Predicting outcome of the comparison of time to death in an oncology clinical trial, using PFS and time to death data.

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Introduction

Metastatic cancer clinical trials compare treatments through:

- **Time to Death (D)**
- **Progression Free Survival (P)** defined as the time to first progression or death
- **Tumor response** (response rate, duration of response, ...).

- **Mature P** data are obtained before mature D data.

**Question:**
Can we use P to predict the difference in D between treatments?
Introduction

In the course of the trial:

- $P$ data can be analyzed earlier than $D$
  - An interim analysis is conducted on $P$ and $D$ or
  - $P$ is analyzed as the primary endpoint and $D$ is updated later

- Information on efficacy of treatment on $D$ is available when $P$ is analyzed.

Early information on the comparison of $D$ would be useful

- For Data Monitoring Committee
- For assessment of risk / benefit to avoid exposition to a potentially ineffective treatment
- For assessment of risk of an early filing based on $P$ to Health Authorities
Current practice:

- Predictive power and conditional power
- Available data analysis (based on early events)
- Medical experience to link all endpoints together to assess the effect of treatment

Methods do not combine statistically the knowledge on $P$ with $D$ data.
Example: NSCL cancer trials

2 trials of first line therapies in advanced NCSL cancer (stage III, IV)

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Arm Size</th>
<th>Progression Median (mths)</th>
<th>Time to Death Median (mths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA139165 - Primary endpoint: Time to Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAXOL + CISPLAPTIN vs</td>
<td>198</td>
<td>4.3</td>
<td>9.3</td>
</tr>
<tr>
<td>ETOPOSIDE + CISPLAPTIN vs</td>
<td>200</td>
<td>2.7</td>
<td>7.4</td>
</tr>
<tr>
<td>TAXOL + CISPLAPTIN + G-CSF</td>
<td>201</td>
<td>4.9</td>
<td>10.0</td>
</tr>
<tr>
<td>CA139271- Primary endpoint: NI in Response Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAXOL + CISPLAPTIN vs</td>
<td>309</td>
<td>4.2</td>
<td>9.8</td>
</tr>
<tr>
<td>TAXOL + CARBOPLATIN</td>
<td>309</td>
<td>3.0</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Dejardin et al. (I-BioStat) Prediction on Time to Death using PFS ISCB 2009 5 / 19
Outline of the Method

Method based on:

1. association between the endpoints
2. model for joint distribution between $P$ and $D$

When $P$ data are mature, we update prior distribution of the hazard ratio ($\theta$) for $D$ based on:

1. mature $P$ data
2. early $D$ data in both treatment arms

using Bayesian MCMC simulations.
Joint Model of $P$ and $D$

The joint distribution between $P$ and $D$ is based on a progressive multi-state model.

- Association modelled through a subject-specific frailty term in transition hazards.
- $Z \sim$ Gamma with mean 1 and variance $\delta$.
- Transition hazards are proportional

$$\lambda_P(p) = Z\lambda_0(p) \quad \text{and} \quad \lambda_{D|P}(d|p) = ZI(p \leq d)e^\beta \lambda_0(d)$$

- $\lambda_0(t)$ is the baseline hazard e.g. a Weibull hazard: $\nu \eta e^{\eta - 1}$
Joint Model of $P$ and $D$ (cont’d)

Measure of association: Kendall’s $\tau$.

- No explicit formulation.
- Depends only on $\beta$ and $\delta$ (variance of the frailty term).

Further:

- This model takes into account ordering of $P$ and $D$
- We use interval censoring for $P$:
  - $P$ is assessed at fixed visits
  - take into account cases where $P = D$
Method: details

Step 1: Based on past trials in same setting, compute:

- $\beta$: proportionality parameter
- $\delta$: frailty variance

Parameters estimates and variance $\Rightarrow$ association between $P$ and $D$ and its distribution
Step 2:  
- At the time we have mature $P$ data  
- model the joint distribution in experimental arm using MCMC simulations  
- using mature $P$ data and incomplete $D$ data from experimental arm  
- use posterior of $\beta$ and $\delta$ from step 1 as prior  
- use an NI prior for $\nu$ and $\eta$ ($\lambda_0$)  
- obtain posterior distribution of the parameters $\beta, \delta, \nu, \eta$

Parameters provide joint distribution in experimental arm  
joint distribution $\Rightarrow$ “extended” marginal distribution for $D$
Method (cont’d)

Step 3:
- Assume proportionality ($\theta$) between the hazards of $D$ in both treatment arms
- Assume NI prior for $\theta$
- $\beta \delta \nu \eta$ not updated at this stage
- fit, with MCMC, proportional distribution of the control, with $\theta$ as parameter

Posterior distribution of $\theta$ (and estimates)
Study 165

Aim: to predict comparisons in study -165, using study -271 as “historical” data:

1. \[ \theta_1 = \frac{\text{Hazard TAXCISP}}{\text{Hazard ETO} + \text{CISP}} \]

2. \[ \theta_2 = \frac{\text{Hazard TAXCISP}}{\text{Hazard TAXCISP} + \text{GCSF}} \]

Choose to predict based on data at 14 mths after first randomization (i.e. 2 months prior to last randomization)
We start with deriving the association for each study:

<table>
<thead>
<tr>
<th>arms</th>
<th>Pooled (std)</th>
<th>Kendall’s $\tau$ in TAXCISP</th>
<th>Kendall’s $\tau$ in comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY 165</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAXCISP vs ETOCISP</td>
<td>0.47 (0.020)</td>
<td>0.48</td>
<td>0.44</td>
</tr>
<tr>
<td>TAXCISP vs TAXCISP+G</td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STUDY 271</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAXCISP vs TAXCARB</td>
<td>0.43 (0.020)</td>
<td>0.45</td>
<td>0.43</td>
</tr>
</tbody>
</table>

- association is similar across studies
- association is similar across treatment arms
Prediction of $\theta_1$

Historical: CA139271  Predicted: CA139165  
Control: TAXCISP experimental to predict: ETOCISP  
Theta at interim analysis : 0.75  
Posterior distribution of Theta : 0.82  
Observed Theta : 0.85
Dejardin et al. (I-BioStat)

Prediction on Time to Death using PFS

Events in ETOCISP

<table>
<thead>
<tr>
<th></th>
<th>Interim (14 mths)</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P$</td>
<td>113</td>
<td>194</td>
</tr>
<tr>
<td>$D$</td>
<td>68</td>
<td>183</td>
</tr>
</tbody>
</table>

Progression in ETOCISP

Turnbull estimator of PFS at final analysis
Predicted PFS distribution
Turnbull estimator of PFS at interim

KM survival for ETOCISP
KM survival TAXCISP
Predicted dist. ETOCISP
Predicted dist. TAXCISP
Prediction of $\theta_2$

Historical: CA139271  Predicted: CA139165
Control: TAXCISP experimental to predict: TAXCISP_G
Theta at interim analysis: 1.14
Posterior distribution of Theta: 1.24
Observed Theta: 1.01
### Events in TAXCISP + GCSF

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<tr>
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<tr>
<td>$P$</td>
<td>97</td>
<td>191</td>
</tr>
<tr>
<td>$D$</td>
<td>46</td>
<td>182</td>
</tr>
</tbody>
</table>

**Progression in TAXCISP_G**

- Turnbull estimator of PFS at final analysis
- Predicted PFS distribution
- Turnbull estimator of PFS at interim

**KM survival**

- KM survival for TAXCISP_G
- KM survival for TAXCISP
- Predicted dist. for TAXCISP_G
- Predicted dist. for TAXCISP
Discussion

Method allows to “extend” $D$ distribution based on mature $P$ data and derive treatment difference.

- In current analysis and analyses not shown: improves on the estimates at interim
- Could be part of a package of techniques for early assessment of treatment effect on $D$

- By incorporating all sources of variations: wide HPD interval
- Relies on proportional hazards for $D$ between the treatment arms
- Parametric assumptions:
  - Baseline hazard, could be relaxed using piecewise constant hazard
  - Frailty distribution
  - Proportionality of transition hazards: important assumption to generalize the association

Our example:

- Association between $P$ and $D$ is not large
Thank you for your attention

Acknowledgment:
We thank Bristol-Myers Squibb Company for providing the NSCL Cancer Datasets