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
Background

Most common cancer in men in developed countries

Local PC 40\%  Advanced PC

Androgen deprivation

Castrate-resistant

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>
</tr>
<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**

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


**Approach 2: One-stage Model**

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

**Step 2**
- Joint-Model linking PSA and survival
- Overall survival data
  - Survival Model
  - Covariates Model
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>

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

\[ h_0(t) = \frac{k}{\lambda} \left(\frac{t}{\lambda}\right)^{k-1} \]
Predicted Survival of Simulated Data by the Joint-Model

- Log Rank test, all arms, p < 0.00001
- Relative % change from baseline in PSA at two months:
  - < -15% (Tertile 1) Median Survival (days) = 483
  - -15% - 30% (Tertile 2) Median Survival (days) = 420
  - > 30% (Tertile 3) Median Survival (days) = 315

Log Rank test, p = 0.0007
Summary & Future Directions

• CRPC disease progression models were developed with 2 approaches

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-stage Model</td>
<td>Joint-Model</td>
</tr>
<tr>
<td>2nd 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>
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</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

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  – Mark Ratain, MD.
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Model Verification of PSA Values

![Graph showing observed and simulated quantiles of PSA values over study time. The graph compares solid lines for observed data and dashed lines for simulated data, with quantiles indicated by colors: 90%, 75%, 50%, 25%, and 10%.]