Journal of Data Science 15(2017), 77-94

DETERMINING AN OPTIMUM BIOLOGICAL DOSE OF A METRONOMIC CHEMOTHERAPY

Atanu Bhattacharjee[1], Vijay M Patil[2]

[1]*Department of Biometrics, Chiltern Clinical Research Ltd*
[2]*Department of Medical Oncology, Tata Memorial Hospital*

Abstract: The surrogate markers(SM) are the important factor for angiogenesis in cancer patients.In Metronomic Chemotherapy (MC) , physicians administer subtoxic doses of chemotherapy (without break) for long periods, to the target tumor angiogenesis. We propose a semiparametric approach, predictive risk modeling and time to control the level of surrogate marker to detect the perfect dose level of MC. It is based on the controlled level of surrogate marker, and the aim is to detect an Optimum Biological Dose (OBD) finding rather than a traditional Maximum Tolerated Dose (MTD) approach. The methods are illustrated with MC trial dataset to determine the best OBD and we investigate the performance of the model through simulation studies.

Key words: MCMC, Angiogenesis, OBD, Predictive Risk Modeling

1. Introduction

The doses of chemotherapy selected in clinical practice are routinely derived by the MTD approaches. It is believed that an increase in dose will lead to an increase in tumor response. The dose selected for phase 2 and further studies is one dose level below the MTD level in Phase I studies [Skipper 1970, Devita 2008, Briasoulis 2009]. However, this conventional dosing of chemotherapy has routinely compromised the QOL of patients and may lead to selection of chemo-resistant clones [Schmid 2005, Golfinopoulos 2007, Saltz 2008]. The MC has been suggested as an alternative strategy to overcome such effects. The strategy in MC is to administer sub-toxic doses of same chemotherapy drugs for long periods to target angiogenesis [Bhattacharjee 2016, Patil 2015,Kerbel 2002, Kerbel 2004,Scharovsky 2009]. The effect on angiogenesis is achieved by targeting CEC. The effect on CEC is restricted to an antiangiogenic window in tumor cell line studies [skipper 1970, Hobson 1984, Vacca 1999]. In tumor cell line studies a drug would start exerting an antiangiogenic effect at a low dose level and it would continue to exert it till an upper dose level. Drug levels below the lower dose level and above the upper dose level won't exert an antiangiogenic effect (Figure 1). The challenge is to establish the optimal biological dose (OBD) of MC which would have maximized inhibiting effect on CEC. The aims of any phase I traditional clinical trial is to detect the MTD of chemotherapy. As when conventional chemotherapy is administered toxicity is a concern.

However, in case of MC the toxicity is not a concern. As the Metronomic doses are nearly $\frac{1}{10^{th}}$ of MTD of conventional chemotherapy. Therefore the aims of phase 1 MC clinical trial is to obtain OBD of a drug [Marshall2012].

The simple phase I trial design is to obtain MTD of a cytotoxic agent through standard '3+3' design accrues patients in cohorts of three and escalates until a pre-defined DLT is observed [Rosemarie1993]. The Continual Reassessment Method (CRM), is an another dose-response finding model and recently gained popularity [O'Quigley2006]. But both the models directly failed to detect the aim of any MC i.e. OBD . This paper is aimed to illustrate the application of OBD in MC. The OBD of MC is determined based on the performance of desired level of Surrogate Marker(SM). The serum creatinine (Scr) is considered as a choice of SM in this study. The OBD for dose-finding designs to search the perfect dose in MC has been proposed in this article.

2. MC trial data set

It is a partial data set considered from ongoing 7-years duration of a longitudinal study. This study is continuing under the supervision of the authors as principal investigator and is not matured enough to state more about it. This work is dedicated only on dose-response modeling section. It is expected that the full data will be matured enough by the end of the year 2020 in terms of completed follow-up of the patients with strong enough statistical power to serve the primary objective as the event of interest i.e. death. In this manuscript, we focused only on initial dose-response modeling of MC with cancer patients. A total of 110 patients MC therapy data has been utilized in this paper. In MC the main goal is to find out the OBD among all different low dose levels. The serum creatinine (SCr) is considered as response of interest for OBD. A total of six doses-levels coded as 10mg/m2,15 mg/m2,20 mg/m2, 25 mg/m2,30 mg/m2 and 35 mg/m2 of IV docetaxel are considered in this study. The data set is observed with individual-specific information for patient 's with doses and corresponding marker levels. The Scr measurements are retrospectively observed for six different cycles of MC therapy. This study is focused on Scr data observed till end of first few weeks of MC Trial.

3. Methods

3.1 Data Exploration with Mixture Distribution

The parametric model is assumed for dose-response curve preparation. The challenge is to specify the dose-response for the optimum biological response modeling. The literature for dose-response modeling is well established through different types of MLE assumptions [islam2016,Aghamohammadi2010,Schmoyer1984], and Kernel estimator [Muller1988].The non-parametric setup has been found suitable for dose-response through Dirichlet Process Prior [Mukhopadhyay 2000] and quantile response [Dette 2010].The application of semi-parametric through mixture of parametric and non-parametric explored for continuous variable [Einsporn 1987]. This mixture approach for density estimation [Olkin 1987], hazard function [Kouassi

1997], robust regression [Mays2001] and the linear mixed model [Waterman 2007] are already established for repeated [Pickle 2008] and non-repeated measurement [Robinson 2010]. This work is extended with the application of semi-parametric estimates of the dose-response relation for the exploratory data analysis. The weight is used to reduce the bias balanced the adaptively borrowed across the two method, i.e. parametric and non-parametric The scenario of parametric model correctly specified, the weights towards the parametric model will be more otherwise non-parametric portion will gain more weight. Let the response of interest is denoted as Y following the Bernoulli distribution with the probability f(x). The dose-response f(x) is estimated through the semi-parametric modeling. The effective dose-response is denoted as

$ED_\alpha = f^{-1}(\alpha)$for $0 < \alpha < 1$\$. The inverse functions f(x) is $f^{-1}(x)$\$. The aim of any toxicology studies is to estimate ED_α for smaller values ofα. The dose-response relation is estimated through parametric and non-parametric modeling. The parametric model is assumed as $f(x,\theta)$ for the dose - response curve and θ is the unknown parameter. Suppose the nonparametric and parametric estimates are $\bar{f}(x)$ and $f(x,\hat{\theta})$ respectively. The estimated value of the parameter of interest is $\hat{\theta}$ obtained by MLE .The dose is denoted as x and corresponding response as Y. The dose-response relation is observed through the mixture of parametric and non-parametric modeling.

The equation is defined as

$$f_\omega(x,\hat{\theta}) = (1-\omega)\bar{f}(x) + \omega f(x,\hat{\theta}) \tag{3.1}$$

The weight ($\omega \in [0,1]$) factor is used to make balance between parametric and non-parametric estimates. The equation (3.1) provides the option to incorporate the parametric and non-parametric both the options simultaneously. The estimates (either parametric or non-parametric) fits more appropriately will gain more weight and complementary value of ω i.e 1- ω will be gained by another one. The dose range is denoted as (x_{max}, x_{min}). The estimated value of \$\omega\$ is obtained from the minimum estimated value of the mean integrated squared error(MISE) (Yuan2011)

$$MISE\left(p_\omega(x,\hat{\theta})\right) = E\left[\int_{xmin}^{xmax}\{p(x) - p_\omega(x,\hat{\theta})\}^2\,dx\right] \tag{3.2}$$

The dose-response relation is explored through semi-parametric estimation. The function values of the above equation are defined as

$$Probit1: -p(x) = \varphi(\tfrac{x-0.5}{0.25}) \tag{3.3}$$

$$Probit2: -p(x) = \varphi(\tfrac{x-0.5}{0.5}) \tag{3.4}$$

The optimum dose level is selected with ED_α =0.5.

Further, x is defined as $x = \frac{d-1}{5}$ for d=1,2,….6.The Probit model in parametric portion and Kernel estimation for non-parametric portion assumed to perform the analysis. A total of 1000 boot strapping has been carried to obtain the estimates of weight ω. The value of ED_αhas been observed through 0.05,0.1,0.15,0.20,0.25,0.30 to avoid the complicated estimation of ED_α Bias

and MSE estimates of ED_α observed simulations of parametric and non-parametric estimates are detailed in Table 1 and Table 2 respectively.

3.2 Predicted Risk Modeling for Optimum Biological Dose (OBD) of a Surrogate Marker (SM)

The event is defined as the presence of a Surrogate Marker (SM) within the controlled limit. Let SM under consideration is Y. The objective is to reduce or induce the level of response Y through specific dose i.e. x. The target level of Y to be controlled by x is decided based on supportive literature of trial. Suppose patients i is having response value Y_i and if $Y_{i=j}$, patients has experienced the controlled level of SM in the jth interval of time,$t_{j-1} < T_i < t_j$ for j=1,2,....C and the sequence of time denoted as $0 < t_0 < t_1 < \cdots \ldots < t_e < \infty$ where $[t_0, t_{e-1}] = [0, t^*]$ is the maximum window of observation.

Further, T_i^0 is the event of time or right censoring time. The indicator $\Delta_i = 1$ if $T_i^0 = T_i$ and $\Delta_0 = 0$ if $T_i^0 < T_i$. The value of $Y_i^0$is the current interval value for the ith patients. Let dose under consideration denoted as $d_1 < d_2 < \cdots . d_m$and *m=1,...M* gives the standard normal cdf of $\Phi(.)$. The binary-time event function is defined as

$$\Phi(\beta_{j,m}) = Pr(Y_i = j/d_m) = \prod_{h=1}^{j}\{1 - \Phi(\beta_{h,m})\} \tag{3.5}$$

for $j \leq C - 1$. Let $\beta_{j,m}$ is the effective dose k on the event in the jth interval. The probability of event for the jth interval is

$$Pr(Y_i = j/d_m) = \Phi(\beta_{j,m}) \prod_{h=1}^{j-1}\{1 - \Phi(\beta_{h,m})\} \tag{3.6}$$

and not occurrence of event $\Pr(Y \geq j|d_m) = \prod_{h=1}^{j}\{1 - \Phi(\beta_{h,m})\}$for $j \leq C - 1$ at any specific point of time, the binary data for the nth patients take the form $D_n = \{(Y_i^0, m(i), \delta_i), i = 1,2, \ldots . n\}$ and denoted as $\beta = (\beta_{1,1}, \ldots . . \beta_{C-1,m}$. The likelihood is defined as

$$L(\beta|D_n) = \prod_{i=1}^{n} \Phi(\beta Y_i^0, m(i))^{\delta_i} \prod_{h=1}^{Y_i^0 - 1}\{1 - \Phi(\beta_{h,m(i)})\} \tag{3.7}$$

The conditional probability is defined as

$$\pi(\beta, d_m, j) = P(Y \leq C - 1|Y \geq j, \beta, d_m) \text{for} j = 1,2, \ldots C - 1 \text{ and m} = 1, \ldots . \text{M} \tag{3.8}$$

Further, $\pi(\beta, d_m, Y^0)$ gives the probability that a patients who successes in $Y^0 - 1$ without event will expereinced by $t^* = t_C - 1$ at dose d_k.

Let the window is [0, t^*] is $\pi(\beta, d_m, 1$.The binary-time event is defined as

$\pi(\beta, d_m, j) = 1 - \prod_{h=1}^{C-1}\{1 - \Phi(\beta_{h,m})\}$and $\pi(\beta, d_m, j) = 1 - \prod_{h=1}^{C}\{1 - \Phi(\beta_{h,m})\}$.

For the patients i, the vector of latent variable $Z_i = (Z_{i,1}, \ldots . Z_{I,Y_i^0})$ if Y_i^0 =C, with $Z_{I,j} \sim N(\beta_{j,k}, 1)$, if the ith patients received the dose d_m. Let $N(\mu, \sigma^2)$shows the density by $(z; \mu, \sigma^2)$.

The likelihood is expressed as

$L(\beta|D_n) =$

$$\prod_{i=1}^{n}\{\int_{-\infty}^{\infty} \varphi\big(\beta\, Y_i^0, m(i)Z_i, Y_i^0, 1\big)dZ_{i,Y_i^0}, 1)dZ_{i,Y_i^0}\}^{\delta_i} \prod_{j=1}^{Y_i^0-1} \int_0^{\infty} \phi\big(Z_{i,j}; \beta_{j,m(i),1}\big)dZ_{i,j} \quad (3.9)$$

The extended function through consideration of latent variable is

$$L(\beta|D_n, Z) = \prod_{i=1}^{n} \varphi(\beta\, Y_i^0, m(i)Z_i, Y_i^0, 1)\{I(Z_i, Y_i^0 < 0)\} \prod_{j=1}^{Y_i^0-1} \phi\big(Z_{i,j}; \beta_{j,m(i),1}\big) I(Z_{i,j} > 0)$$

(3.10)

Patients safety also been considered to obtain the OBD controlled surrogate markers. It is assumed that when a group of new patients entered in a trial and treated with specific dose but not fully followed then two scenario may occurs to them either all of them are having controlled surrogate markers or none of them have controlled surrogate markers at time t^*. Since, none of the dose is having problem for occurrence of high toxicity level so six different desirable doses are administered simultaneously to the randomly selected patient and level of surrogate markers observed in the follow-up visits. The basic intention is to develop probability measures of either tiny or large surrogate markers levels observed at the specific dose d_{k} to be fixed and OBD dose or move their dose to near at dose d_{m+1} or d_{m-1}.

Let the random variable $\beta(a_m, b_k)$ having the mean $E\{\bar{\pi}(\beta, d_m|D_n)\}$ and variance $Var\{(\beta, d_m|D_n)\}$. Suppose, v_m is the number of patients treated with d_m and not fully evaluated levels are as $i_1, i_2 \ldots . . i_{v_m}$. Further , the indicator W_{ir}=I($Y_{ir} \leq C - 1$) that patients i_r have the controlled surrogate level in the assessment period and total number of patients not $S(W_m) = W_{i_1} + .. + W_{iv_m}$properly evaluated and failed to achieve controlled surrogate markers is t^*. The prior probability is obtained from $\beta(a_m + S(W_m, b_m + k_m - S(W_m)))$. The criteria is fixed with

$$P_{1m}(D_n) = \sum_w I[(\Pr\{p_m(w, v_m, a_m, b_m) > \pi^*\} \leq \xi]\Pr(W_n = w|D_n) \quad (3.11)$$

and

$$P_{2m}(D_n) = \sum_w I[(\Pr\{p_k(w, v_m, a_m, b_m) > \pi^*\} \leq \xi]\Pr(W_m = w|D_n) \quad (3.12)$$

The above equations gives the probability measures that d_k with either tiny or large surrogate markers levels and $P_m(D_n) = 1 - P_{1m}(D_n) - P_{2m}(D_n)$ is measured probability with dose level d_m . The marginal posterior of β is defined as $f(\beta, D_n)$ and $E(W_{ir}|\beta, D_n) = \bar{\pi}\big(\beta, d_m, Y_{ir}^0\big)$. The summation over above equations is computed through MCMC and is defined as

$\Pr(W_m = w|D_n) = \int \prod_{r=1}^{v_m}\{\pi(\beta, d_m, Y_{ir}^0)\}^{w_r}\{1-\pi(\beta, d_m, Y_{ir}^0)\}^{1-w_r} f(\beta|D_n)d\beta$ (3.13)

Further, suppose dose is mentioned as m, the total number of patients received the dose denoted as k_m, and partially evaluated patients for dose m is n_m . Now

$$\bar{P}_{1m}(D_n) = \begin{cases} 1 \; if \; k_m = 0 \\ P_{1m}(D_n) if \; k_m > 0 \end{cases} \quad (3.14)$$

$$\bar{P}_{2m}(D_n) = \begin{cases} 1 \; if \; k_m = 0 \\ P_{2m}(D_n) if \; k_m > 0 \end{cases} \quad (3.15)$$

Further $\bar{P}_{1m}(D_n) = 1$ if all n_m all patients fully evaluated, and $\bar{P}_{2m}(D_n) = P_{2m}(D_n)$otherwise. Here, we didn't check the de-escalation process and simultaneously applied different dose to the patients.

4. Probability Model for Surrogate Marker(SM) levels Distribution

Let the duration between initiation of trial and evaluation of surrogate marker is $"t^{*}"$ about the decision of n^*, the number of patients enrolled up to "t^*", the study duration when the patients enrolled is $e_i$and i=1,2,... n^*. Suppose T_i the duration and possibly unobserved duration when patient 'i' successes the controlled level of surrogate marker. The amount of time patients i is observed that

$$Y_i = \begin{cases} T_i \text{ if } e_i + T_i \leq t^* \\ t^* - e_i \text{ if } e_i + T_i > t^* \end{cases} \quad (4.16)$$

It is defined as $\Delta_i = 1$ if $Y_i = T_i$ otherwise $\Delta_i = 0$. Let $S_i = \{s_{i,1}, \ldots . s_{i,m_i}\}$ gives the successive patient times at which the ith patient receives the MC agent. This notation is useful to capture the actual patients administration time to deviate from his/her scheduled times. It is the provision that if the investigator wish to study m treatment i.e. $S^{(1)}, S^{(2)}, \ldots . . S^{(q)}$where $s^{(j)} = (s_1, s_2, \ldots \ldots, s_q^j)$ and that the jth dose has a total of $s^{(j)}$ administration. Further, q_{i} gives the index of the last administration received by patient 'i' at the interim study time t^*. However, $q^{(j)}$ administration are scheduled for any patient to schedule $s^{(j)}$at t^*it may be $q_i < q^{(j)}$ due to administrative reason.

Let τ shows the maximum duration of follow-up of each patients decided by oncologist. A fixed target probability p_τ is decided from the medical oncologist to define the targeted threshold changes of the surrogate marker for any time from enrollment to τ.

4.1 Monitoring

Let the total number of patients are N, and each patient assigned to a treatment dose. Each patient is assumed to follow τdays. Let the desired threshold value of surrogate marker is p_τ for $F(\tau|\theta, v^{(j)}$.Here, two criteria's are selected

C_1:- time t^*, for each j=1,2,...k calculate $\varphi_j(\tau)$ =Pr {F(τ|v,$s^{(j)}$>$p_\tau|D^*$}.

It follows that $\varphi_1(\tau) \leq \varphi_2(\tau) \leq \cdots . \leq \varphi_k(\tau)$.. Further the best dose is defined as $\varphi_j(\tau), \bar{p}$.

C_2 time t^*, for each j=1,2,...k calculate $F_j^*(\tau) = E\{F(\tau|v; s^{(j)})|D^*\}$.

The best dose is defined as having

$F_j^*(\tau)$ near to $\bar{p}_\tau$, by minimizing $|F_j^*(\tau) - p_\tau|$

The processes are similar to the CRM criteria [O'Quigley 2006]. The best dose is assigned to the patients $n^* + 1$.

4.2 Surrogate Marker Distribution

The patient index is i. It is assumed that same dose of MC has been administered in different visits. Let $h(\mu|v)$ is the event of high CEC level (i.e. more than 166 cells/ml) attributes to a single administration and parameter of interest is v. The event at time t for a patient treated with schedule s is defined as

$$\lambda(Y|v, s) = \sum_{l=1}^{m} h(Y - s_l|v) \tag{4.17}$$

with $h(\mu|v)$=0 if μ <0 . The patient's i event i.e. surrogate failure is defined as (4.17) Y, the patient's time to study (2)The number of administrations and received up to t^* , Further the patients cumulative hazard function at time t^* is defined as

$$\Delta(Y|v, s) = \int_0^Y \sum_{l=1}^{m} h(\mu - s_l|v)d\mu \tag{4.18}$$

$$\Delta(Y|v, s) = \int_0^Y \sum_{l=1}^{m} H(Y - s_l|v)d\mu \tag{4.19}$$

where

$$H(Y - s_l|v) = \int_0^{Y^0} h(\mu - s_l|v)d\mu \tag{4.20}$$

4.3 Specifying the Single-Administration to Control Surrogate Marker

The single-administration's treatment failure $h(\mu|v)$ can be quite general, provided that it reasonably reflects the risk of toxicity for the agent under study and is sufficiently tractable to facilitate the necessary computations. In general, because certain toxicities may be hard to identify before the trial, one can include in the definition of toxicity any adverse event sufficiently severe that it precludes further administration of the agent. We assume that the hazard of toxicity from a single administration has a finite duration and vanishes to zero within $v_3$days. In this trial, based on the physicians' experience, it is assumed that the hazard vanishes after $v_3 = 18$ days. Because we assume that $h(.)$has a finite duration, we cannot model $h(.)$as the hazard of a typical parametric lifetime distribution, such as the gamma or Weibull, unless $h(.)$ is truncated appropriately. As a simple, practical alternative, we assume that h increases linearly to a maximum and decreases linearly thereafter. Therefore it is defined as,

$$h(\mu|v) = \begin{cases} v_2 \frac{\mu}{v_1} 0 \le \mu \le v_1 \\ v_2 \frac{v_3 - \mu}{v_3 - v_1} v_1 \le \mu \le v_3 \\ 0, \mu > v_3 or\ \mu < 0 \end{cases} \quad (4.21)$$

Thus, $v(v_1, v_2, v_3)$ with $v_1$the time at which $h(\mu|v)$ reaches its maximum, v_2, and $v_3$the time when h(.) vanishes to zero. Figure 4 illustrates this function. Initially, we assumed that $h(.)$had only the two parameters $v_1$and v_2, with v_3 fixed and assumed known. However, we found that fixing v_3 severely hindered the method's ability to locate the optimal schedule when the actual duration of h.was much longer than the assumed value of v_3.

Other forms for $h(\mu|v)$are possible, depending on the particular application. For example, the Weibull hazard $h_1(\mu|v) = v_1 v_2 (v_1 \mu)^{v_2 - 1}$ allows the risk of toxicity to continue indefinitely, with the shape parameter v_2 determining whether the risk increases, decreases, or remains constant over time. One also could vary the hazard of toxicity for each administration.

4.4 Likelihood and Posterior

The most recent data at study time t^* collected on patient i for $i = 1,2, \ldots n^*$, are $D_i = (s_i, Y_i, \delta_i)$.. The optimal treatment sequence assigned to patient $n^* + 1$$ who enters the trial at t^* is based on the posterior of v given the data available at t^*, which we denote by $D^* = (t^*, D_1, D_2, \ldots . D_n{}^*)$.

The likelihood at D^* is

$$L(D^*|v) = \prod_{i=1}^{n} \{ f(Y_i|v, s_i)^{\delta_i} \{1 - F(Y_i|v, s_i)\}^{1-\delta_i} \quad (4.23)$$

through the prior of p(v) , the posterior of v is

$$g(v|D^*) = \frac{L(D^*|v)p(v)}{\int L(D^*|v)p(v)dv} \quad (4.23)$$

because the above integral cannot be obtained analytically under the assumed model, we compute posterior quantities via Markov chain Monte Carlo(MCMC). The simulation study results with semi-parametric approach are given in Figure 2. The Dose-Curve modeling simulation is shown Figure 3.

5. Application to MC trial data set

The idea is to study the level of Scr to a restricted cycles of $m=6$ for duration of administration 1,3,5,7,9 and 11th weeks. The maximum days to monitor the controlled level of SM is specified as $\tau = 80$ days. However, during the MC therapy the schedule has been finalized for each patient. With individual specific prognostic function. The physician assumed that the event of controlled level of SM for a single administration will be achieved by 10 days,

with a range of 7 to 80 days. The therapy is assigned to administer with different dose level with 110 patients with parameter $\pi_i{}^* = 0.30, \varepsilon = 0.05, \xi = 0.30$ and $\bar{\varepsilon} = 0.90$. It is assumed that patients will attend the clinic in 7 days intervals. It is assumed that the parameter v_1 will be having the maximum value at the end of 7 days after the first administration. The derivation of a_3, b_3, for $p(v_3)$, and a_1 and b_1 for $p(v_1/v_3)$ are computed. The probabilities of event for 80days for each are detailed in Table6.

The proposed method has been illustrated on MC therapy. The results are detailed in Table 6 and corresponding data explored in Figure 4. It gives the dose-response estimation through parametric, non-parametric and semi-parametric methods. The estimation of dose-increases rapidly from 0.05 to 0.15, and thereafter slowly increases with dose. For doses, 0.20 and above response started to decrease. Parametric, non-parametric and semi-parametric fits are more or less identical with different doses. The weight assigned through semi-parametric method is 0.3 and parametric close to 0.4 and non-parametric with 0.05.

Criteria 1 and 2 are selected with 0.2< $\bar{p}$ <0.6. It has been found that $\bar{p}$=0.60 performed best over others. The table is formulated for $\bar{p}=0.6$ for both the criteria. The parameter $v_1$is assumed to be occurring at 7 days and v_2 as 10 days to 40 days. The designs performed are observed for criteria 1 and criteria 2. In different scenarios, the value of v_2 is varied to reflect which schedule is optimal for different values in Table1. The decision is obtained from the Table of detailed value of η_m,$P_{1m}(D_n)$, $\bar{P}_{1m}(D_n)$, and $\bar{P}_{2n+1}(D_n)$. The numerical values of the different states are also detailed in Table 3. The Operating Characteristics of PRMOBD design based on the choice of six different doses choice for the maximum duration of 80 days are detailed in Table 4. The corresponding simulation result for the OBD design for the maximum duration of 80 on $P_{1m}(D_n)$, $\bar{P}_{2m}(D_n)$, and$\bar{P}_{2m+1}(D_n)$ with the space of 5,10,20,40,60 and 80 days are given in table 5.The PRMOBD model suggests deciding the OBD with $0.20mg$ for 20days. It is expected that the trial with dose 0.35mg because it provides$\xi = 0.20$. It's the value of $\eta=1$, then there would be a fixed OBD decided based on particular observed all cases. Similarly, $\eta = 0$ may influence to observe a less number of patients towards control the CEC and the decision about OBD.

6. **Discussion**

The trinomial continual reassessment method is found suitable for OBD through highest probability of but failed to consider the toxic effect suitably [Zhang2006]. The two stage design is proposed on interim analysis for detecting the optimal dose [Polley 2008, Zang 2014] proposed dose-finding designs to search for the OBD by three adaptive dose-finding designs on molecularly targeted agents. Low-dose chemotherapy drugs are more effective to suppress tumors by restraining tumor vessel growth and preventing the repair of damaged vascular endothelial cells [Shen 2010]. High dose chemotherapy drugs like Cisplatin contributes to serious side effects [Shen 2010]. The target of MC therapy is the vascular endothelial cells [Shaked 2006,Wu 2007]. The growth of new vessels for a long run survival time treated with traditional maximum tolerated dose (MTD) through high dose chemotherapy has been confirmed [Lam 2007]. The anti-angiogenic plays the important role as clinical potential [Lu

2007]. The metastasis and the growth of tumor cells depends on neovascularization [Folkman 2003]. The anti-tumor drugs could cause inhibition of tumor neovascularity [Moreira 2007]. The Scr have emerged as a promising candidate surrogate marker to assess the efficacy of antiangiogenic therapies [Malka 2011,Jubb 2006,Bhatt 2007,Bertolini 2006].The low-dose chemotherapy drugs, as one-tenth of the MTD, administered continuously and frequently, could selectively suppress vessel growth in tumor tissues and prevent the repair of damaged vascular endothelial cells (VECs) [Shen 2010].This model is appropriate in dose-response modeling having the avoidable level of toxicity in any clinical trial. Based on our knowledge this is the first statistical methodological attempt that has been considered to deal with OBD in MC trial. It is expected that this above mentioned methods will be useful for OBD detection in MC trials in future as well.

Acknowledgments

The authors would like to thank the two anonymous referees for their cautious reading and constructive suggestions which have led to improvement on earlier versions of the manuscript.

Conflict of Interest

None declared.

References

[1] Aghamohammadi, A, Meshkani, MR and Mohammadzadeh, M. (2010). A bayesian approach to successive comparisons. Journal of Data Science 8(4), 541-553.

[2] Bertolini, F., Y.Shaked, Mancso, P. and others. (2006). The multifaceted circulating endothelial cell in cancer:towards marker and target identi_cation. . Nat Rev Cancer 6, 835-845.

[3] Bhatt, RS., Seth, P. and Sukhatme, VP. (2007). Biomarkers for monitoring antiangiogenic therapy. Clin Cancer Res 13, 777-780.

[4] Bhattacharjee, Atanu and Patil, Vijay M. (2016). Time-dependent area under the roc curve for optimum biological dose detection. Turkiye Klinikleri Journal of Biostatistics 8(2),103-109.

[5] Briasoulis, Evangelos, Pappas, Periklis, Puozzo, Christian, Tolis, Christos, Fountzilas, George, Dafni, Urania, Marselos, Marios and Pavlidis, Nicholas. (2009). Dose-ranging study of metronomic oral vinorelbine in patients with advanced refractory cancer. Clinical Cancer Research 15(20), 6454-6461.

[6] Dette, H. and Scheder, R. (2010). A _nite sample comparison of nonparametric estimates of the effective dose in quantal bioassay. Journal of Statistical Computation and Simulation 80,527-544.

[7] DeVita, T, Vincent and Chu, Edward. (2008). A history of cancer chemotherapy. Cancer research 68(21), 8643-8653.

[8] Einsporn, R.L. (1987). A link between least squares regression and nonparametric curve estimation. PhD Dissertation, Virginia Tech. Blacksburg.

[9] Folkman, J. (2003). Angiogenesis and apoptosis. Semin. Cancer Biol 13, 159-167.

[10] Golfinopoulos, Vassilis, Salanti, Georgia, Pavlidis, Nicholas and Ioannidis, John PA. (2007). Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. The lancet oncology 8(10), 898-911.

[11] Hobson, B and Denekamp, J. (1984). Endothelial proliferation in tumours and normal tissues: continuous labelling studies. British journal of cancer 49(4), 405.

[12] Islam, Tamanna and Tsuiki, Mikinori. (2016). Spatial distribution of air dose rate in grazing grassland. Journal of Data Science 14(1), 133-148.

[13] Jubb, Am., Oates, AJ., Holden, S. and others. (2006). Predicting bene_t for monitoring antiangiogenic agent in malingnancy. Nat Rev Cancer 6, 626-635.

[14] Kerbel, RS., G.Klement, Pritchard, K. and B.Kamen. (2002). Continuous low-dose antiangiogenic/metronomic chemotherapy: from the research laboratory into the oncology clinic. Ann Oncol 13, 12-15.

[15] Kerbel, Robert S and Kamen, Barton A. (2004). The anti-angiogenic basis of metronomic chemotherapy. Nature Reviews Cancer 4(6), 423-436.

[16] Kouassi, D.A. and Singh, J. (1997). A semiparametric approach to hazard estimation with randomly censored observations. Journal of the American Statistical Association 92, 1351-1355.

[17] Lam, T., Hetherington, J.W., Greenman, J., Little, S. and Maraveyas, A. (2007). Metronomic chemotherapy dosing-schedules with estramustine and temozolomide act synergistically with anti-vegfr-2 antibody to cause inhibition of human umbilical venous endothelial cell growth. Acta Oncol 46, 1169-1177.

[18] Lu, Q .B. (2007). Molecular reaction mechanisms of combination treatments of low-dose cisplatin with radiotherapy and photodynamic therapy. J. Med. Chem 50, 2601-2604.

[19] Malka, D., V.Boige, N.Jacques, N.Vimond, .Adenis, A, E.Boucher, Pierga, J.Y.,T.Conroy, B.Chauffert, E.Francois, Gichard, P., Galais, M.P. and others. (2011). Clinical value of circulating endothelial cell levels in metastatic colorectal cancer patients treated with first-line chemotherapy and behacizumab. Annals of Oncology 23, 919-927.

[20] Marshall, J.L. and Ruech, O.J. (2012). Maximum-tolerated dose, optimum biologic dose,or optimum clinical value: Dosing determination of cancer therapies. Journal of Clinical Oncology 30(23), 2815-2816.

[21] Mays, J. E., Birch, J.B and, B. A.Starnes. (2001). Model robust regression: Combining parametric, nonparametric, and semiparametric methods. Journal of Nonparametric Statistics 13, 245-277.

[22] Moreira, I.S., Fernandes, P.A. and Ramos, M.J. (2007). Vascular endothelial growth factor (vegf) inhibition aAS a critical review. Anticancer Agents Med. Chem 7, 223-245.

[23] Mukhopadhyay, S. (2000). Bayesian nonparametric inference on the dose level with specified response rate. Lancet Oncol 56, 220-226.

[24] Muller, H.G. and Schmitt, T. (1988). Kernel and probit estimates in quantal bioassay. Journal of the American Statistical Association 83, 750-759.

[25] Olkin, I. and Spiegelman, C.H. (1987). A semiparametric approach to density estimation.Journal of the American Statistical Association 82, 858-865.

[26] O'Quigley, J., Pepe, M. and L.Fisherr. (2006). Continual reassessment method: A practical design for phase 1 clinical trials in cancerl. Biometrics 46(1), 33-48.

[27] Patil, Vijay Maruti, Noronha, Vanita, Joshi, Amit, Muddu, Vamshi Krishna, Dhumal, Sachin, Bhosale, Bharatsingh, Arya, Supreeta, Juvekar, Shashikant, Banavali, Shripad, D^a_A _ZCruz, Anil and others. (2015). A prospective randomized phase ii study comparing metronomic chemotherapy with chemotherapy (single agent cisplatin), in patients with metastatic, relapsed or inoperable squamous cell carcinoma of head and neck. Oral oncology 51(3), 279-286.

[28] Pickle, M. G. S. M., T. J. Robinsonand, J. B. Birch and .Anderson-Cook, C. (2008). A semi-parametirc approach to robust parameter design. Journal of Statistical Planning and Inference 138, 114-131.

[29] Polley, M.Y. and Cheung, Y.K. (2008). Two-stage designs for dose-finding trials with a biologic end-point using stepwise tests. Biometrics 64, 232-241.

[30] Robinson, T. J., Birch, J. B. and Starnes, A. (2010). A semiparametric approach to dual modeling when no replication exists. Journal of Statistical Planning and Inference 140, 2860-2869.

[31] Rosemarie, M. and Ratain, M. J. (1993). Model-guided determination of maximum tolerated dose in phase i clinical trials: Evidence for increased precision. JNCI J Natl Cancer Inst 85(3), 217-223.

[32] Saltz, Leonard B. (2008). Progress in cancer care: the hope, the hype, and the gap between reality and perception. Journal of Clinical Oncology 26(31), 5020-5021.

[33] Scharovsky, O.G., Mainetti, L.E. and Rozados, V.R. (2009). Metronomic chemotherapy: changing the paradigm that more is better. Curr Oncol 16(2), 7-15.

[34] Schmid, Peter, Schippinger, Walter, Nitsch, Thorsten, Huebner, Gerdt, Heilmann, Volker, Schultze, Wolfgang, Hausmaninger, Hubert, Wischnewsky, Manfred and Possinger, Kurt. (2005). Up-front tandem high-dose chemotherapy compared with standard chemotherapy with doxorubicin and paclitaxel in metastatic breast cancer: results of a randomized trial. Journal of clinical oncology 23(3), 432-440.

[35] Schmoyer, R.L. (1984). Sigmoidally constrained maximum likelihood estimation in quantal bioassay. Journal of the American Statistical Association 79, 448-453.

[36] Shaked, Y., Ciarrocchi, A., Franco, M. and others. (2006). Therapyinduced acute recruitment of circulating endothelial progenitor cells to tumors. Science 313, 1785^a_A_S1787.

[37] Shen, F.Z., Wang, J., Liang, J., Mu, K., Hou, J.Y. and Wang, Y.T. (2010). Low-dose metronomic chemotherapy with cisplatin: can it suppress angiogenesis in h22 hepatocarcinoma cells? Int J Exp Pathol 91(1), 10-16.

[38] Skipper, Howard E, Schabel Jr, Frank M, Mellett, L Bruce, Montgomery, John A, Wilkoff, Lee J, Lloyd, Harris H and Brockman, R Wallace. (1970). Implications of biochemical, cytokinetic, pharmacologic, and toxicologic relationships in the design of optimal therapeutic schedules. Cancer chemotherapy reports. Part 1 54(6), 431.

[39] Vacca, Angelo, Iurlaro, Monica, Ribatti, Domenico, Minischetti, Monica, Nico, Beatrice, Ria, Roberto, Pellegrino, Antonio and Dammacco, Franco. (1999). Antiangiogenesis is produced by nontoxic doses of vinblastine. Blood 94(12), 414-4155.

[40] Waterman, M. J., Birch, J. B. and Schabengerger, O. (2007). Linear mixed model robust regression. Wu, H., Chen, H. and Hu, P.C. (2007). Circulating endothelial cells and endothelial progenitors as surrogate biomarkers in vascular dysfunction. Clin. Lab 53, 285-295.

[41] Yuan, Y. and Ying, G. (2011). Dose-response curve estimation: A semiparametric mixture. Biometrics 67, 1543-1554.

[42] Y.Zang, Lee, J.J. and Y.Yuan. (2014). Adaptive designs for identifying optimal biological dose for molecularly targeted agents. Clin Trials 11, 319-327.

[43] Zhang, W., Sargent, DJ. and Mandrekar, SJ. (2006). An adaptive dose-finding design incorporating both toxicity and efficacy. Statistics in Medicine 25, 2365-2383.

Received June 24, 2015; accepted December 13, 2016.

Atanu Bhattacharjee
Department of Biometrics
Chiltern Clinical Research Ltd
Bangalore, India.

Vijay M Patil
Department of Medical Oncology
Tata Memorial Hospital
Mumbai, India.

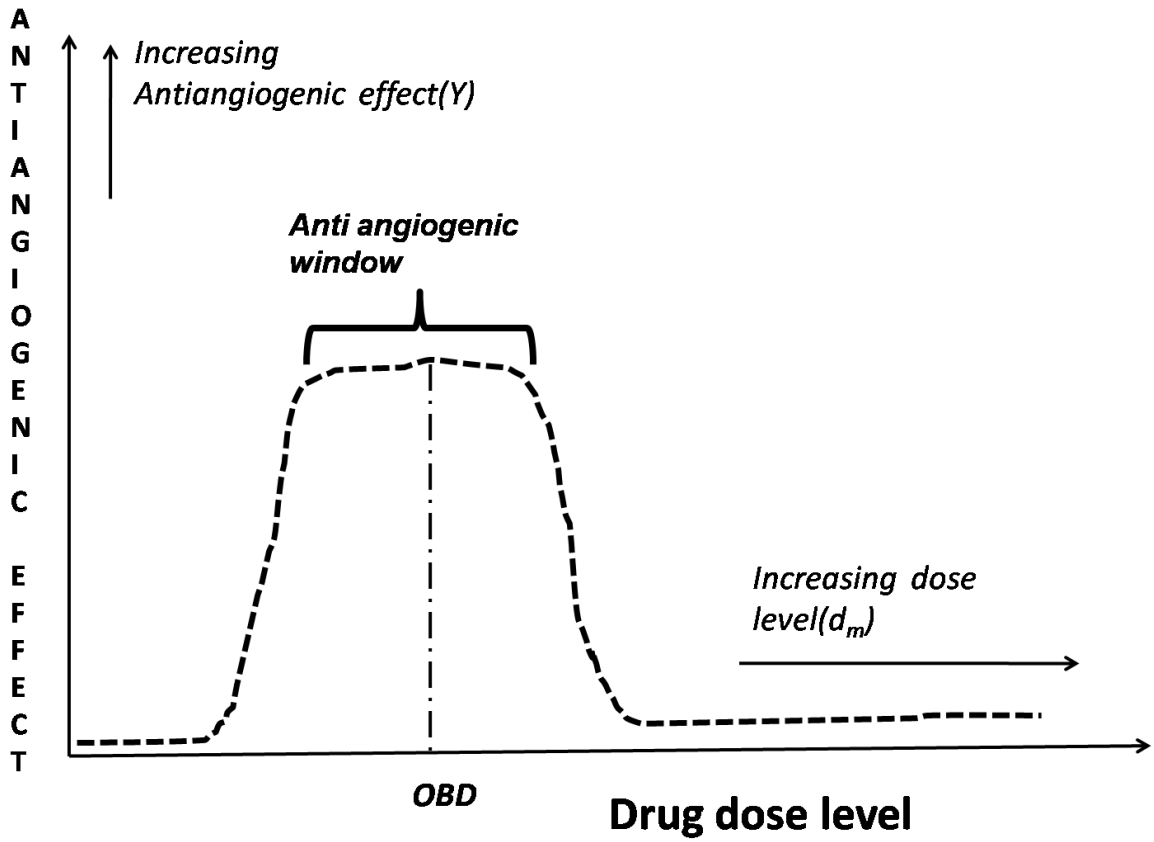

Fig1. Antiangiogenic Distribution

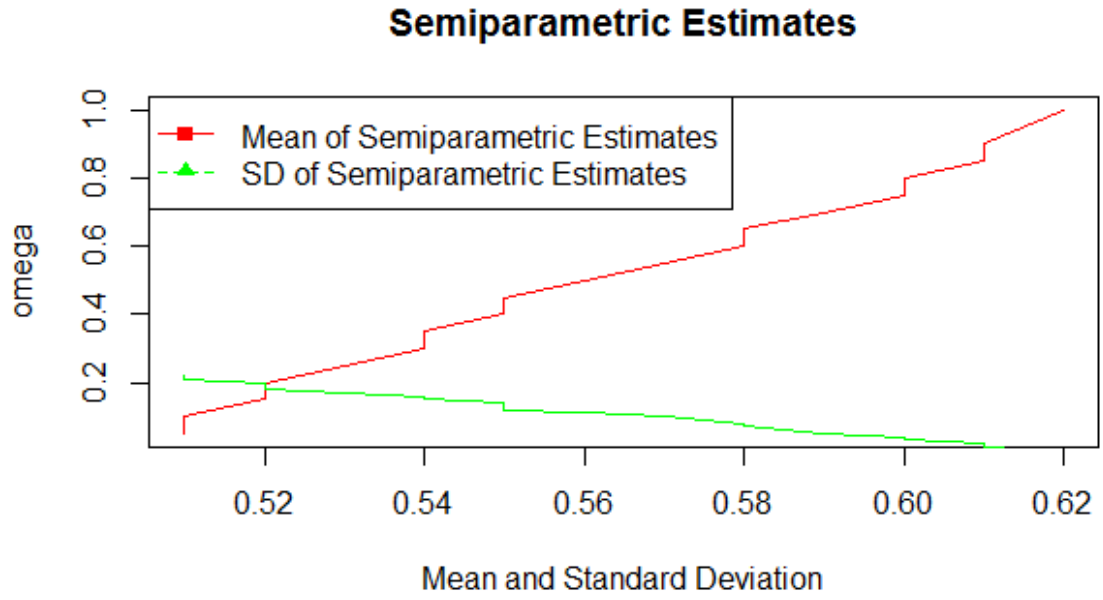

Fig2. Results of a simulation study with 200 markers

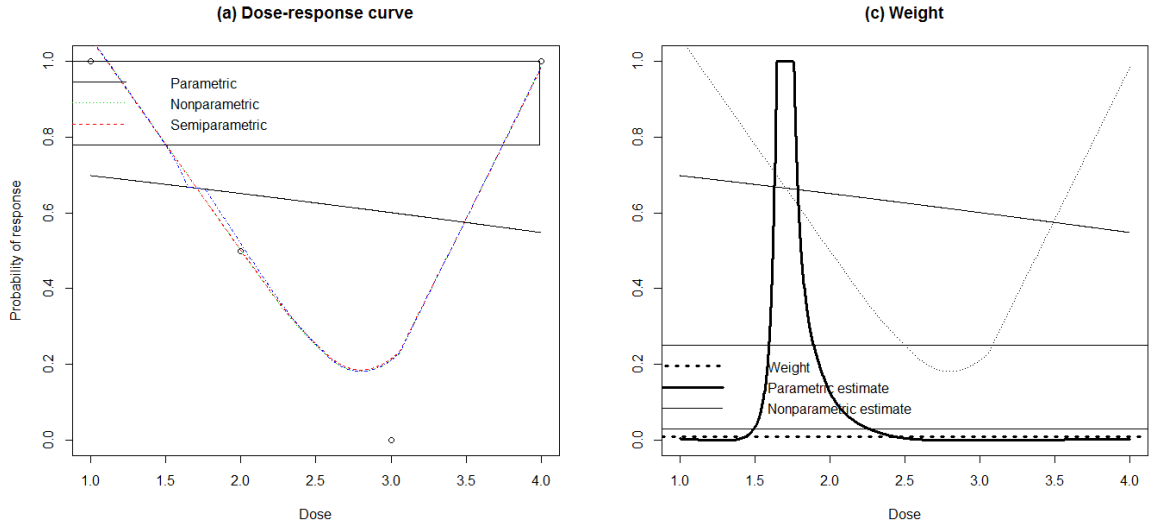

Fig3. Results of a simulation study with 200 markers

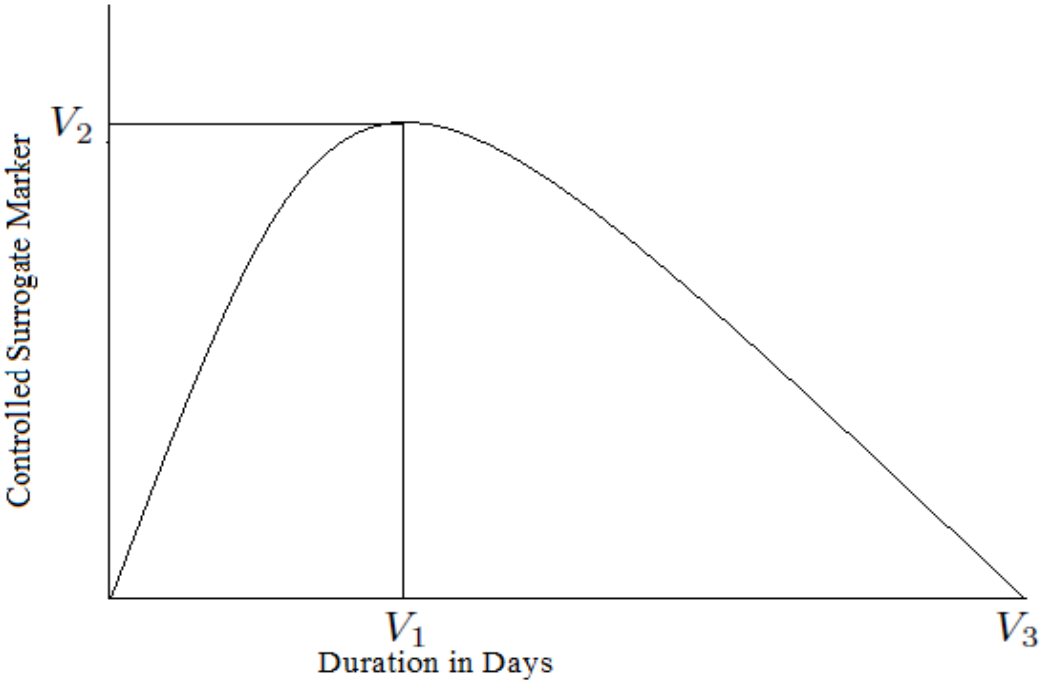

Fig4. Single administration of surrogate marker's distribution

Table 1 Simulation Different Dose Levels with 10 subject per dose

Model	Different Dose Level					
	0.05	0.10	0.15	0.20	0.25	0.30
Probit 1	0	1.2	0	0	0	0.02
Probit 2	0	63.2	18.3	2.3	4.7	4.2

Table 2 Different Dose Levels with 10 subject per dose

Model	Method	Value of ED_α for α					
			0.1	0.20	0.3	0.4	0.5
Probit 1	Kernal	Bias($x10^{-3}$)	9	3	2	1	0
		MSE($x10^{-3}$)	4	3	3	2	2
Probit 2	Kernal	Bias ($x10^{-3}$)	-8	-5	-3	0	1
		MSE($x10^{-3}$)	30	15	6	4	3

Table 3 Simulation Study Results of PRMOBD design

	True Probability						Total	Duration
	d_1	d_2	d_3	d_4	d_5	d_6		
S1	0.05	0.10	0.15	0.20	0.25	0.30		
%Selected	0.10	0.20	0.13	0.06	0.26	0.31		60 days
No. of Patients	5	9	6	3	12	14	45	
No .of Successive Event	3	8	5	4	2	8		
S2	0.10	0.15	0.20	0.25	0.30	0.35		
%Selected	0.07	0.11	0.16	0.19	0.23	0.21		60 days
No. of Patients	5	8	12	14	17	15	45	
No .of Successive Event	4	5	3	5	7	6		
S3	0.10	0.12	0.17	0.20	0.22	0.25		
%Selected	0.26	0.22	0.12	0.16	0.16	0.08		60 days
No. of Patients	13	11	6	8	8	4	45	
No .of Successive Event	5	4	4	7	6	3		

Table4 Operating Characteristics of PRMOBD Design

	True Probability						Total	Duration
	d_1	d_2	d_3	d_4	d_5	d_6		
	10	15	20	25	30	35		
PRMOBD								
%Selected	0.12	0.17	0.20	0.19	0.14	0.15		80 days
No. of Patients	8	11	13	12	9	10	63	
No .of Successive Event	6	8	7	6	5	1		

Table5: Simulation Results for OBD Design

	5	10	20	40	60	80
ε_1	0.12	0.14	0.06	0.32	0.25	0.49
$\bar{P}_{1m}(D_n)$	0.56	0.51	0.52	0.49	0.47	0.39
$\bar{P}_{2m}(D_n)$	0.32	0.36	0.29	0.31	0.35	0.33
$\bar{P}_{2m+1}(D_n)$	0.18	0.12	0.19	0.20	0.18	0.28

Table6: Decision Table for OBD in Different Days

	7	10	20	40	80
ε_1	0.15	0.12	0.03	0.85	0.36
$\bar{P}_{1m}(D_n)$	0.53	0.57	0.69	0.39	0.35
$\bar{P}_{2m}(D_n)$	NA	NA	NA	0.02	0.03
$\bar{P}_{2m+1}(D_n)$	NA	NA	0.01	NA	NA

Table7: The surrogate Marker performance during MC Trial

Scenario	Duration of Event	$100v_2$	Different Schedule in Weeks					
			1(1)	2(3)	3(5)	4(7)	5(0)	6(11)
1	7	3.32	0.4	0.46	0.49	0.53	0.59	0.61
	40	4.09	0.4	0.46	0.49	0.53	0.59	0.61
2	7	3.56	0.23	0.29	0.31	0.35	0.52	0.59
	40	4.23	0.23	0.23	0.31	0.35	0.52	0.59
3	7	3.89	0.17	0.23	0.33	0.39	0.52	0.57
	40	4.38	0.17	0.23	0.33	0.39	0.43	0.57
4	7	4.01	0.11	0.17	0.31	0.4	0.43	0.57
	40	4.52	0.11	0.17	0.31	0.4	0.51	0.57
5	7	3.95	0.09	0.11	0.17	0.29	0.51	0.49
	40	4.49	0.09	0.11	0.17	0.23	0.45	0.49
6	7	3.79	0.05	0.1	0.17	0.23	0.4	0.59
	40	4.29	0.05	0.1	0.15	0.26	0.42	0.57