Early-phase Dose-finding Design for Molecularly Targeted Agents

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Outline

- Background
- Models & inference
- Dose-finding algorithm
- Simulation results
- Conclusions

Traditional Dose-finding

- Primary goal for a cytotoxic agent is to identify MTD
- Recommended dose further investigated in Phase II to evaluate efficacy
- Common assumption for cytotoxics is both efficacy and toxicity increase monotonically with dose
- Recent development of molecularly targeted agents (MTA's) challenges this assumption

Dose-finding For Molecularly Targeted Agents

- Toxicity may be minimal
  - Often reasonable to assume monotonicity
- Dose-efficacy curves may be non-monotonic
- Goal is to find optimal biological dose (OBD)
  - Defined by dose with acceptable toxicity that maximizes efficacy

Published Methods For MTA's

- Hunsberger, Rubinstein, Dancey, Korn; *Statist Med* 2005
- Mandrekar, Cui, Sargent; *Statist Med* 2007
- Polley, Cheung; *Biometrics* 2008
- Hoering, LeBlanc, Crowley; *Clin Cancer Res* 2011
- Hoering, Mitchell, LeBlanc, Crowley; *Clin Trials* 2013
- Yin, Zheng, Xu; *Statist Med* 2013

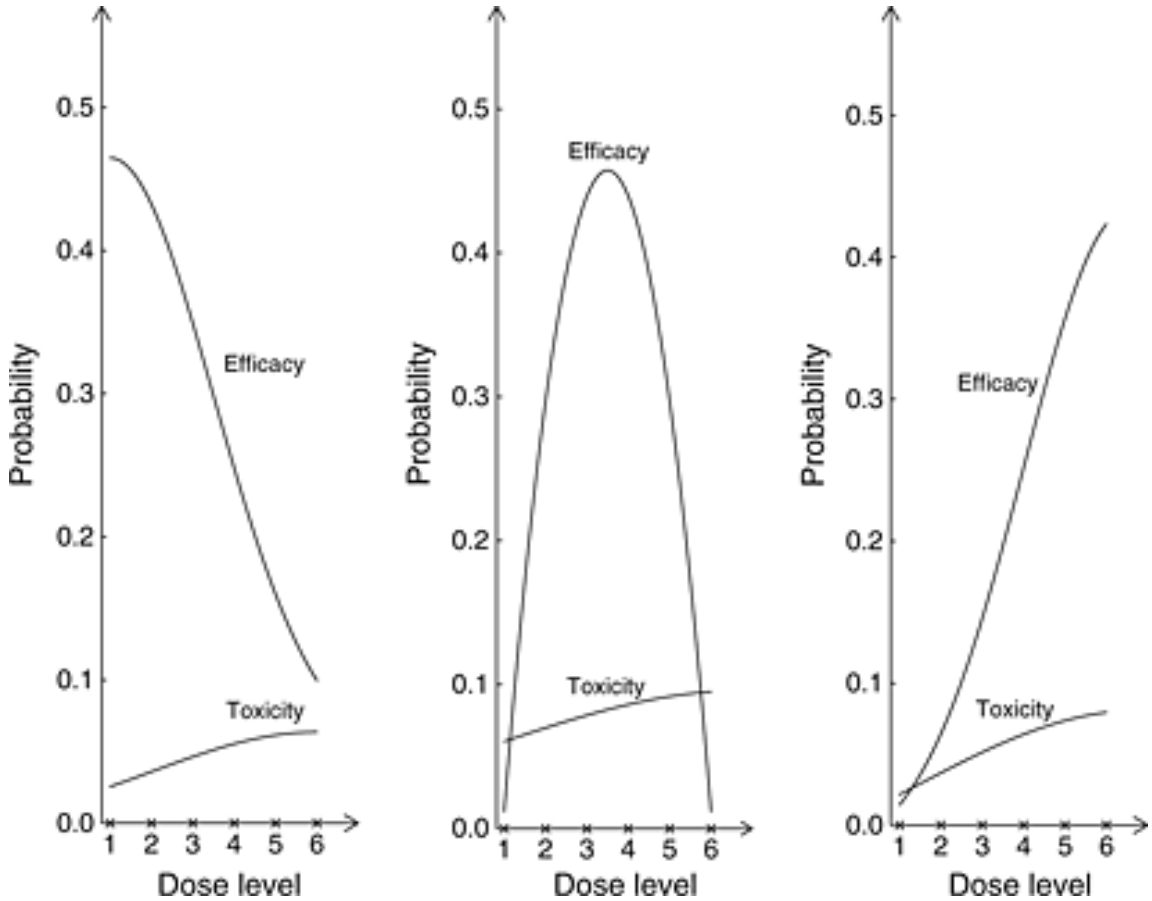
Non-monotone Dose-efficacy Curves

- May exhibit unimodal or plateau relationships
  - Increase initially, then decrease or remain constant
- Suppose we have a set of I doses, $\{d_1, \ldots, d_I\}$ and probability of efficacy at d_i is denoted, $\pi_E(d_i)$
- The goal is to find OBD, $d_\nu \in \{d_1, \ldots, d_I\}$, defined by

$$\pi_E(d_1) \leq \cdots \leq \pi_E(d_\nu) \geq \cdots \geq \pi_E(d_I).$$

Possible Dose-toxicity/efficacy Curves

Yin, Zheng, Xu; *Statist Med* 2013



Example

- Phase I study of Bavituximab in patients with advanced solid tumors (Gerber et al.; *Clinical Cancer Research*, 2011)
- Four available dose levels $(0.1, 0.3, 1, 3$ mg/kg)
- Goal of the study was dose escalation to the OBD, rather than MTD
- "...for monoclonal antibodies, the MTD may not correspond to optimal efficacy..."

Overall Strategy

- d_ν corresponds to the peak of unimodal curve or beginning of plateau
- Peak could occur at any of the I available levels
  - Non-decreasing probabilities before the peak, non-increasing probabilities after peak
- Overall strategy is to formulate a set of possible dose-efficacy relationships corresponding to various “peak” locations

Possible Dose-efficacy Curves

1. monotone decreasing: peak at d_1
   $\pi_E(d_4) \leq \pi_E(d_3) \leq \pi_E(d_2) \leq \pi_E(d_1)$
2. monotone increasing: peak at d_4
   $\pi_E(d_1) \leq \pi_E(d_2) \leq \pi_E(d_3) \leq \pi_E(d_4)$.
3. unimodal or plateau: peak at d_2
   $\pi_E(d_1) \leq \pi_E(d_3) \leq \pi_E(d_4) \leq \pi_E(d_2)$
4. unimodal or plateau: peak at d_3
   $\pi_E(d_1) \leq \pi_E(d_2) \leq \pi_E(d_4) \leq \pi_E(d_3)$.

Modeling Toxicity - CRM

- The probability of DLT at dose level d_i is

$$\pi_T(d_i) \approx F(d_i, \beta) = p_i^{\exp(\beta)}$$

- After j inclusions, DLT probability estimates

$$\widehat{\pi}_T(d_i) = F(d_i, \widehat{\beta}_j)$$

define an acceptable set of doses based on a maximum acceptable toxicity rate ϕ_T

Models For Efficacy

- Suppose there are K dose-efficacy model possibilities under investigation.
- For a particular model, k, the probability of efficacy modeled by

$$\pi_E(d_i) \approx G_k(d_i, \theta) = q_{ik}^{\exp(\theta)}$$

  for a class of working dose-efficacy models, $G_k(d_i, \theta)$
- $0 < q_{1k} < \cdots < q_{Ik} < 1$ represents the skeleton of model k.

Inference

- Prior probabilities on each model $\tau(k) = \{\tau(1), \ldots, \tau(K)\}$ and prior distribution, $g(\theta)$, on θ
- After inclusion of the first j patients into the study, the likelihood under model k is given by

$$L_k(\theta \mid \mathcal{D}_j) = \prod_{\ell=1}^{j} \{G_k(x_\ell, \theta)\}^{z_\ell} \{1 - G_k(x_\ell, \theta)\}^{(1-z_\ell)}$$

which, for each model, can be used in order to generate the posterior mean, $\widehat{\theta}_{jk}$, of parameter θ.

Model Selection

- The posterior probabilities of the models given the data are

$$\omega(k \mid \mathcal{D}_j) = \frac{\tau(k) \int L_k(\theta \mid \mathcal{D}_j) g(\theta) d\theta}{\sum_{k=1}^{K} \tau(k) \int L_k(\theta \mid \mathcal{D}_j) g(\theta) d\theta}.$$

- When a new patient is to be enrolled, we choose a single model, k^*, with the largest posterior probability such that

$$k^* = \arg\max_k \omega(k \mid \mathcal{D}_j)$$

Model Selection in CRM

- Bayesian model averaging CRM (Yin, Yuan; *JASA* 2009)
- Extended model-based designs for more complex dose-finding studies (O'Quigley, Conaway; *Statist Med* 2011)
- Posterior maximization and averaging for Bayesian working model choice in the CRM (Daimon, Zohar, O'Quigley; *Statist Med* 2011)
- CRM for partial ordering (Wages, Conaway, O'Quigley; *Biometrics* 2011)

Efficacy Probability Estimates

- Take the working model, $G_{k^*}(d_i, \theta)$, associated with k^* to generate efficacy probability estimates at each dose.
- Compute the posterior probability of a response for d_i

$$\widehat{\pi}_E(d_i) = G_{k^*}(d_i, \widehat{\theta}_{jk^*})$$

from which we can make decisions regarding allocation.

Dose-finding Algorithm

- Overall, allocate the next entered patient to the dose estimated to be the most efficacious, among those with acceptable toxicity.
- Define the set of "acceptable" doses as

$$\mathcal{A}_j = \{d_i : \widehat{\pi}_T(d_i) \leq \phi_T;\ i = 1, \ldots, I\}.$$

- The allocation algorithm depends upon the amount of data that has been observed so far in the trial.

Randomization Phase

- For doses in $\mathcal{A}_j$, calculate a randomization probability R_i,

$$R_i = \frac{\widehat{\pi}_E(d_i)}{\sum_{d_i \in \mathcal{A}_j} \widehat{\pi}_E(d_i)}$$

  and randomize the next patient or cohort of patients to dose d_i with probability R_i.
- Switch to a phase in which we simply allocate according to the maximum estimated efficacy probability among the acceptable doses.

Maximization Phase

- Among the doses contained in $\mathcal{A}_j$, we allocate the $(j+1)$th patient cohort to the dose x_{j+1} according to the estimated efficacy probabilities, $\widehat{\pi}_E(d_i)$, such that

$$x_{j+1} = \arg\max_{d_i \in \mathcal{A}_j} \widehat{\pi}_E(d_i)$$

- The optimal dose is the recommended dose $d_i = x_{n+1}$ for the hypothetical $(n+1)$th patient after the inclusion of the maximum sample size of n patients.

Design Specifications

- Skeleton for toxicity, $p_i = \{0.01, 0.08, 0.15, 0.22, 0.29, 0.36\}$
- Define maximum acceptable toxicity rate $\phi_T = 0.33$
- Total sample size $N = 48$
- Randomization phase sample size $n_R = 12$
- Each of the k models has Normal prior distribution on θ

$$g(\theta) \sim \mathcal{N}(0, 1.34)$$

Skeletons For Unimodal Relationships

- peak at $d_6[k = 1]$
  $\{0.10, 0.20, 0.30, 0.40, 0.50, 0.60\}$
- peak at $d_5[k = 2]$
  $\{0.20, 0.30, 0.40, 0.50, 0.60, 0.50\}$
- peak at $d_4[k = 3]$
  $\{0.30, 0.40, 0.50, 0.60, 0.50, 0.40\}$
- peak at $d_3[k = 4]$
  $\{0.40, 0.50, 0.60, 0.50, 0.40, 0.30\}$
- peak at $d_2[k = 5]$
  $\{0.50, 0.60, 0.50, 0.40, 0.30, 0.20\}$
- peak at $d_1[k = 6]$
  $\{0.60, 0.50, 0.40, 0.30, 0.20, 0.10\}$

Skeletons For Plateau Relationships

- plateau at $d_1[k = 7]$
  $\{0.60, 0.60, 0.60, 0.60, 0.60, 0.60\}$
- plateau at $d_2[k = 8]$
  $\{0.50, 0.60, 0.60, 0.60, 0.60, 0.60\}$
- plateau at $d_3[k = 9]$
  $\{0.40, 0.50, 0.60, 0.60, 0.60, 0.60\}$
- plateau at $d_4[k = 10]$
  $\{0.30, 0.40, 0.50, 0.60, 0.60, 0.60\}$
- plateau at $d_5[k = 11]$
  $\{0.20, 0.30, 0.40, 0.50, 0.60, 0.60\}$
- Assume, a priori, that each skeleton is equally likely and set $\tau(k) = 1/11$

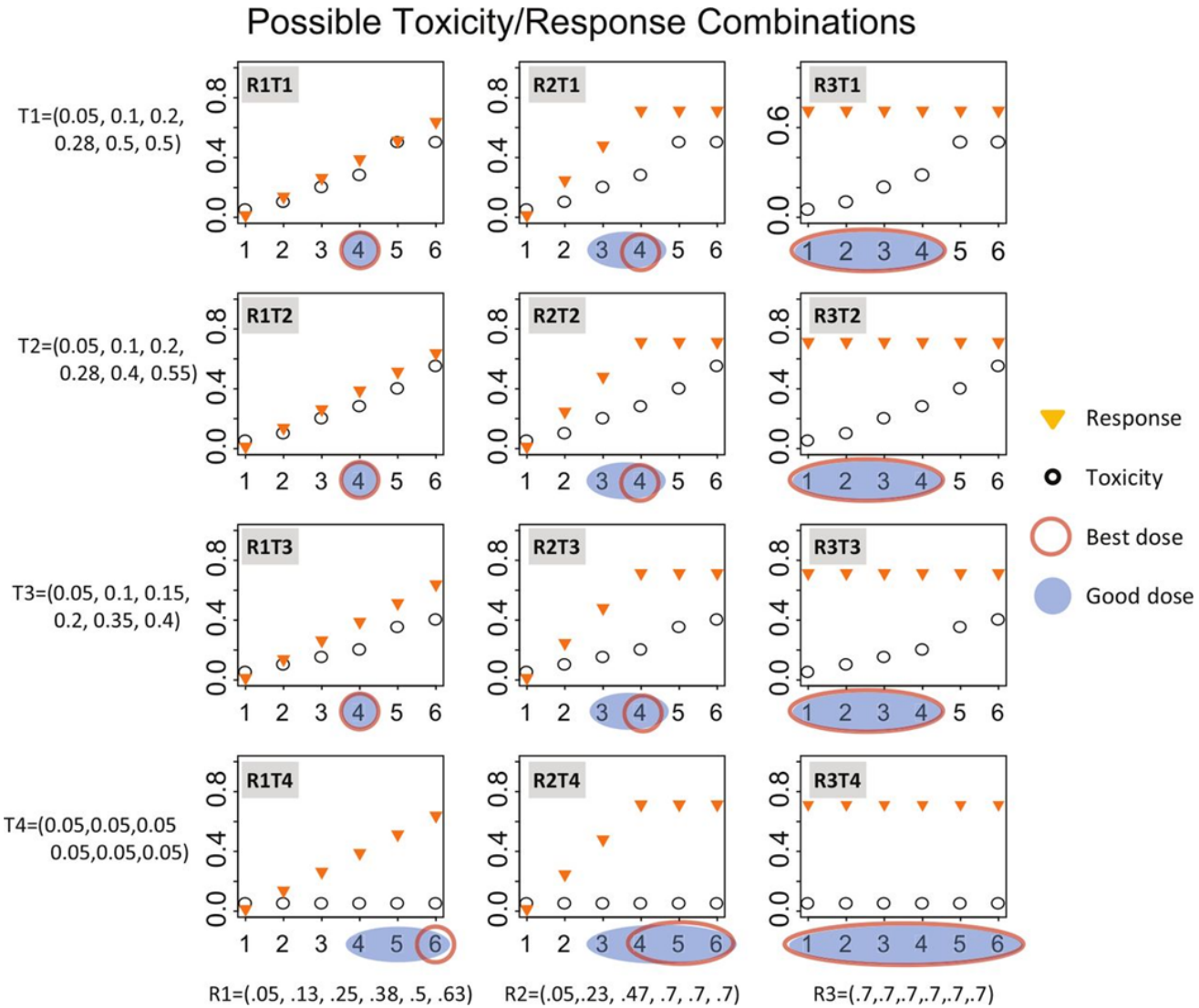
Association Between Toxicity & Efficacy

- Association between toxicity and efficacy is ignored in modeling
- Simulation studies assess the sensitivity of method to association between toxicity and efficacy
- Correlated binary responses generated under various values of association parameter ψ
- Results presented with $\psi = 4.6$ as in Hoering et al. (*Clinical Trials*, 2013)

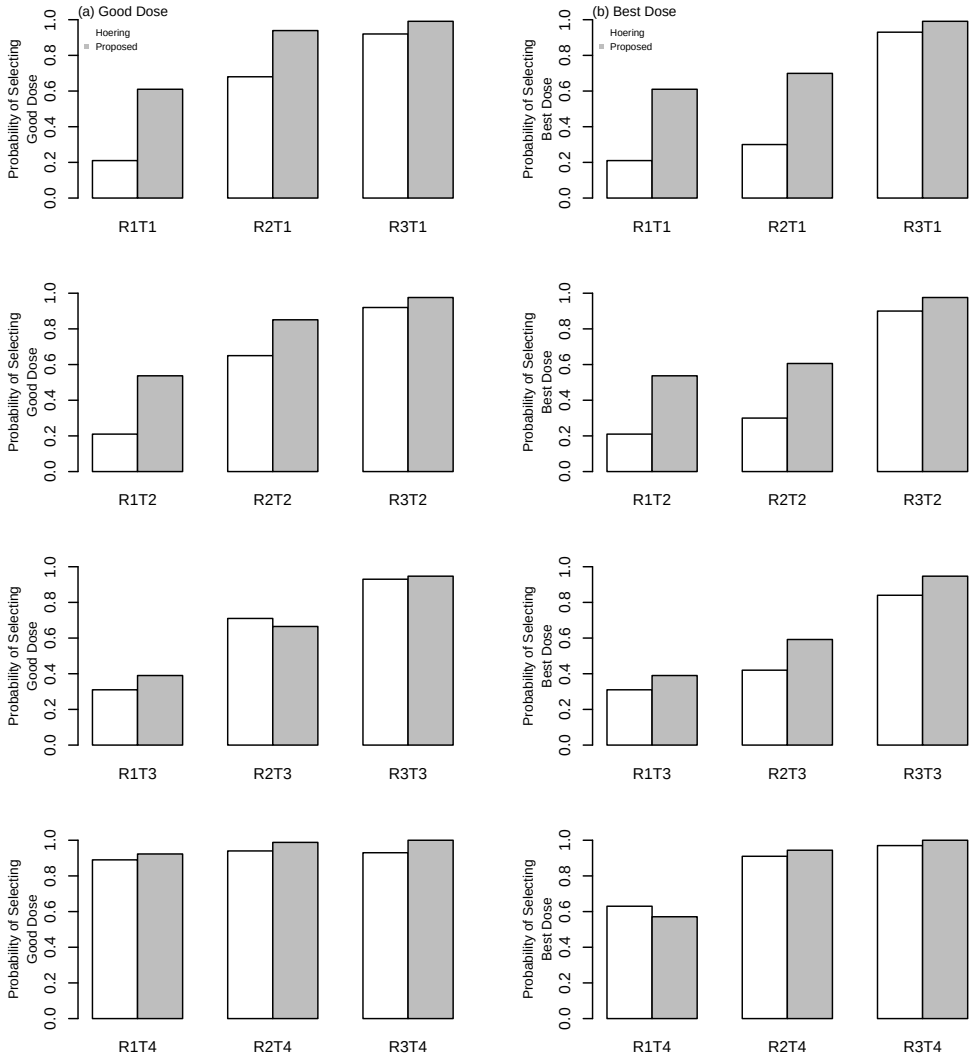
Dose-finding in Hoering et al. (2013)

- 3+3 design in Phase I to find recommend dose (RD) for Phase II
- In Phase II, randomize 48 patients to one of three arms (dose levels)
  - RD-1, RD, RD$+1$
- Choose dose with highest efficacy that is also safe (DLT rate $\leq$ 33%.
- Authors define **best** dose as the level that maximizes efficacy while assuring safety; **good** dose as level where efficacy is above predefined boundary while maintaining safety.

Hoering et al. Scenarios



Simulation Results



Unimodal Dose-efficacy Curves

- Scenario 1 (π_T, π_E)
  - $\{(0.05, 0.20), (0.10, 0.40), (0.25, 0.60), (0.45, 0.80), (0.60, 0.55)\}$
  - Peak of d-e curve occurs outside acceptable set
- Scenario 2 (π_T, π_E)
  - $\{(0.08, 0.20), (0.12, 0.40), (0.20, 0.60), (0.30, 0.80), (0.42, 0.55)\}$
  - Peak of d-e curve occurs at edge of acceptable set
- Scenario 3 (π_T, π_E)
  - $\{(0.06, 0.20), (0.08, 0.40), (0.14, 0.60), (0.20, 0.80), (0.30, 0.55)\}$
  - Peak of d-e curve occurs inside acceptable set

Results

True DLT prob.	0.05	0.10	0.25	0.45	0.60
True Eff prob.	0.20	0.40	0.60	0.80	0.55
% selection	0.04	0.19	**0.53**	0.24	0.00
% allocation	0.12	0.26	**0.35**	0.23	0.03
True DLT prob.	0.08	0.12	0.20	0.30	0.42
True Eff prob.	0.20	0.40	0.60	0.80	0.55
% selection	0.04	0.17	0.29	**0.50**	0.01
% allocation	0.13	0.23	0.25	**0.34**	0.05
True DLT prob.	0.06	0.08	0.14	0.20	0.30
True Eff prob.	0.20	0.40	0.60	0.80	0.55
% selection	0.04	0.13	0.19	**0.62**	0.03
% allocation	0.10	0.19	0.20	**0.43**	0.07

$N = 30$; $n_R = 10$; $\phi_T = 0.35$, $\psi = -2$

Conclusions

- Bivariate extension of CRM for effectively estimating optimal dose in early-phase trials of targeted agents.
- Good operating characteristics when compared to published method in area.
- Extension includes relaxing monotonicity assumption for toxicity
  - For trials of dual-agent combinations
  - Use partial order CRM (Wages, Conaway, O'Quigley; *Biometrics* 2011) to estimate DLT probabilities
- Exploring stopping rules for toxicity and efficacy
- Modifications for delayed response outcomes

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