A Joint Model Relating Changes in Prostate Specific Antigen to Survival in Castrate Resistant Prostate Cancer

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Conflict of Interest Statement

The authors have nothing to disclose
Most common cancer in men in developed countries

Local PC

Advanced PC

Androgen deprivation

Castrate-resistant

OS~ 35 months

No cure

Drug development:
- Time consuming (12-15 years)
- Costly ($1 billion)

Evaluation of efficacy depends on overall survival (OS)

Goal: Determine an early endpoint that is predictive of OS benefit for clinical trial design using model-based approach
Prostate-Specific Antigen (PSA) as a Biomarker

- PSA was recognized as a biomarker for monitoring the progression of patients with CRPC
- Easily measured in serum
- Accessible longitudinal data

Phase III Clinical Trials

- Project Data Sphere allows access to control-arm data from phase III cancer clinical trials

<table>
<thead>
<tr>
<th>ProjectDataSphere ID</th>
<th>N</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prostat_Pfizer_2008_81</td>
<td>201</td>
<td>Prednisone + Drug A</td>
</tr>
<tr>
<td>2. Prostat_Sanofi_2000_80</td>
<td>253</td>
<td>Prednisone + Mitoxantrone + Drug B</td>
</tr>
<tr>
<td>3. Prostat_Sanofi_2007_79</td>
<td>282</td>
<td>Prednisone + Mitoxantrone + Drug C</td>
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<tr>
<td>4. Prostat_Sanofi_2007_83</td>
<td>457</td>
<td>Prednisone + Docetaxel + Drug D</td>
</tr>
<tr>
<td>5. Prostat_CougarB_2008_101</td>
<td>253</td>
<td>Prednisone + Drug E</td>
</tr>
<tr>
<td>6. Prostat_Novacea_2006_89</td>
<td>312</td>
<td>Prednisone + Docetaxel + Drug F</td>
</tr>
</tbody>
</table>

Total: 1758 patients
Modeling Strategies

\[ PSA(t) = BSL \times (e^{(-d \times t)} + e^{(g \times t)} - 1) \]


Approach 2: One-stage Model

Step 1
- PSA Progression Model
  - PSA data
  - Statistical Model
  - Covariates Model

Joint-Model linking PSA and survival

Step 2
- Survival Model
  - Overall survival data
  - Baseline Model
  - Covariates Model

BSL: estimated baseline PSA
\(d\): rate of decrease in PSA
\(g\): PSA growth rate
## Estimation of the Parameters

### Approach 1: Two-stage model

#### Estimates of the PSA progression model

<table>
<thead>
<tr>
<th>Population Parameters</th>
<th>Estimates</th>
<th>Units</th>
<th>BSV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (BSL)</td>
<td>138</td>
<td>ng/mL</td>
<td>162</td>
</tr>
<tr>
<td>Growth</td>
<td>0.00069</td>
<td>1/day</td>
<td>138</td>
</tr>
<tr>
<td>Decay</td>
<td>0.0113</td>
<td>1/day</td>
<td>110</td>
</tr>
<tr>
<td>Baseline Hazard of dropout</td>
<td>0.0122</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Significant covariates in the Cox-regression survival model

- PSA doubling time
- Prior treatment with Docetaxel
- Hemoglobin
- Age
- Performance status (ECOG)
- Alkaline phosphatase
- Diagnosis
- Day
### Estimation of the Parameters

#### Approach 2: Joint-model

<table>
<thead>
<tr>
<th>Population Parameters</th>
<th>Estimates</th>
<th>Units</th>
<th>BSV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (BSL)</td>
<td>91.4</td>
<td>ng/mL</td>
<td>156</td>
</tr>
<tr>
<td>Growth</td>
<td>0.00058</td>
<td>1/day</td>
<td>140</td>
</tr>
<tr>
<td>Decay</td>
<td>0.0114</td>
<td>1/day</td>
<td>114</td>
</tr>
<tr>
<td>Baseline Hazard of Survival (BSHZ)</td>
<td>0.00087</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta</td>
<td>0.248</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[
h_i(t | \text{PSA}(t)) = h_0(t) \exp(\beta \text{PSA}(t))
\]

\[
h_0(t) = \frac{k}{\lambda} \left(\frac{t}{\lambda}\right)^{k-1}
\]

### Significant Covariates

- **Growth**: Prior Docetaxel treatment, Alkaline phosphatase, Performance status
- **Decay**: Drug, Age, Performance status
- **BSHZ**: Prior Docetaxel treatment, Alkaline phosphatase
- **Beta**: Hemoglobin, Performance status, Drug, Age
- **BSL**: Hemoglobin, Performance status, Alkaline phosphatase
Predicted Survival of Simulated Data by the Joint-Model

- Relative % change from baseline in PSA at two months:
  - < -15% (Tertile 1): Median Survival (days) 483
  - -15% - 30% (Tertile 2): 420
  - > 30% (Tertile 3): 315

- Log Rank test, all arms, p < 0.00001
- Log Rank test, p = 0.0007
- Log Rank test, p < 0.00001
CRPC disease progression models were developed with 2 approaches:

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Two-stage Model</strong></td>
<td><strong>Joint-Model</strong></td>
</tr>
<tr>
<td>• 2\textsuperscript{nd} stage can be easily implemented by non-modelers</td>
<td>• Evaluate PSA kinetics and survival simultaneously</td>
</tr>
<tr>
<td>• Estimates of PSA kinetics are fixed in cox survival model</td>
<td>• More difficult to implement for non-modelers</td>
</tr>
<tr>
<td>• Requires 2 steps during development</td>
<td></td>
</tr>
</tbody>
</table>

**FUTURE DIRECTIONS:**

- Simulations will be run to determine the superior model by VPC for survival
- Early PSA-based endpoints will be evaluated by simulations to be used in drug development
Acknowledgement

- Manish R. Sharma, MD.
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- Committee on Clinical Pharmacology and Pharmacogenomics
  - Eileen Dolan, Ph.D.
  - Mark Ratain, MD.
  - Michelle Domecki, MS.
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Model Verification of PSA Values

The diagram plots the logarithm of PSA (log g/L) against study time (day). It compares observed and simulated quantiles with solid and dashed lines, respectively. The quantiles are marked at 90%, 75%, 50%, 25%, and 10%.