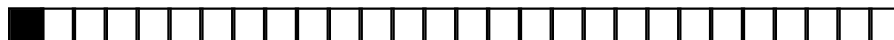


INDIVIDUALIZED PATIENT DOSING IN CANCER CLINICAL TRIALS

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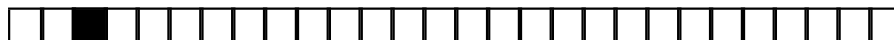
Overview

- Phase I Cancer Clinical Trials
- EWOC
- Accounting for Patients Individual Characteristics
- Examples
- Conclusions



Phase I Cancer Clinical Trials

- Last year 1.4 M new cancer cases in US, more than 1,500 per day die of cancer.
- \approx 650 new medicines to cure cancer in development.
- \approx 900 Phase I trials open to patients in US (6/2008).
- Subjects: Patients with cancer who have exhausted standard treatment options.
- Goal of a Phase I Cancer Clinical Trial is to estimate the highest dose of a cytotoxic agent associated with a tolerable level of toxicity (CTC guidelines by NCI).
- Dose referred as: Maximum Tolerated Dose (MTD), Working Dose, Target Dose, Recommended Phase II Dose (RPTD).



Phase I Clinical Trials (Contnd.)

■ Dose-Limiting Toxicity (DLT) is the manifest of a toxic effect of a drug that prevents further dosage increase or stops the treatment. *Medically unacceptable toxicity.*

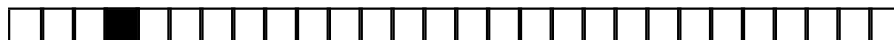
■ Maximum Tolerated Dose (MTD) is dose γ for which:

$$\text{Prob}(\text{DLT}|\text{dose} = \gamma) = \theta,$$

where θ depends on nature and consequences of dose-limiting toxicity.

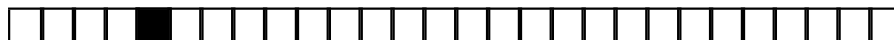
■ θ is set relatively high when the DLT is a transient, correctable condition, and low when it is life threatening; $\theta = 1/3$ often used in practice.

■ Reviews: Rosenberger and Haines, SiM 2002; Ting 2006; Elder and Burkholder, 2006.



Desirable Properties of Phase I Designs

- A priori information about the drug (from lab/animal) should be easily incorporated in the model.
- Design should be adaptive; uncertainty about toxicity associated with dose level to be given to next patient should be reduced when data collected thus far are taken into account.
- Design should control probability of overdosing patients at each stage.
- Design should produce a sequence of doses that approaches MTD as rapidly as possible.
- Design should take into account relevant heterogeneity of patients enrolled in Phase I clinical trial.



Bayesian Designs

■ Sci. Citation Index database 1996-2006: 1235 Phase I CCT (Rogatko et al., 2007).

■ 1215/1235 (98.4%) variations of “modified Fibonacci up-and-down.” 17/1235 variations of CRM, and 3/1235 EWOC.

■ Bayesian approaches: Tsutakawa (1972, 1980), Grieve (1987), Racine et al. (1986);

CRM O’Quigley et al. (1990), Chevret (1993), Faries (1994), Goodman et al. (1995), Möller (1995), Piantadosi et al (1998), Storer (2001), etc.

EWOC Babb et al. (1998), Zacks et al (1998), Shih et al. (1999), Tighiouart et al. (2005), Rogatko et al (2008), Chu et al. (2009), etc.



EWOC

■ Dose-Toxicity Logistic Model:

$$\text{Prob}(\text{DLT}|\text{dose} = x) = \frac{\exp\{\beta_0 + \beta_1 x\}}{1 + \exp\{\beta_0 + \beta_1 x\}}, \quad \beta_1 > 0$$

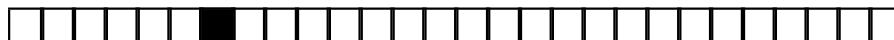
■ dose $\in [X_{min}, X_{max}]$,

$$\rho_0 = \text{Prob}(\text{DLT}|\text{dose} = X_{min}), \gamma = MTD$$

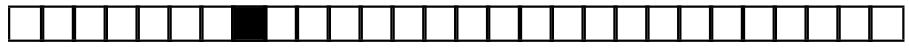
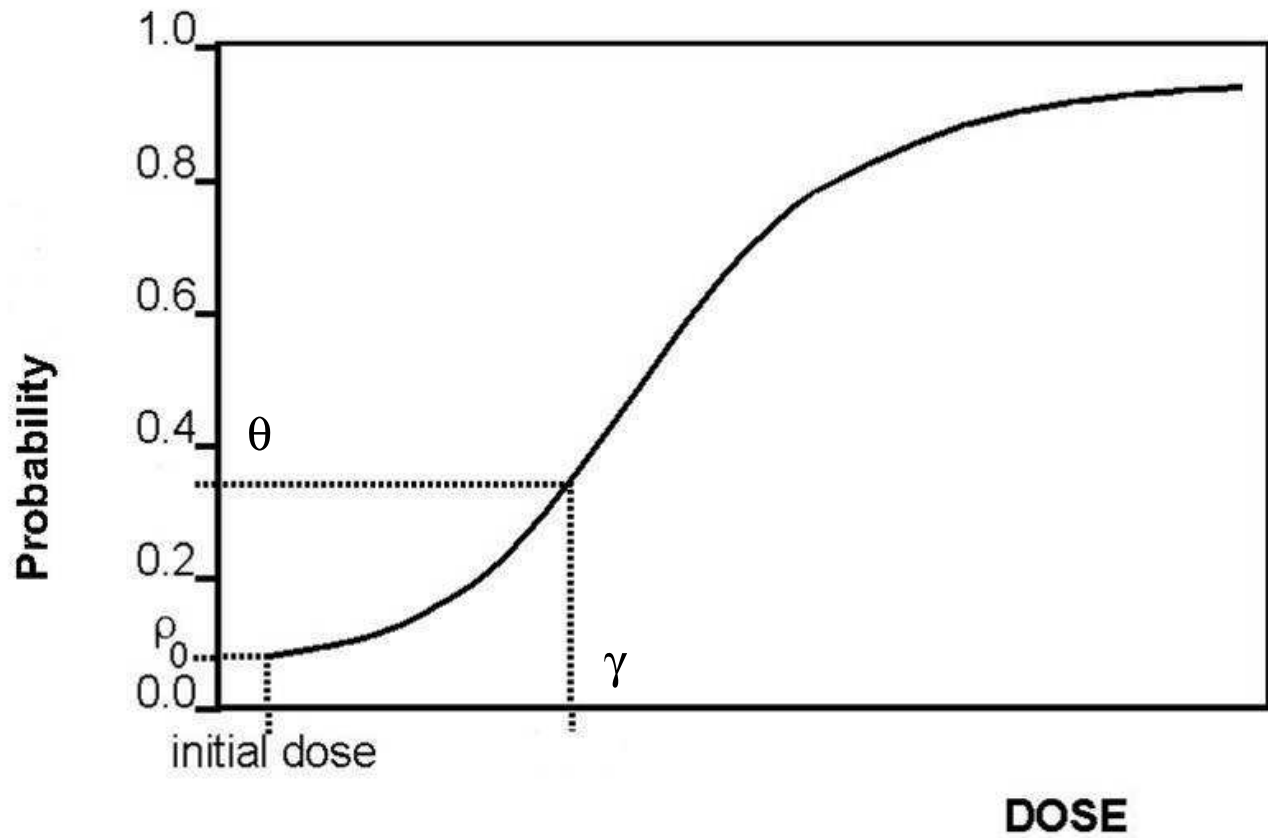
■ Reparameterize $(\beta_0, \beta_1) \longrightarrow (\gamma, \rho_0)$

$$\beta_0 = \frac{1}{\gamma - X_{min}} [\gamma \text{logit}(\rho_0) - X_{min} \text{logit}(\theta)]$$

$$\beta_1 = \frac{1}{\gamma - X_{min}} [\text{logit}(\theta) - \text{logit}(\rho_0)].$$



EWOC



EWOC

- x_i - dose administered to the i th patient
- $y_i = 1$ if the i th patient exhibits DLT, $y_i = 0$ otherwise
- $\mathcal{D}_k = \{(x_i, y_i), i = 1, \dots, k\}$ data after observing k patients
- Likelihood after observing the toxicity outcomes of the k patients

$$L_k(\rho_0, \gamma | \mathcal{D}_k) = \prod_{i=1}^k p(\rho_0, \gamma, x_i)^{y_i} (1 - p(\rho_0, \gamma, x_i))^{1-y_i}.$$

- Straightforward to consider cohorts of m patients at each stage.



EWOC

- $h(\rho_0, \gamma)$ - prior distribution for (ρ_0, γ) on $[0, \theta] \times [X_{min}, X_{max}]$
- $\Pi(\gamma|\mathcal{D}_k)$ - marginal posterior cdf of the MTD.
- First patient receives dose $x_1 = X_{min}$ and conditional on $\{y_1 = 0\}$, the $(k + 1)$ st patient receives the dose

$$x_{k+1} = \Pi^{-1}(\alpha|\mathcal{D}_k),$$

so that the posterior probability of exceeding the MTD is equal to the *feasibility bound* α .

- If a trial is based on pre-specified set of doses d_1, \dots, d_r , the $(k + 1)$ st patient receives the dose $x_{k+1}^* = \max\{d_1, \dots, d_r : d_i - x_{k+1} < T_1 \text{ and } \Pi(x_{k+1}|\mathcal{D}_k) - \alpha < T_2\}$ where T_1, T_2 are prespecified tolerances.



EWOC

- The sequence of doses generated by this design is weakly consistent,

$$x_k \rightarrow \gamma, \text{ in probability as } k \rightarrow \infty.$$

- Decision Theoretic Interpretation: The dose x_k selected by EWOC for the k th patient minimizes risk with respect to the loss function,

$$L(x, \gamma) = [\alpha \mathbf{1}(x \leq \gamma) + (1 - \alpha) \mathbf{1}(x > \gamma)] |x - \gamma|.$$

- Loss of overestimating γ $\frac{1-\alpha}{\alpha}$ -times exceeds the loss of underestimating it; $\alpha = 1/4$ often used in practice.

- EWOC is coherent: $y_i = 1, x_{i+1} < x_i$; $y_i = 0, x_{i+1} > x_i$.



EWOC: Design with Binary Covariate

■ O'Quigley et al. (1999), O'Quigley and Paoletti (2003) applied it to a real trial. Babb and Rogatko (2001) designed a trial with a continuous covariate.

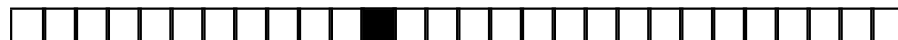
■ Denote by $Z \in \{0, 1\}$ an observable binary covariate and consider the logistic dose-toxicity model

$$p_z(x) = \frac{\exp\{\beta_0 + \beta_1 x + \beta_2 z\}}{1 + \exp\{\beta_0 + \beta_1 x + \beta_2 z\}}.$$

■ Two groups of patients: Group A with $Z = 0$ and Group B with $Z = 1$.

■ The MTD for a patient with covariate $Z = z$ is defined as

$$\text{Prob}(\text{DLT} | \text{dose} = \gamma_z) = \theta_z.$$



EWOC: Design Using Binary Covariate

$\gamma_0 =$ MTD for patients in Group A

$\gamma_1 =$ MTD for patients in group B

$\rho_{0,0} =$ Probability of DLT for patients in Group A at dose $= X_{min}$.

$$\gamma_z = \frac{\text{logit}(\theta_z) - \beta_0 - \beta_2 z}{\beta_1}, \quad \text{logit}(\rho_{0,0}) = \beta_0 + \beta_1 X_{min}.$$

Reparametrization: $(\beta_0, \beta_1, \beta_2) \longrightarrow (\gamma_0, \gamma_1, \rho_{0,0})$

- $\pi(\gamma_1)$ is independent of the joint prior distribution for $(\rho_{0,0}, \gamma_0)$.
- Design more powerful than the two separate EWOC's, one for each group.
- Extensive simulations in Tighiouart, Rogatko, and Xu (2007).



EWOC: Using Software

- 12 patients with malignant solid tumor were treated with antimetabolite 5-fluorouracil (5-FU) combined with 20 mg/m^2 leucovorin and 0.5 mg/m^2 topotecan
- Goal: Find dose of 5-FU that will result in probability $\theta = 1/3$ that grade 4 hematologic or grade 3 or 4 non-hematologic toxicity is manifest within two weeks.
- Previous studies showed 140 mg/m^2 of 5-FU was well tolerated when given with 0.5 mg/m^2 topotecan. The MTD of 5-FU alone was estimated as 425 mg/m^2 .

■ **Setup:** $X_{min} = 140, X_{max} = 425$. Cohorts of size 2.

$(\rho_0, \gamma) \sim \mathcal{U}([0, 0.33] \times [140, 425])$. Feasibility bound $\alpha = 1/4$.



EWOC: Using Software

- Rogatko, A., Tighiouart, M., Xu, R. **EWOC2.1**
http://sisyphus.emory.edu/software_ewoc.php

EWOC - DIALOG

Required

Probability of Dose Limiting Toxicity: 0.33333
Probability of Exceeding Target Dose: 0.25000
Minimum Dose: 140.00000
Maximum Dose: 425.00000

Data File: C:\Program Files\EWOC C View

Optional

Title: MDAnderson
Minimum Dose Increment: 10.00000
 Bayesian Confidence Interval: 90.0 %
 Marginal Posterior Distribution Plot
 Cohort size: two Patients
 Tree of Doses for Next: four Cohort
 Variable Alpha Increment: 0.00000

Prior Distributions

for the Target Dose

Uniform
 Beta with Mode: 200.00
and Standard Deviation: 30.00

for the Probability of DLT at Initial Dose

Uniform between: 0.00000
and: 0.33333

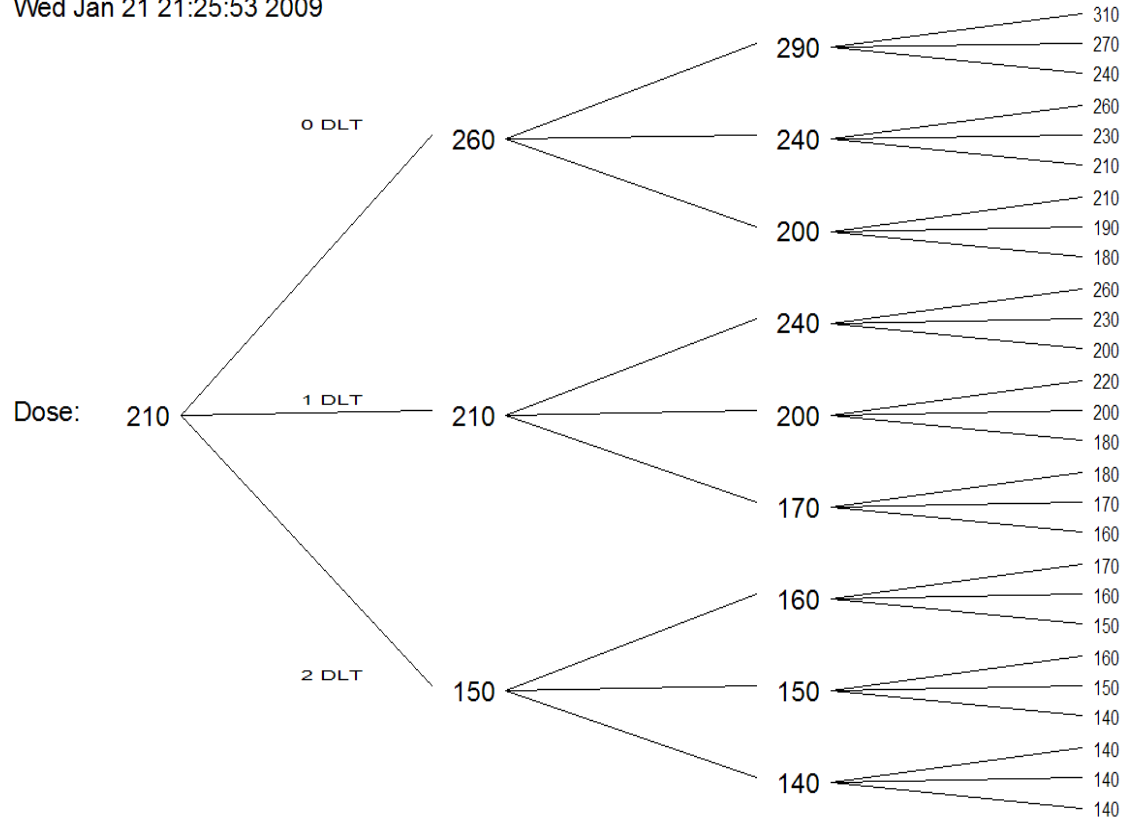
Open Parameter File Cancel
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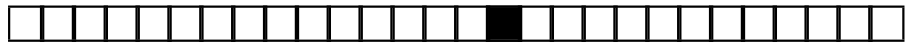
MDAnderson

Wed Jan 21 21:25:53 2009

Theta= 0.33 Alpha= 0.25
Mindose= 140.00 Maxdose= 425.00



Alpha: 0.250	0.250	0.250	0.250
Patient: 3 - 4	5 - 6	7 - 8	9 - 10



EWOC: PNU-214565 Study

- Phase I study of PNU-214565 (PNU) involving patients with advanced adenocarcinomas of gastrointestinal origin
- Previous clinical and preclinical studies demonstrated that the action of PNU is moderated by the neutralizing capacity of anti-SEA antibodies.
- EWOC with continuous covariate anti-SEA was used

$$\text{Prob}(\text{DLT} | \text{dose} = x, \text{anti-SEA} = c) = \frac{\exp\{\beta_0 + \beta_1 x + \beta_2 c\}}{1 + \exp\{\beta_0 + \beta_1 x + \beta_2 c\}}$$

- $\beta_1 > 0, \beta_2 < 0,$

- $\theta = 0.1$



EWOC: PNU-214565 Study

- Model is reparametrized in terms of

$$\rho_1 = P(\text{DLT} | \text{dose} = 0.5, \text{anti-SEA} = 0.01)$$

$$\rho_2 = P(\text{DLT} | \text{dose} = 0.5, \text{anti-SEA} = 1800)$$

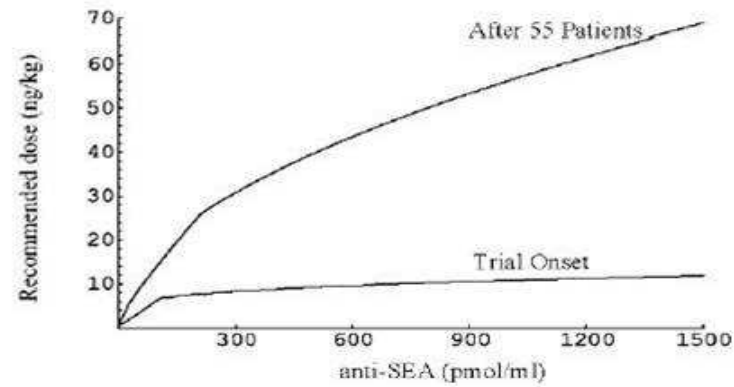
$$\gamma_{max} = \gamma(1800)$$

- Prior distribution

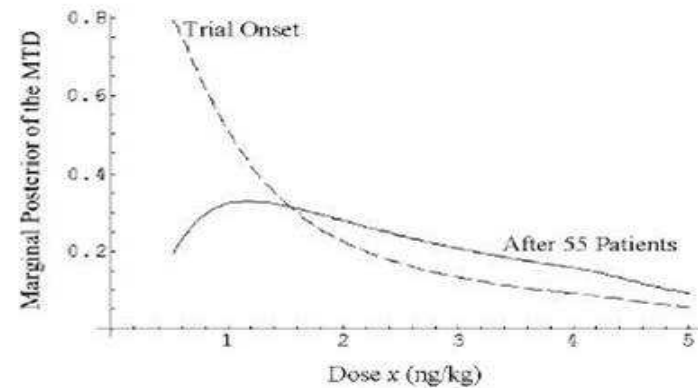
$$H(\gamma_{max}, \rho_1, \rho_2) = \frac{\theta^2}{2} \ln(2000/7) \frac{1}{\gamma_{max}} I_{[3.5, 1000]}(\gamma_{max}) I_{\Omega}(\rho_1, \rho_2),$$

where $\Omega = \{(x, y) : 0 < x < \theta, 0 < y < x\}$





The recommended dose of PNU as a function of anti-SEA concentration at both the onset and the conclusion of the phase I trial.



The marginal posterior distribution of the MTD for patients with anti-SEA concentration equal to 5 pmol/ml, at both the onset and the conclusion of the phase I trial.



EWOC: AAA-280411 Study

- Phase I dose-escalation study of AAA-280411 in patients with advanced non-small cell lung cancer
- Determine the MTD of AAA-280411 as a function of pre-treatment Anti-Staphylococcus Enterotoxin A/E-120 Antibody (anti-SEA/E-120) levels in patients with advanced non-small cell lung cancer.
- This agent (and its variants) were developed with the intension of eliminating the neutralizing effect of anti-SEA on the chemo agent



EWOC: AAA-280411 Study

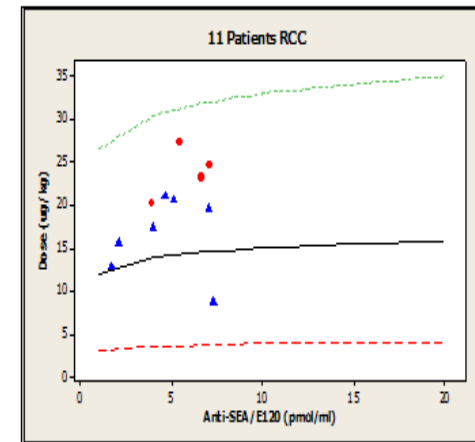
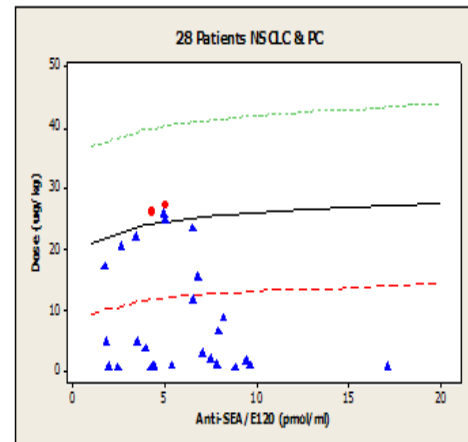
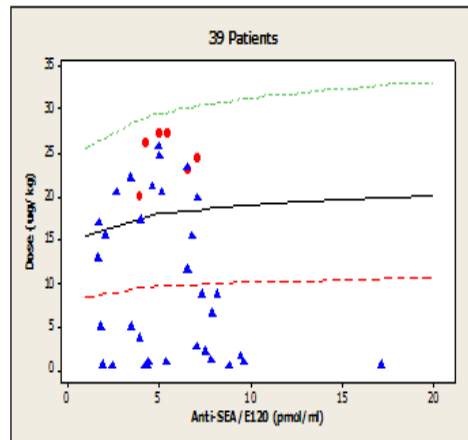
- Trial was designed using EWOC with continuous covariate anti-SEA

$$P(\text{DLT} | \text{dose} = x, \text{anti-SEA} = c) = \frac{\exp\{\beta_0 + \beta_1 x + \beta_2 c\}}{1 + \exp\{\beta_0 + \beta_1 x + \beta_2 c\}}$$

- $\beta_1 > 0$ and $\beta_2 < 0$
- $\theta = 0.2$



39 Patients → 28 w/NSCLC&PC + 11 w/RCC



- Solid Black Line: Recommended Dose;
- Blue Triangles: NO DLT; Red Circles: DLT;
- Dashed Green Line: Upper 95% Credible Region Bound; Dashed Red Line: Lower 95% Credible Region Bound



EWOC: AAA-280411 Study; Inference

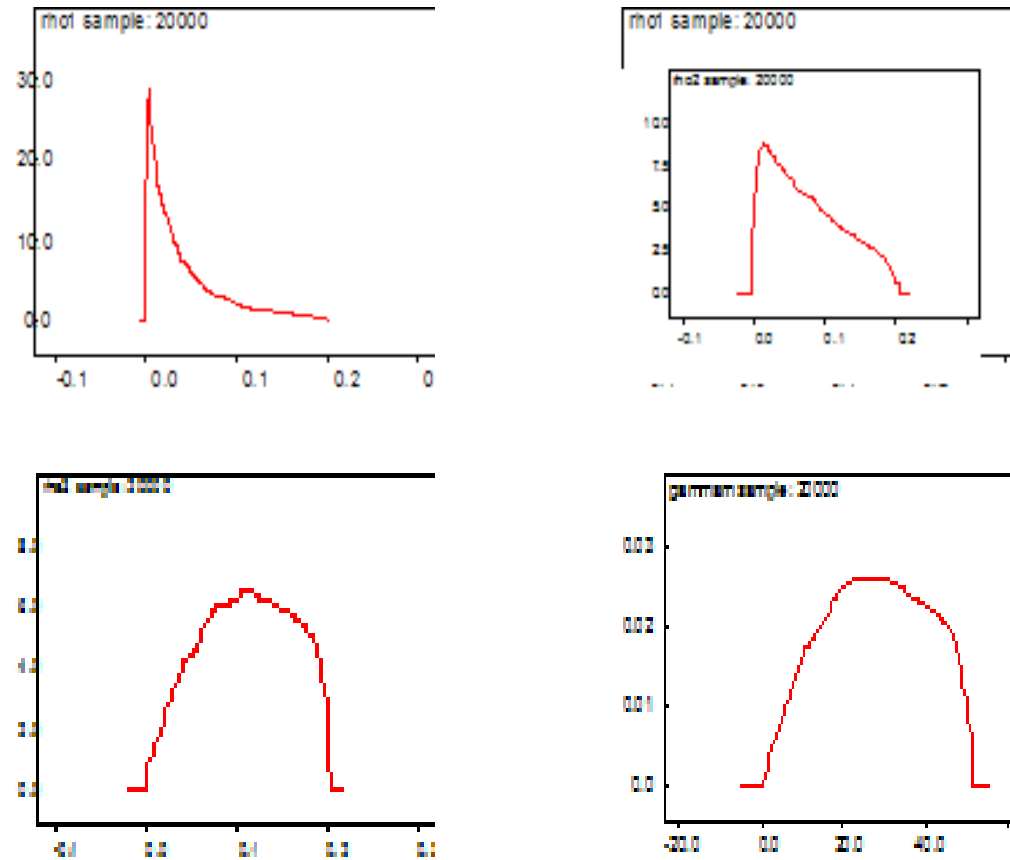
$$P_{c,z}(x) = P(\text{DLT} | \text{dose} = x, C = c, Z = z) = \frac{\exp\{\beta_0 + \beta_1 x + \beta_2 c + \beta_3 z\}}{1 + \exp\{\beta_0 + \beta_1 x + \beta_2 c + \beta_3 z\}}$$

- C is baseline anti-SEA/E 120, $C \in [c_1, c_2]$.
- Z is binary; $Z = 1$ ($= z_1$) for NSCLC and PC patients and $Z = 0$ ($= z_0$) for RCC patients
- Reparameterize Model:

$$\gamma_{max} = \gamma(c_2, z_0);$$

$$\rho_1 = P_{c_1, z_0}(X_{min}), \quad \rho_2 = P_{c_2, z_0}(X_{min}), \quad \rho_3 = P_{c_1, z_1}(X_{min})$$

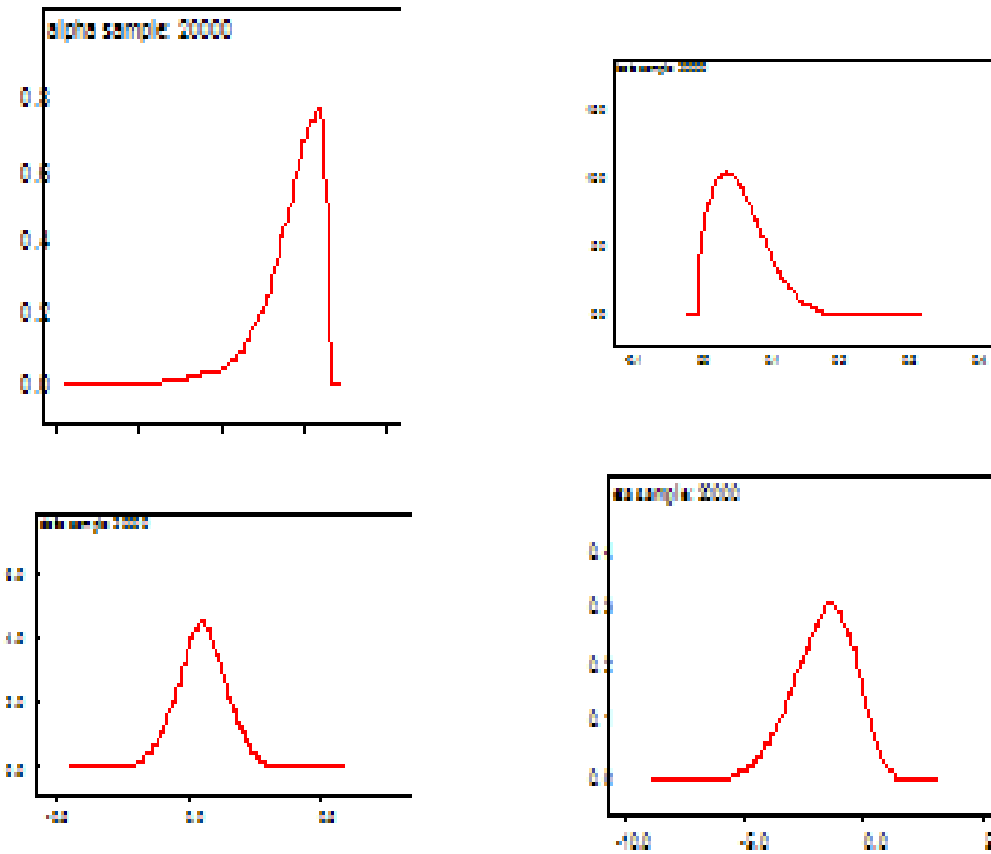




■ Panel NW: Posterior Density for ρ_1 ; Panel NE: Posterior Density for ρ_2 ; Panel SW: Posterior Density for ρ_3

■ Panel SE: Posterior Density for γ





■ Posterior densities for NW: β_0 , NE: β_1 , SW: β_2 , SE: β_3



Patients (# Pts; # DLTs)	Baseline antiSEA/ E120	Recom Dose mg/kg < .5	95% HPD Lower Limit	95% HPD Upper Limit	95% HPD Ampl
ALL (39; 6)	1	15.4394	8.37	25.54	17.17
	20	19.9898	10.50	33.23	22.73
	NO COV	18.7280	9.428	29.533	20.105
NSCLC & PC (28; 2)	1	20.7469	9.50	36.89	27.39
	20	27.6503	14.30	43.95	29.65
	NO COV	26.163	13.932	49.116	35.184
RCC (11; 4)	1	12.0948	3.11	26.61	23.50
	20	15.8682	4.04	34.97	30.93
	NO COV	14.875	2.027	39.559	37.532



Conclusions

- EWOC is Bayesian-adaptive, consistent, coherent, and controls the probability of overdosing patients.
- Prior information on the agent can be incorporated via the prior distribution of the MTD.
- EWOC accounts for patients specific characteristics.
- Deciding whether to keep or drop a covariate during the course of the trial is under consideration.
- Adapting EWOC to time to DLT is under work.
- Adapting EWOC to dual endpoints DLT and Efficacy for Phase I/II trials is under work.



EWOC: Some References

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