Statistical methods for phase I/II trials of molecularly targeted agents in oncology

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Brief reminder

Phase I trials in oncology

- Assessment of safety of the new treatment, i.e. toxicity
- Determination of a range of sufficiently safe doses and the maximum tolerated dose
- Pharmocokinetics and pharmacodynamics in patients

Phase II trials in oncology

- More information gathered around the activity of the treatment
- Additional information on pharmocokinetics and pharmacodynamics
Molecularly targeted therapies

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules, that are involved in the growth, progression, and spread of cancer\(^1\)

- Targeted therapies act on specific molecular targets
- Targeted therapies are deliberately designed to interact with their target
- Targeted therapies are often cytostatic

Current challenges I
Current challenges I

- Cytotoxic agents → MTD → High Efficacy
- Molecularly targeted agents → MTD → ? Efficacy

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Current challenges I

Association of activity and dose in molecularly targeted agents
Current challenges II

Evaluation of the MTD, using data collected during the *first* treatment cycle.

1. Ignore late onset toxicities
2. Ignore cumulative toxicities after extensive exposure to a specific dose level
3. Ignore information on activity measurements

Objective

- Propose an adaptive design for phase I/II trials

- Define an optimal dose
  - A dose that maximizes the activity while providing acceptable level of toxicity

- Combine data of time to first severe toxicity and biomarker activity
Solution

➢ Joint modelling$^3$ of

- interval censored time to first severe toxicity data$^4$
- repeated activity measurements on a continuous scale

❖ Shared random effects

Joint Model

Repeated measurements

\[ Y_j = x_j^T \beta + a_j^T U + Z_j, \quad j = 1, 2, ..., l \]

where \( Y \) measured on continuous scale, \( U \sim N(0, \Sigma) \) random effects and \( Z \sim MVN(0, \nu^2 I) \) mutually independent measurement errors

Event times

\[ P(S = s | S > s - 1, U) = 1 - \Phi \left\{ \tilde{x}_s^T \beta + \sum_{k=1}^{p} \gamma_{sk} W_k(s) \right\}, \quad s = 1, 2, ..., m \]

where \( \Phi \) standard normal distribution and \( W(s) \) vector of linear combinations of random effects \( U \)
Model evaluation

- Assessment of joint modelling parameter estimations on small sample sizes

- Time to event: Time to first severe toxicity
  - Evaluation after each treatment cycle
  - Discrete time scale
  - Allowing for censoring

- Repeated measurements: Activity of biomarker → e.g. tumor size per visit
  - Measurements provided on a continuous scale
Scenario

- 9 dose levels → target dose 5\(^{th}\) → 31.6\% after 3 cycles
- 3 treatment cycles
- max 10 visits per patient
- 5 different sample sizes \(n_1 = 15, n_2 = 20, n_3 = 30, n_4 = 60, n_5 = 100\)
Models

**Linear mixed effects model**

\[ Y_j = \beta_0 + \beta_1 t + \beta_2 d + a_1 t + Z_j, \quad j = 1, 2, \ldots, l \]

**Probit model**

\[ P(S = s | S > s - 1, U) = 1 - \Phi \{\delta_0 + \delta_1 t + \delta_2 d + \gamma_1 W(s)\}, \quad s = 1, 2, \ldots, m \]

\[ t \mapsto \text{time} \quad d \mapsto \text{dose} \quad j \mapsto \text{patients’ visits} \quad s \mapsto \text{treatment cycles} \]
Table 1: Bias of parameter estimations of time to event and longitudinal joint model, within 5000 simulations per sample size

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<thead>
<tr>
<th>Parameters</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
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<td>n=15</td>
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<tr>
<td>Longitudinal Intercept</td>
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<tr>
<td>Longitudinal Time</td>
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<tr>
<td>Longitudinal Dose</td>
<td>2.23 x 10^{-6}</td>
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<td>Survival Intercept</td>
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<td>Survival Dose</td>
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<td>Longitudinal Residual Variance</td>
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<tr>
<td>Longitudinal Slope Variance</td>
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<tr>
<td>Survival Gamma</td>
<td>4.86 x 10^{-1}</td>
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Table 2: Coverage of parameter estimations of time to event and longitudinal joint model, within 5000 simulations per sample size

<table>
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<tr>
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<tr>
<td>Survival Gamma</td>
<td>0.99</td>
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</tbody>
</table>
Conclusions

- Small bias
- Satisfying coverage
- Suggested after 30 subjects
Why joint modelling?

- Incorporate information on activity \(\rightarrow\) utilize all available information

- Take into account missing at random

- Exact likelihood inference
  - Avoid numerical integration of approximate likelihood \(\rightarrow\) biased estimations due to small sample size
  - Better parameter estimations
  - More rapid estimations

Further...

- Define an optimal dose
- Propose an adaptive design for early phase I trials based on joint modelling
Thank you!

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