Shaping the Future of Drug Development

Single and Double Agent Oncology Dose-Escalation Designs in East 6.4:

A communication tool

Pantelis Vlachos, Ph.D.
Cytel Inc. | Geneva
Agenda

- What’s new?
- Single-Agent dose escalation
  - Demo/Workshop
- Combination agent dose escalation
  - Review of methods
  - Demo/Workshop
- Q&A
Phase I Dose-Escalation Trials

- Assess dose-toxicity relationship
- First-in-human (FIH) studies – single agent
  - Determine maximum tolerated dose (MTD) or recommended phase II dose (RP2D)
  - Observe Dose limiting toxicities (DLTs)
- Combination dose finding studies (Phase Ib)
  - Same primary objective as FIH studies
    - Combination of two (or more) drugs
    - Addition of a new drug to a registered treatment to increase efficacy
What’s new?

• mTPI: User specified decision table
• More flexible stopping rules
• Accelerated titration
• Combination designs
• And much more!
mTPI: User specified decision table

Max. Number of Doses: 7

<table>
<thead>
<tr>
<th>Design Parameters</th>
<th>Stopping Rules</th>
<th>Trial Monitoring Table</th>
<th>Response Generation</th>
<th>Simulation Controls</th>
</tr>
</thead>
</table>

- **E**: Escalate to the next higher dose
- **S**: Stay at the current dose
- **D**: De-escalate to the next lower dose
- **DU**: The current dose is unacceptably toxic

Number of patients treated at current dose

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Target Toxicity (%) = 30%
Sample Size = 30
More flexible stopping rules

Escalations continue until declaration of the MTD. This dose level must meet the following conditions:

1. At least 6 patients treated at this dose level
2. and
   a) The probability of targeted toxicity at this dose level exceed 50%
   or
   b) A minimum of 15 patients should have already been treated in
Accelerated titration

Design Parameters

Max. Sample Size: 30
Cohort Size: 3

Stopping Rules

- Start With Accelerated Titration
- Switch to 3+3 L
- Switch to 3+3 H
- Switch to 3+3 L (Modified)

Subject-wise Dose Allocation

- No DLT_StageI
- DLT_StageI
- No DLT_StageII
- DLT_StageII

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Combination designs

Increased popularity!

Pubmed search ((cancer) AND combination) and phase I

Number of articles indexed in pubmed

Year


0, 200, 400, 600, 800, 1000, 1200, 1400
Single-Agent Dose Escalation
Phase I dose-escalation (general frame)

Only consider trials with fixed doses.

- A sequence of $K$ doses, $d_1, d_2, \ldots, d_K$, as candidates.
- Dose $i$ has a toxicity probability of $p_i$ (unknown).
- Monotonicity: $p_i < p_{i+1}$
- **Goal:** to find the MTD, defined as the highest dose with toxicity rate lower (or close to) a fixed rate, $p_T$, e.g., $p_T = 0.30$. 
# Rule-based vs Model-based

<table>
<thead>
<tr>
<th>Design Type</th>
<th>Bayesian?</th>
<th>Model dose-toxicity? (number of parameters)</th>
<th>Probability Intervals?</th>
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<tr>
<td><strong>Single Agent Designs</strong></td>
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<td>3+3</td>
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<td>CRM</td>
<td>Yes</td>
<td>Yes (1)</td>
<td>No</td>
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<tr>
<td>BLRM</td>
<td>Yes</td>
<td>Yes (2)</td>
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<td>mTPI</td>
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<td><strong>Double Agent Designs</strong></td>
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<td>comb2BLRM</td>
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<td>Yes (5)</td>
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<tr>
<td>PIPE</td>
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</table>
Regulatory Guidelines

• FDA Guidance (Clinical Considerations for Therapeutic Cancer Vaccines)

  Therefore, this “3 + 3 design” may not be the most suitable approach to gathering information from early phase trials of cancer vaccines, and alternative trial designs should be considered.

  Given the relatively acceptable safety profile of some classes of cancer vaccines, alternative dose-escalation approaches, such as accelerated titration or continuous titration, may be considered. These alternative designs allow the use of multiple dose levels.

• EMEA / CHMP Guidelines

  Alternative approach needed to meet design requirements

A variation of response-adaptive designs is those used for dose finding – they are typically referred to as ‘continual re-assessment’ methods. They are sometimes, but rarely, used. The properties of such methods far outstrip those of conventional ‘up and down’ dose finding designs. They tend to find the optimum (however defined) dose quicker, they treat more patients at the optimum dose, and they estimate the optimum dose more accurately. Such methods are encouraged.
Bayesian Framework

Bayesian Statistics:
- All uncertainty is expressed probabilistically
- Critical input: “Likelihood” (Statistical Model) and “Prior”
- Bayes Theorem: Posterior ∝ Likelihood × Prior
- Statistical Inference: well-defined (unique!)

“Bayes” (Probability!) + Contextual Evidence + Observed Data = Updated Evidence ⇒ Predictions Decisions

(Based on Matano. Bayesian Adaptive Designs for Oncology Phase 1 Trials, 2013)
Critical aspects of the Bayesian approach to phase I cancer trials

Beat Neuenschwander*, †, Michael Branson and Thomas Gsponer

Novartis Pharma AG, Lichstrasse 35, 4056 Basel, Switzerland

SUMMARY

The Bayesian approach to finding the maximum-tolerated dose in phase I cancer trials is discussed. The suggested approach relies on a realistic dose–toxicity model, allows one to include prior information, and supports clinical decision making by presenting within-trial information in a transparent way. The modeling and decision-making components are flexible enough to be extendable to more complex settings. Critical aspects are emphasized and a comparison with the continual reassessment method (CRM) is performed with data from an actual trial and a simulation study. The comparison revealed similar operating characteristics while avoiding some of the difficulties encountered in the actual trial when applying the CRM. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS: maximum-tolerated dose; continual reassessment method; logistic model
**Bayesian Logistic Regression Model (BLRM)**

- Two parameter logistic: \( \log \left( \frac{p}{1-p} \right) = \log(\alpha) + \beta \log(d/d^*) \)
- \( d^* \) is the “reference dose” (arbitrary scaling dose)
- \( \alpha > 0 \) is the odds of DLT at \( d^* \)
- \( \beta > 0 \) is the increase in log-odds of DLT for unit increase in log-dose
Choose dose that maximizes targeted toxicity probability, given not overdosing.
Prior Specification (direct vs indirect)

- Enter directly bivariate normal for $\log(\alpha)$ and $\log(\beta)$:

- Indirectly:
BLRM Stopping Rules

Design Parameters | Stopping Rules | Response Generation | Simulation Control

Stop Trial Early (MTD not determined) if
- MTD Above Highest Dose: Prob.(P_h < P_T I data) ≥ 0.9
- Min SS on Dose

Stop Trial Early (MTD determined) if
- Minimum SS Observed in the Trial ≥ 12
- Target Rule: Prob.(Target Toxicity) ≥ 0.5
- CI Rule: 90% CI for P(DLT) at MTD > 0.05 and < 0.6
- Allocation Rule: SS Already Allocated to Next Recommended Dose ≥

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BLRM Interim Monitoring

Interval Probabilities by Dose

Posterior Probability

Dose

Pr(Under dosing)  Pr(Target)  Pr(Excessive)
Predictive Distribution of DLTs

Predictive Distribution Of Number Of DLTs

Number of Toxicities

Probability

Cytel

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Interim Monitoring

Dose Probability

Probability of Toxicity

Dose

Target Probability
Standard Error
Targeted Toxicity Interval
Median of Posterior p(DLT)
95% CI (Target)
Posterior Probability (Mean)
Observed Proportions
Plug-in Estimates (Mean)
95% CI (Underdosing)
95% CI (Overdosing)
Combination-Agent Dose Escalation
# Rule-based vs Model-based

<table>
<thead>
<tr>
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<th>Bayesian?</th>
<th>Model dose-toxicity? (number of parameters)</th>
<th>Probability Intervals?</th>
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About combination therapies

• Becoming increasingly common in the treatment of many diseases (e.g. cancer, HIV)

• Many designs are still quite naïve
  – e.g. fix dose of one agent, and dose-escalate the other (using single-agent designs)

• Require simultaneous dose-escalation

• Aims and objectives must differ from single-agent trials
  – Multiple MTDs may exist
  – More prior information (from single-agent trials)
  – Interaction
Rationale

• Recent FDA draft guidance on “Co-development of two or more unmarketed investigational drugs for use in combination”

“Combination therapy is an important treatment modality in many disease settings, including cancer, cardio-vascular disease, and infectious diseases. Recent scientific advances have increased our understanding of the pathophysiological processes that underlie these and other complex diseases. This increased understanding has provided further impetus for new therapeutic approaches using combinations of drugs directed at multiple therapeutic targets to improve treatment response or minimize development of resistance.”
Methods in East

6

A Bayesian Industry Approach to Phase I Combination Trials in Oncology

Beat Neuenschwander, Alessandro Matano, Zhongwen Tang, Satrajit Roychoudhury, Simon Wandel, and Stuart Bailey

Research Article

Received 12 September 2014, Accepted 9 January 2015, Published online 29 January 2015 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.6434

A product of independent beta probabilities dose escalation design for dual-agent phase I trials

Adrian P. Mander\textsuperscript{a,†} and Michael J. Sweeting\textsuperscript{b}

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The general approach

• Specify an initial dose-combination for first cohort, $x = (x_A, x_B)$
• Record the observed number of toxicities
• Given a parametric dose-toxicity model, $\pi(x, \theta)$, with priors on the parameter vector $\theta$
  – Update inferences to obtain new posterior distribution
• Choose next dose combination based on
  – A set of admissible dose combinations
  – A decision rule to choose between admissible doses, using the posterior distribution
• Continue recruiting patients until either
  – a fixed sample size is obtained
  – A stopping rule is satisfied
comb2BLRM: Model components

• Model has three components which stand for
  1. Single-agent 1 toxicity, represented by parameters $\alpha_1, \beta_1$
  2. Single-agent 2 toxicity, represented by parameters $\alpha_2, \beta_2$
  3. Interaction, represented by parameter $\eta$.

• $\pi_{12}$ is the probability of a DLT for dose combination $(d_1, d_2)$,

\[
\text{odds}_{12} = \pi_{12} / (1 - \pi_{12}) = \alpha_1 d_1^{\alpha_1} + \alpha_2 d_2^{\beta_2} + \alpha_3 (d_1^{\alpha_1} d_2^{\beta_2})^{\beta_3}
\]

To ensure interpretation of the parameters, we simplify the model as

\[
\text{odds}_{12} = \text{odds}_{12}^0 \times \exp(\eta \, d_1 \, d_2)
\]
Prior distribution

• For the single-agent parameters proceeds as in the univariate BLRM

• For the interaction log-odds multiplier $\eta$ we use

$$\eta \sim N(m_\eta, s^2_\eta)$$

which allows for synergistic and antagonistic interaction

• $m_\eta, s^2_\eta$ determined from two prior quantiles of $\eta$, for example the median (set to 0 for the case of no a priori evidence for interaction) and 97.5% quantile.

• If it is known that only synergistic interaction is possible, a prior for $\eta$ confined to positive values could be used (e.g., log-normal).
Escalation with Overdose Control (EWOC)

- Choose dose combination that maximizes targeted toxicity probability, given not overdosing (set of admissible doses).
comb2BLRM priors

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<th>Distribution</th>
<th>Parameters</th>
<th>Mean</th>
<th>Std. Dev.</th>
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<td>ln(β1)</td>
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If there is no relevant historical DLT data available, we use the following default weakly-informative BVN prior of \((\log(\alpha), \log(\beta))\) in (6.6)

\[
(m_1, m_2, s_1, s_2, \text{cor}) = (\text{logit}(p^*), 0, 2, 1, 0).
\]  (6.9)
# Multiple true MTDs

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<th>Toxicity Intervals</th>
<th>Lower Limit</th>
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<td>Overdosing</td>
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</table>

EWOC: Prob. (Overdosing) < 0.25

## Agent 2

<table>
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<tr>
<th>Doses</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
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<tbody>
<tr>
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<td>0.145</td>
<td>0.24</td>
<td>0.335</td>
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<td>200</td>
<td>0.145</td>
<td>0.19</td>
<td>0.28</td>
<td>0.37</td>
</tr>
<tr>
<td>300</td>
<td>0.24</td>
<td>0.28</td>
<td>0.36</td>
<td>0.44</td>
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<td>400</td>
<td>0.335</td>
<td>0.37</td>
<td>0.44</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Agent 1
Multiple true MTDs
Interval Probabilities by Dose

Webinar - May 4, 2016
PIPE: Design components

- Target a MTD contour (MTC)
- A-priori and a-posteriori the probability of toxicity ($\pi_{12}$) at a specific dose combination is a Beta random variable
- Posterior probability of toxicity at each dose level easily calculated
- MTC needs to satisfy monotonicity assumption to drive dose escalation
- Next dose combination is chosen from a set of admissible doses that are “close” to the MTC
Discrete Dose Combination Space

- $\pi_{ij}$ represent unknown true probabilities of toxicity at each dose combination
- Assume strict monotonicity
MTC monotonicity

For an $I \times J$ matrix, there exist $\text{(I+J) @I}$ monotonic contours

<table>
<thead>
<tr>
<th>$d^B_2$</th>
<th>1</th>
<th>1</th>
<th>1</th>
</tr>
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<tbody>
<tr>
<td>$d^B_1$</td>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>$d^B_2$</td>
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<td>0</td>
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<tr>
<td>$d^B_1$</td>
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<td>0</td>
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<tr>
<td>$d^A_1$</td>
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<td>$d^A_2$</td>
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</tbody>
</table>
Priors in PIPE: Uniform

<table>
<thead>
<tr>
<th>Specify Prior Using:</th>
<th>Prior Beta Parameters</th>
</tr>
</thead>
</table>

**Prior Specification**

**Prior parameter a:**

<table>
<thead>
<tr>
<th>Doses</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
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<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>D2</td>
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<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>D3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>D4</td>
<td>1</td>
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</tr>
</tbody>
</table>

**Prior parameter b:**

<table>
<thead>
<tr>
<th>Doses</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>D2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>D3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>D4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Priors in PIPE: Uniform

- Unrealistic prior DLTs? Too strong prior sample sizes?
Priors in PIPE: Weak

- Prior DLTs assume all combinations are 'safe' (if $p_T = 0.33$)
- But prior belief is weak
Process

• Dose a new cohort of patients on best combination
• Record the number of DLTs
• For each dose combination calculate the posterior DLT probability
• Calculate the probability of being above the TTL (averaged over the contour distribution) for Safety
• Use the most likely contour for Decision making

Product of Beta Tail Probabilities

- Bayesian update:
  \[ (\pi_{ij} | Y, \alpha_{ij}, \beta_{ij}) \sim Beta(\alpha_{ij} + r_{ij}, \beta_{ij} + n_{ij} - r_{ij}) \]
  for dose combination \( d_{ij} \)

- Define tail probability
  \[ p_{ij} p_{T} Y = F(p_{T}; r_{ij}, n_{ij}, \alpha_{ij}, \beta_{ij}) \]
  where \( F() \) is the cdf of Beta.

- Product of tail probabilities
  \[ PMTC = C_{i,j} Y = \prod_{i,j} (1 - p_{ij} C_{i,j}) p_{ij} \]
  \[ \uparrow 1 - C_{i,j} [i,j] \]

MTC monotonicity

- Use most likely contour for Decision Making: define admissible doses
- Average over all contours for Safety Constraint: expected probability of exceeding $p_{\downarrow T}$
Define “closest” doses to MTC

- Select one of "closest" doses
- Avoid dose skipping
- If there are multiple closest doses to the MTC then the doses are chosen with smallest sample size (random if ties)
Dose Skipping: Neighborhood

- Cannot select doses outside dashed line (* = highest combination)
- Neighborhood constraint: Not more than one dose level higher than current dose combination.
Dose Skipping: Non-Neighborhood

- Cannot select doses outside dashed line (* = highest combinations)
- Non-Neighborhood constraint: Not more than one dose level higher than any previously visited combination.
References

3+3

mTPI

CRM

BLRM

Combination
Demo Time
Pantelis Vlachos, Ph.D.
Pantelis.Vlachos@cytel.com
Cytel Inc. | Geneva

Connect with Pantelis on LinkedIn