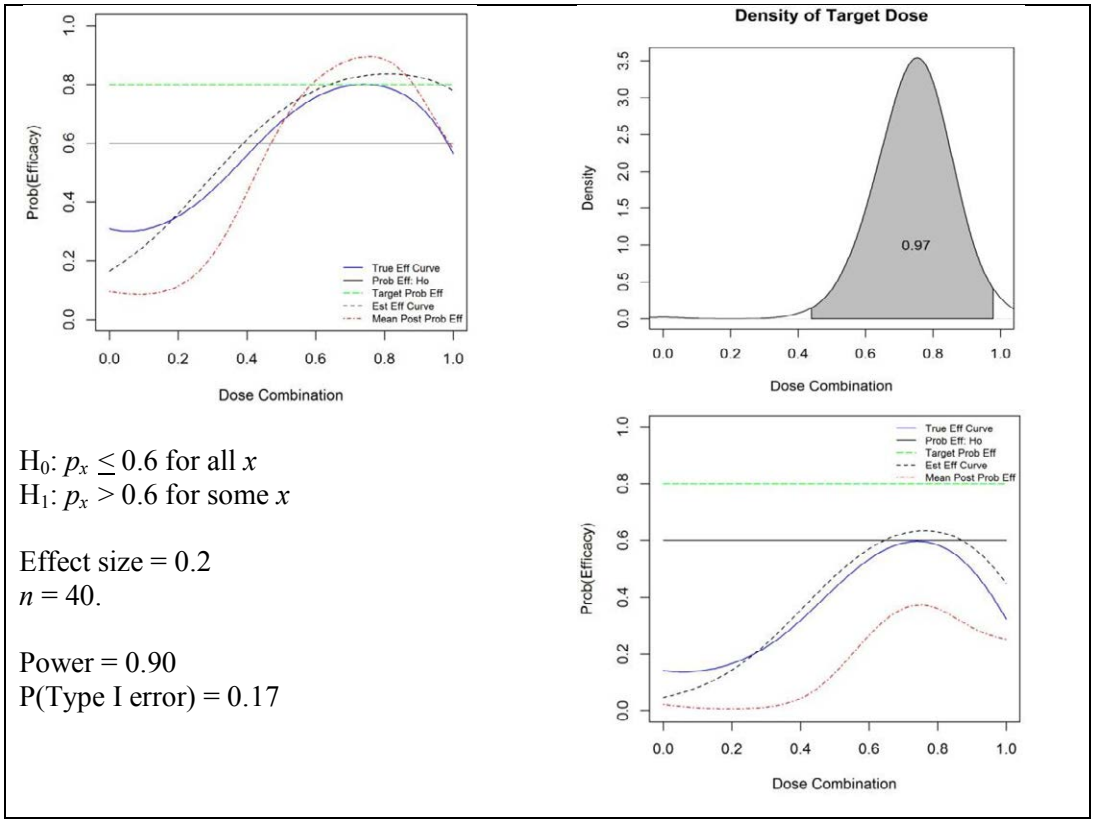
H_0: $p_x \leq 0.2$ for all x
H_1: $p_x > 0.2$ for some x

Effect size = 0.2
$n = 40$.

Power = 0.86
P(Type I error) = 0.11

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

Figure 4 shows the true and estimated MTD curve from two scenarios that are expected by the clinician Dr. Edwin Posadas. This shows that the estimated curves are close to the true ones and this is also supported by the pointwise average bias and percent selection (graphs not shown). Other scenarios showed similar findings. For stage 2, we presented simulations based on two scenarios supporting the null and alternative hypothesis. Since the effect size is 0.25, higher than the one in the simulations in section 3, similar power and type I error probabilities (87% and 8%) were obtained with a sample size of 30 patients. Other simulations testing the same hypotheses showed similar results. Hence, the design has good operating characteristic in identifying tolerable dose combinations with maximum benefit rate.



H_0: $p_x \leq 0.6$ for all x
H_1: $p_x > 0.6$ for some x

Effect size = 0.2
$n = 40$.

Power = 0.90
P(Type I error) = 0.17

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

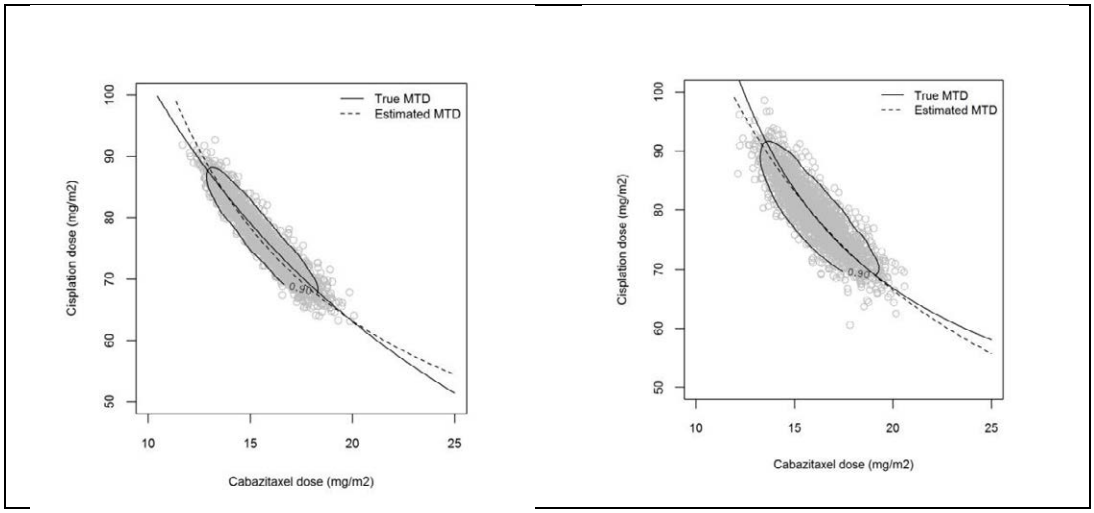
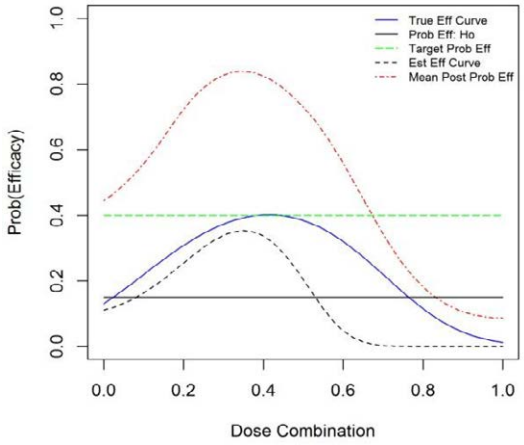
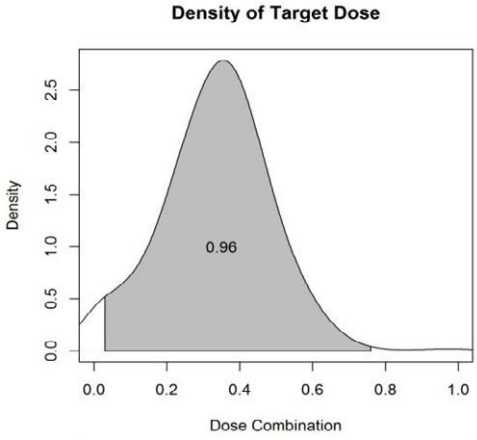


Figure 4. True and estimated MTD curve under two different scenarios for the MTD curve. The grey diamonds represent the last dose combination from each simulated trial along with a 90% confidence region.





H_0: $p_x \leq 0.15$ for all x
H_1: $p_x > 0.15$ for some x

Effect size = 0.25
n = 30.

Power = 0.87
P(Type I error) = 0.08

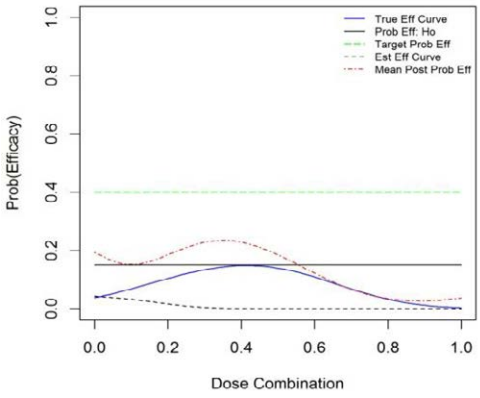


Figure 5. Power (top left), type I error probability (bottom right), and distribution of selected dose combination with desired probability of efficacy.

5. 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, 24] or CRM [15]. In the context of the CisCab trial, we showed that good operating characteristics are obtained using informative prior distributions and sample size of 30 patients. In stage 2, we modeled treatment efficacy as a binary indicator of treatment response using a cubic spline form of the dose combination-treatment response relationship. This is a very flexible form for the efficacy curve 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. 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 [22] to comparing an infinite number of arms.

We studied the properties of this design under various 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 30 for the CisCab trial but with higher effect size. Based on these scenarios and proposed models, we conclude that this two-stage design is feasible with a total sample size of 60 patients.

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