A Bayesian Phase I/II Design for Oncology Clinical Trials of Combining Biological Agents

Ying Yuan

Department of Biostatistics, MD Anderson Cancer Center

March 12, 2014
Outline

- Introduction
- Probability model
- Dose finding algorithm
- Simulation study
- Conclusion
The paradigm of oncology drug development is expanding from traditional cytotoxic agents to novel biological (or molecularly targeted) agents.

Examples of biological agents:

- **Biospecimens** targeting a specific tumor pathway.
- **Gene products** aiming for DNA repair.
- **Immunotherapies** stimulating the immune system to attack a tumor.
Biological agents versus cytotoxic agents

- **Cytotoxic agents**
  - Toxicity and efficacy are assumed to *monotonically* increase with dose.
  - The goal is to find the *maximum tolerated dose (MTD)*.

- **Biological agents**
  - The toxicity is usually tolerable within the therapeutic dose range and may plateau at higher dose levels.
  - The dose-efficacy curves often follow a *non-monotonic* pattern.
  - The goal is to find the *optimal biological dose (OBD)*, defined as the dose yielding the most desirable treatment effect.
Drug-combination Trials

- Treating patients with a combination of agents is becoming common in cancer clinical trials.
- Most existing drug-combination trial designs concern cytotoxic agents (e.g., Thall et al., 2003; Wang and Ivanova, 2005; Yin and Yuan, 2009), thus are not applicable to the trials combining biological agents.
- **A phase I/II trial design is imperative** for biological agent combination trials because of non-monotonic dose-efficacy and -toxicity relationship.
Motivating trial

- A lymphoma trial combining two novel biological agents to target two components in the PI3K/AKT/mTOR signaling pathway.
  - Agent A is a PI3K kinase inhibitor.
  - Agent B inhibits mTOR kinase downstream in the pathway.
- 4 doses of agent A combined with 4 doses of agent B.
- Goal: to find the biologically optimal dose combination (BODC), defined as the dose combination with the highest efficacy and tolerable toxicity.
Targeting PI3K/AKT/mTOR signaling Pathways in Lymphoma

- PI3K
- Akt
- Rheb
- mTOR
- 4E-BP1
- SGK1

Cell growth, proliferation, survival, immune regulation, angiogenesis
We propose a phase I/II trial design to identify the BODC.

- **A change-line model** is used to reflect the property that the dose-toxicity surface of the combinational agents may plateau at higher dose levels.

- **A logistic model with quadratic terms** is used to accommodate the possible non-monotonic pattern for the dose-efficacy relationship.

- We devise **a novel adaptive dose-finding algorithm** to encourage sufficient exploration of the two-dimensional dose space.
Consider a trial of combinational biological agents

- $J$ doses of agent A: $a_1 < a_2 < \cdots < a_J$
- $K$ doses of agent B: $b_1 < b_2 < \cdots < b_K$
- $(a_j, b_k)$: combination of dose $a_j$ and dose $b_k$
- $p_{jk}$ and $q_{jk}$ denote the toxicity and efficacy probabilities of dose combination $(a_j, b_k)$

Goal: identify the BODC in the $J \times K$ dose matrix.
We model toxicity probability $p_{jk}$ using a change-line model:

$$
\text{logit}(p_{jk}) = (\beta_0 + \beta_1 a_j + \beta_2 b_k) I(\beta_0 + \beta_1 a_j + \beta_2 b_k \leq \omega) + \omega I(\beta_0 + \beta_1 a_j + \beta_2 b_k > \omega)
$$

- $I(\cdot)$: indicator function
- $\beta_1 > 0$ and $\beta_2 > 0$ such that $p_{jk}$ initially increases with the doses of A and B
- When it reaches a plateau, the toxicity probability: $e^\omega/(1 + e^\omega)$.
- We did not include an interactive effect for the two agents because the estimation of that needs large sample

Figure: Surface of the toxicity probabilities
Assume the efficacy probability $q_{jk}$ follows a logistic model

$$\text{logit}(q_{jk}) = \gamma_0 + \gamma_1 a_j + \gamma_2 b_k + \gamma_3 a_j^2 + \gamma_4 b_k^2$$

- The quadratic terms render the model adequate flexibility to capture the non-monotonic pattern.
- We model the marginal distributions of toxicity and efficacy.
- Joint modeling is possible, but small sample size $\rightarrow$ cannot reliably estimate the correlation parameter.
Likelihood

Suppose that at a certain stage of the trial

- $n_{jk}$ patients are treated at the paired dose $(a_j, b_k)$
- $x_{jk}$ and $y_{jk}$ patients have experienced toxicity and efficacy, respectively.

- The marginal likelihood for the toxicity data $\mathbf{x}$ is

$$
L(\mathbf{x}|\omega, \beta) \propto \prod_{j=1}^{J} \prod_{k=1}^{K} p_{jk}^{x_{jk}} (1 - p_{jk})^{n_{jk} - x_{jk}};
$$

for the efficacy data $\mathbf{y}$ is

$$
L(\mathbf{y}|\gamma) \propto \prod_{j=1}^{J} \prod_{k=1}^{K} q_{jk}^{y_{jk}} (1 - q_{jk})^{n_{jk} - y_{jk}}.
$$
The posterior distribution is
\[ f(\omega, \beta, \gamma|x, y) \propto L(x|\omega, \beta)L(y|\gamma)f(\omega)f(\beta)f(\gamma) \]
where \( f(\omega), f(\beta), \) and \( f(\gamma) \) denote the prior distributions for \( \omega, \beta, \) and \( \gamma, \) respectively.

Vague priors are used:

- \( \gamma_0 \sim \text{Cauchy}(0,10), \quad \gamma_1, \cdots, \gamma_4 \sim \text{Cauchy}(0, 2.5). \quad \beta_0 \sim \text{Cauchy}(0, 10), \quad \beta_1, \beta_2 \sim \text{Gamma}(0.5, 0.5) \quad \omega \sim \mathcal{N}(0, 4) \)
Trial design

Our design is conducted in two stages:

- **Stage I (run in):** We escalate doses along the diagonal to explore the dose-combination space quickly and collect some preliminary data.

- **Stage II (dose finding):** Based on observed efficacy and toxicity data, we continuously update the posterior estimates of toxicity and posterior means of efficacy and assign patients to the most appropriate dose.

**Def:** dose \((a_j, b_k)\) is deemed safe if \(\Pr(p_{jk} < \phi | D) > \delta\); otherwise toxic.

- \(\phi\) is the target toxicity upper limit and \(\delta\) is a prespecified safety cutoff.
Stage I: Run-in period

The trial starts with the treatment of the first cohort of patients at the lowest dose \((a_1, b_1)\).

I1 If current dose is safe, escalate the dose along the diagonal. If \((a_1, b_1)\) is deemed toxic, terminate the trial.

I2 Stage I completes when either current dose is deemed toxic or the highest dose combination is reached. Stage II starts.
Assume that the current dose combination is \((a_j, b_k)\),

- Define \textit{\(g\)-degree neighbors} of \((a_j, b_k)\), denoted by \(\mathcal{N}_g\), as dose combinations \(\{(a_j', b_k')\}\) whose dose levels are different from \((a_j, b_k)\) no more than \(g\) levels, i.e.,
  \[
  \mathcal{N}_g = \{(a_j', b_k') : |j' - j| \leq g \text{ and } |k' - k| \leq g\}.
  \]

- Further define a \textit{\(g\)-degree admissible dose set} \(\mathcal{A}_g\), which is a subset of the \(g\)-degree neighbors \(\mathcal{N}_g\) satisfying the pre-specified safety requirement \(Pr(p_{j'k'} < \phi_T|\mathcal{D}) > \delta\).
Stage I: Run-in period

Stage II: Systematic dose finding
Stage II: Systematic dose finding

II1 Based on the observed data, identify $A_{g^*}$ as the nonempty set of safe neighbors of $(a_j, b_k)$ with minimum degree $g^*$. If $A_{g^*}$ does not exist (i.e., all experimental doses are deemed toxic), terminate the trial.

II2 Among the doses in $A_{g^*}$, identify the dose $(a^*_j, b^*_k)$ with the highest posterior mean of efficacy $\hat{q}_{j^*k^*}$. 
First-degree neighbors of current dose combination, $\mathcal{N}_1$
First-degree admissible dose set of current dose combination, $A_1$
The dose \((a_{j^*}, b_{k^*})\) with the highest posterior mean of efficacy \(\hat{q}_{j^*k^*}\)
The commonly used algorithm is to assign the next cohort of patients to \((a_j^*, b_k^*)\).

- Problem: this greedy algorithm is easily trapped in locally optimal doses due to
  - small sample size
  - model misspecification

- Solution: a novel dose-finding algorithm to adaptively encourage the exploration of untried doses
Overview
Stage I: Run-in period
Stage II: Systematic dose finding

- Current dose
- Admissible dose
- Non-admissible dose
Overview
Stage I: Run-in period
Stage II: Systematic dose finding

- Current dose
- Admissible dose
- Non-admissible dose
Overview
Stage I: Run-in period
Stage II: Systematic dose finding

- Current dose
- Admissible dose
- Non-admissible dose
Overview
Stage I: Run-in period
Stage II: Systematic dose finding

- Current dose
- Admissible dose
- Non-admissible dose
Stage II: Systematic dose finding

II3 1 If $n_{j^*k^*} = 0$ or $n_{rs} \neq 0$ for all $(a_r, b_s) \in A_{g^*}$, treat the next cohort at dose $(a_{j^*}, b_{k^*})$.

2 Otherwise,

$$\begin{align*}
\text{If } \hat{q}_{j^*k^*} > \left( \frac{N-n}{N} \right)^\alpha & \quad \text{treat the next cohort at } (a_{j^*}, b_{k^*}), \\
\text{If } \hat{q}_{j^*k^*} \leq \left( \frac{N-n}{N} \right)^\alpha & \quad \text{remove dose } (a_{j^*}, b_{k^*}) \text{ from } A_{g^*} \text{ and go to step II2.}
\end{align*}$$

- $N$: prespecified maximum sample size
- $n = \sum_{j,k} n_{jk}$: the total number of patients treated in the trial
- $\alpha$ is a known tuning parameter.

II4 Repeat steps II2-4 until exhaustion of the sample size. Select as the BODC the dose combination with the highest $\hat{q}_{jk}$ among all safe doses.
- Consider 4 dose levels for each agent:
  - Dose levels of A and B are (0.075, 0.15, 0.225, 0.3) and (0.08, 0.16, 0.24, 0.32), respectively.
- The maximum sample size was 15 cohorts of size 3.
- Set the target toxicity upper limit $\phi = 0.3$ and the safety cutoff $\delta = 0.4$.
- Set the tuning parameter $\alpha = 2$. 
We compared the proposed design with a greedy design that is otherwise identical except that it uses the greedy dose-assignment rule (i.e., always assign the next cohort to the dose with the highest estimate of efficacy).

2000 simulated trials under each scenario.
## Simulation results

**Table : Scenario 1**

<table>
<thead>
<tr>
<th>Agent B</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>.25</td>
<td>.25</td>
<td>.25</td>
<td>.25</td>
<td>.42</td>
<td>.60</td>
<td>.38</td>
<td>.32</td>
</tr>
<tr>
<td>3</td>
<td>.15</td>
<td>.25</td>
<td>.25</td>
<td>.25</td>
<td>.19</td>
<td>.44</td>
<td>.20</td>
<td>.18</td>
</tr>
<tr>
<td>2</td>
<td>.10</td>
<td>.25</td>
<td>.25</td>
<td>.25</td>
<td>.12</td>
<td>.29</td>
<td>.15</td>
<td>.10</td>
</tr>
<tr>
<td>1</td>
<td>.05</td>
<td>.10</td>
<td>.15</td>
<td>.25</td>
<td>.05</td>
<td>.22</td>
<td>.10</td>
<td>.08</td>
</tr>
</tbody>
</table>

The blue dose is the target BODC.
Table: The selection percentage and the percentage of patients treated at each dose combination (shown as the subscripts) for scenario 1.

<table>
<thead>
<tr>
<th>B</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>23.8</td>
<td>31.0</td>
<td>10.8</td>
<td>8.9</td>
<td>18.2</td>
<td>21.5</td>
<td>7.8</td>
<td>21.8</td>
</tr>
<tr>
<td>3</td>
<td>3.5</td>
<td>5.5</td>
<td>1.2</td>
<td>1.1</td>
<td>4.5</td>
<td>4.3</td>
<td>1.1</td>
<td>2.2</td>
</tr>
<tr>
<td>2</td>
<td>0.9</td>
<td>2.7</td>
<td>0.8</td>
<td>0.5</td>
<td>1.2</td>
<td>4.2</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>1</td>
<td>0.7</td>
<td>2.1</td>
<td>1.0</td>
<td>0.9</td>
<td>0.8</td>
<td>2.2</td>
<td>1.4</td>
<td>2.1</td>
</tr>
</tbody>
</table>

The blue dose is the target BODC.
### Simulation results

#### Table: Scenario 2

<table>
<thead>
<tr>
<th>Agent B</th>
<th>Tox. probability</th>
<th>Effic. probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>.25</td>
<td>.25</td>
</tr>
<tr>
<td>3</td>
<td>.15</td>
<td>.25</td>
</tr>
<tr>
<td>2</td>
<td>.10</td>
<td>.25</td>
</tr>
<tr>
<td>1</td>
<td>.05</td>
<td>.10</td>
</tr>
</tbody>
</table>

The **blue** dose is the target BODC.
The blue dose is the target BODC.
### Simulation results

**Table: Scenario 3**

<table>
<thead>
<tr>
<th>Agent B</th>
<th>Toxicity probability</th>
<th>Efficacy probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>.17</td>
<td>.25</td>
</tr>
<tr>
<td>3</td>
<td>.12</td>
<td>.16</td>
</tr>
<tr>
<td>2</td>
<td>.08</td>
<td>.10</td>
</tr>
<tr>
<td>1</td>
<td>.05</td>
<td>.08</td>
</tr>
</tbody>
</table>

The **blue** dose is the target BODC.
Table: The selection percentage and the percentage of patients treated at each dose combination (shown as the subscripts) for scenario 3.

<table>
<thead>
<tr>
<th>B</th>
<th>Proposed design</th>
<th>Greedy design</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Agent A</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>46.3_{18.9}</td>
<td>39.1_{13.8}</td>
</tr>
<tr>
<td>3</td>
<td>7.8_{5.5}</td>
<td>7.3_{3.9}</td>
</tr>
<tr>
<td>2</td>
<td>5.3_{5.0}</td>
<td>3.9_{2.7}</td>
</tr>
<tr>
<td>1</td>
<td>5.5_{10.2}</td>
<td>8.6_{16.1}</td>
</tr>
</tbody>
</table>

The blue dose is the target BODC.
Our proposed design explicitly accounts for the unique features of the biological agents, i.e., dose-efficacy and -toxicity relationships may take non-monotonic patterns.

The proposed design adaptively encourages dose exploration in the two-dimensional dose space.

Our design identifies the BODC with substantially higher selection percentage and allocates more patients to the target dose combination than the greedy design.

In the case that efficacy plateaus, a similar change-line model can be used.
Thank you!