Background: The results from the CHAARTED and STAMPEDE trials that docetaxel plus androgen-deprivation therapy (ADT) significantly improves survival over ADT alone among men with metastatic, hormone-sensitive and hormone-naïve prostate cancers, represents a potential practice-changing movement. Clinical data exist to support the role of various predictive markers for taxane response, including low or negative class III beta tubulin (TUBB3), positive transducin-like enhancer of split 3 (TLE3) and low or negative p-glycoprotein (PGP/ABCBI). We examined a database of molecularly-profiled prostate cancer patients for taxane sensitivity markers for insight into the mechanism behind the clinical effect of docetaxel.

Methods: 297 patients with prostate cancer were included in the study and tested centrally at a CLIA laboratory (Cars Life Sciences, Phoenix, AZ). Tests included one or more of the following: gene sequencing (Sanger or next generation sequencing [NGS]), protein expression (immunohistochemistry [IHC]) and gene amplification (C/FISH). Antibodies and cutoffs for are as follows, or can be obtained by request:

Metastatic TUBB3 (beta tubulin-II) is suggestive of response to taxanes, in vitro data suggests that high levels of beta-tubulin II could replenish microtubule assembly and overcome the microtubule destabilization induced by taxanes.

TUBB3 (transducin-like enhancer of split II) represents a subgroup of patients that may have best response to taxane therapy.

PGP (P-glycoprotein) indicates the potential for drug efficacy before cellular concentrations of the drug accumulate to induce cytotoxic effects.

Results: In all prostate cases tested, protein levels for taxane markers are shown in the table below.

<table>
<thead>
<tr>
<th>TLE3</th>
<th>TUBB3</th>
<th>PGP</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLE3+</td>
<td>TUBB3</td>
<td>PGP</td>
</tr>
<tr>
<td>58.6%</td>
<td>12%</td>
<td>75%</td>
</tr>
<tr>
<td>41%</td>
<td>3%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Results, contd.

Table 1: Distribution of disease site utilized for profiling, Androgen Receptor (AR) status and age of patients with prostate adenocarcinoma included in this analysis.

Conclusions: Taxane sensitivity markers are observed at a statistically significant higher frequency in AR-positive prostate cancer patients, providing a potential molecular hypothesis for the increased effectiveness of chemo-hormonal therapy observed in hormone-sensitive prostate cancers. A substantial number of both AR-positive and negative patients have sub-optimal biomarker profile for taxanes responsiveness highlighting an unmet need for on-going drug development in this disease.

References