Randomized dose-escalation design for drug combination cancer trials with immunotherapy

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Immunotherapy in Phase I clinical trials

**Phase I conventional paradigm:** the more the better

**Important exceptions:** molecularly targeted agents (e.g. immunotherapy).

- Immune system can regulate/eliminate tumours
- Low toxicity profile

**Example:**
immune-checkpoint proteins blocker anti-programmed-death-receptor-1 (PD1)
Pembrolizumab

- None of the trials reached MTD
- Plateau found. Same toxicity/activity probability for 2 and 10 mg/kg
- FDA requested to focus on a lower dose level
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Combinations with immunotherapy

Immunotherapy is enough not efficacious in cancer treatment by itself

Current investigations:
- the added value of immune checkpoint blockers to backbone therapy
- the added value of a new drug to an immune checkpoint blocker.

One drug is administered at full dose while the other is escalated.

Objectives of the trial:
- To find the maximum tolerated combination (MTC)
- To detect clinically significant difference between the MTC and standard therapy alone (required by EMA)
- To detect a possible dose effect in the combination
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Current approach

Current design: **one parameter CRM design** for single agent trial

**Advantages:**
- Ability to find MTC with high probability
- Well-known properties

**Disadvantages:**
- Strong monotonicity assumption
- No possibility of a plateau detection
- Does not allow a statistical comparison of toxicities
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Proposals

**Flexible model:**

- $E_{max}$ model
- A plateau in a dose-toxicity relation
- Ability to model the toxicity probability on the single agent alone independently

**Randomization** between a control and an investigation arm

- control is standard therapy
- prevents a selection bias
- allows statistical comparison of the toxicity
- ethical
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Bayesian CRM

Combination of A (fixed) and B: \( \tilde{d}_0 = \{a, b_0\}, \tilde{d}_1 = \{a, b_1\}, \ldots, \tilde{d}_m = \{a, b_m\} \)

Model \( p_i = \psi(d_i, \theta) \); \( d_i \) is a unit-less amount of drug
\( \theta \) is a vector of parameters

Given binary outcomes, the CRM updates the posterior \( f_j(\theta) \)

\[
f_j(\theta) = \frac{f_{j-1}(\theta)\mathcal{L}(d, y, \theta)}{\int_{\mathbb{R}^d} f_{j-1}(u)\mathcal{L}(d, y, u)du}
\] (1)

The posterior mean (!)

\[
\hat{p}_k^{(j)} = \mathbb{E}(\psi(d_k, a) | Y_j) = \int_{\mathbb{R}^d} \psi(d_k, u)f_j(u)du
\] (2)

Main debate: choice of model \( \psi(d_k, a) \)
Bayesian CRM

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Given binary outcomes, the CRM updates the posterior $f_j(\theta)$

$$f_j(\theta) = \frac{f_{j-1}(\theta)L(d, y, \theta)}{\int_{\mathbb{R}^d} f_{j-1}(u)L(d, y, u)du} \quad (1)$$

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$$\hat{p}_k^{(j)} = \mathbb{E}(\psi(d_k, a)|Y_j) = \int_{\mathbb{R}^d} \psi(d_k, u)f_j(u)du \quad (2)$$

Main debate: choice of model $\psi(d_k, a)$
$E_{\text{max}}$ model

$$\psi(d_i, E_0, E_{\text{max}}, \lambda, ED_{50}) \equiv \psi(d_i, \theta) = E_0 + \frac{d_i^\lambda E_{\text{max}}}{d_i^\lambda + ED_{\text{max}}^{\lambda}}$$ (3)

- $E_0$ is the probability of toxicity on the control
- $E_{\text{max}} + E_0$ is the maximum probability of toxicity
- $ED_{50}$ is the combination which produces $E_0 + \frac{E_{\text{max}}}{2}$
- $\lambda \geq 0$ is the slope factor

Skeleton construction:

$$d_i = ED_{50}^{(0)} \times \left( \frac{\hat{p}_i(0) - \hat{E}_{0}^{(0)}}{\hat{E}_{\text{max}}^{(0)} + \hat{E}_{0}^{(0)} - \hat{p}_i(0)} \right) \frac{1}{\lambda^{(0)}}$$

By definition, $\hat{p}_0(0) \equiv \hat{E}_{0}^{(0)} \rightarrow d_i = 0$
$E_{\text{max}}$ model

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By definition, $\hat{p}_0(0) \equiv \hat{E}_0^{(0)} \rightarrow d_i = 0$
Randomization

Assignment cohort-by-cohort

\[ c = c_1 + c_2 \]

- \( c_1 \) be the number of patients assigned to the current best combination
- \( c_2 \) be the number of patients assigned to the control, \( d_0 \).

For instance, taking \( c_1 = 3 \) and \( c_2 = 1 \), one will end up with 25% of the total sample size being assigned to the control.

CRM with randomization results in the majority of patients on two combinations: control and MTC.
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Simulations setting

- Sample size $n = 48$
- $m = 7$ combinations
- Target probability $\gamma = 0.25$
- Clinically significant difference $\tau = 0.05$
- Confidence level $\alpha = 0.9$
- $c_1 = 3, c_2 = 1 \rightarrow 25\%$ on the control treatment.
Characteristics

(i) Proportion of correct recommendations

(ii) Proportion of times the clinically significant difference is found

\[ P \equiv P \left( P \left( p_{MTC} - p_{control} \geq \tau \right) > \alpha \right) \]  

(iii) Goodness of fit measure

\[ NMSE = \frac{1}{N} \sum_{j=1}^{N} \sqrt{\sum_{i=1}^{n} \left( p_i - \psi(d_i, \hat{\theta}(j)) \right)^2 / \left( \sum_{i=1}^{n} (p_i - \hat{p}_i^{opt})^2 \right)} \]
Prior and comparators

Skeleton

\[ P_0 = [0.08, 0.25, 0.35, 0.45, 0.55, 0.65, 0.70, 0.75]^T \]

Information to construct prior distributions for model parameters:
(i) Control: upper bound of the 95\% credibility interval is 0.25.
(ii) Prior MTC: upper bound of the 95\% credibility interval is 0.80.

\[ E_0 \sim \mathcal{B}(0.8, 10-0.8); \quad \lambda \sim \Gamma(1, 1); \quad E_{max|E_0} \sim \mathcal{U}[0, 1-E_0]; \quad ED_{50} \sim \Gamma(0.4, 0.4); \]
Comparators

(P1) **One-parameter** power model (**no randomization**):

\[ \psi(d_i, z) = d_i^z. \]

(L2) **Two-parameter** logistic models

\[ \psi(d_i, \beta_1, \beta_2) = \frac{\exp(\log(\beta_1) + \beta_2 d_i)}{1 + \exp(\log(\beta_1) + \beta_2 d_i)} \]

with (R) and without randomization.
Scenarios

Figure: Considered dose-toxicity shapes. The MTC is marked by a triangle.

Scenario 1

Scenario 2

Scenario 3

Scenario 4

Scenario 5

Scenario 6

Toxicity

combination
## Results (I)

<table>
<thead>
<tr>
<th></th>
<th>$d_0$</th>
<th>$d_1$</th>
<th>$d_2$</th>
<th>$d_3$</th>
<th>$d_4$</th>
<th>$d_5$</th>
<th>$d_6$</th>
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## Results (II)

<table>
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<tr>
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<td>0.51</td>
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<td>$L2(R)$</td>
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<td>8.4</td>
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## Results (III)

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<td>$\mathcal{P}$</td>
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<td>99.7%</td>
<td>99.7%</td>
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<td>2.1</td>
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Fitted curves

Figure: 1000 fitted curves (black lines) using the Emax model, Logit model with and without randomization (R) and Logit model without randomization and n = 48 patients in scenarios 1, 4 and 6. The true underlying dose-toxicity relation is plotted by red line.

P. Mozgunov, T. Jaki and X. Paoletti
Sensitivity analysis

Prior distributions:

\[ E_0 \sim \mathbb{B}(0, 8, 10–0.8), \quad \lambda \sim \Gamma(c_1, c_2), \quad E_{max}|E_0 \sim \mathbb{U}[0, 1–E_0], \quad ED_{50} \sim \Gamma(c_3, c_4). \]

★ Recommendation: An informative for \( \lambda \) and an uninformative for \( ED_{50} \)

Randomization proportion

★ Recommendation: 20%-25% on the control arm
Randomization and $E_{max}$ model allow to identify clinically significant differences with higher probability than alternatives.

The cost of randomization: a small reduction in the proportion of correct recommendations in some scenarios.

The randomization helps to overcome problems with fitting.

This design should be considered if not only MTC identification is of interest.
Further work

⋆ Large variance of number of patients on the MTC.
⋆ Further investigation on the fitting problem
⋆ Phase II trials: a statistical comparison of the optimal combination and control effectivenesses