Association of Radiographic Progression-free Survival (rPFS) Adapted from Prostate Cancer Working Group 2 (PCWG2) Consensus Criteria With Overall Survival (OS) in Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC): Results From COU-AA-302

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Disclosures

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Purpose of Current Analysis

- **Assess performance of rPFS**
  - modified PCWG2 criteria\(^1\) using blinded central review (independent) in COU-AA-302

- **Compare investigator and independent review**
  - rPFS at 2 different interim analyses

- **Quantify the relationship between co-primary end points of rPFS and overall survival**

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PCWG2, Prostate Cancer Clinical Trials Working Group; rPFS, radiographic progression-free survival.


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Phase 3, Multinational, Randomized, Double-Blind, Placebo-Controlled Study

Patients
- Progressive chemo-naïve mCRPC patients (N = 1088)
- Asymptomatic or mildly symptomatic
- No visceral metastases

Randomized 1:1

AA 1000 mg daily Prednisone 5 mg BID (n = 546)

Placebo daily Prednisone 5 mg BID (n = 542)

Efficacy end points
Co-primary:
- rPFS by central review
- OS
Secondary:
- Time to opiate use (cancer-related pain)
- Time to initiation of chemotherapy
- Time to ECOG-PS deterioration
- TTPP

- Conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada
- Stratification by ECOG performance status 0 vs 1
- Patients treated until radiographic progression or unequivocal clinical progression
- First use of rPFS adapted from PCWG2 criteria\(^1\) using independent review

AA, abiraterone acetate; BID, twice daily; ECOG, Eastern Cooperative Oncology Group; TTPP, time to PSA progression.


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Adaptation of PCWG2 Consensus Criteria

**COU-AA-302 Definition**

- **Progressive disease (PD) by bone scan:** Adapted from PCWG2 consensus criteria
  - Review < 12 weeks after randomization
    - ≥ 2 new bone lesions plus 2 additional lesions on a subsequent scan (“2+2”)
  - ≥ 12 weeks after randomization
    - ≥ 2 new bone lesions with new lesions confirmed at subsequent scan
- **PD (soft tissue lesions) by CT/MRI** by modified Response Evaluation Criteria in Solid Tumors (RECIST)
- **Death from any cause**

Using Bone Scans To Monitor Disease Progression*

Protocol-Defined Confirmation of Progression
2 BL + 2 New + 2 New = 6 total

Disease Progression
2 BL + 2 New = 4 total

Failure to Confirm Progression (ie, Bone Flare)
2 BL + 2 New + 0 = 4 total
“4 + 0 = Flare”

BL, baseline.
*Images provided by Dr. Matthew Smith.
# COU-AA-302 rPFS Determinations

<table>
<thead>
<tr>
<th>Review</th>
<th>Interim Analysis</th>
<th>Total rPFS Actual Events</th>
<th>Corresponding Planned OS Events*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent review</td>
<td>Dec 2010</td>
<td>401</td>
<td>116†</td>
</tr>
<tr>
<td>Independent review (including investigator assessment of unequivocal clinical progression)‡</td>
<td>Dec 2010</td>
<td>468</td>
<td>116</td>
</tr>
<tr>
<td>Investigator review</td>
<td>Dec 2010</td>
<td>435</td>
<td>116</td>
</tr>
<tr>
<td>Investigator review</td>
<td>Dec 2011</td>
<td>607</td>
<td>311</td>
</tr>
</tbody>
</table>

*Final analysis = 773 planned OS events.
†Corresponding to 378 planned rPFS events.
‡Cancer pain requiring opiates, deterioration to Grade 3 ECOG status, initiation of cytotoxic chemotherapy, radiation/surgical intervention for prostate cancer.
Statistically Significant Improvement in rPFS Primary End Point – Independent Review (Dec 2010)¹

### Survival Analysis

<table>
<thead>
<tr>
<th>Time to Progression or Death (Months)</th>
<th>Abiraterone</th>
<th>Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>546 542</td>
<td>489 400</td>
</tr>
<tr>
<td>3</td>
<td>489 400</td>
<td>340 204</td>
</tr>
<tr>
<td>6</td>
<td>340 204</td>
<td>164 90</td>
</tr>
<tr>
<td>9</td>
<td>164 90</td>
<td>46 30</td>
</tr>
<tr>
<td>12</td>
<td>46 30</td>
<td>12 3</td>
</tr>
<tr>
<td>15</td>
<td>12 3</td>
<td>0 0</td>
</tr>
</tbody>
</table>

- **Abiraterone median (mos):** NR
- **Prednisone median (mos):** 8.3
- **HR (95% CI):** 0.43 (0.35-0.52)
- **P value:** < 0.0001


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### rPFS Benefit Demonstrated Across Full Spectrum of Prespecified Subgroups*1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Favors Abiraterone</th>
<th>Medians (months)</th>
<th>Favors Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subgroup</td>
<td>AA</td>
<td>Pred</td>
</tr>
<tr>
<td>All subjects</td>
<td>NE</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>Baseline ECOG</td>
<td>NE</td>
<td>13.7</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>NE</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>Baseline BPI</td>
<td>NE</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.1</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Bone metastasis only at entry</td>
<td>NE</td>
<td>13.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.3</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>13.7</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>NE</td>
<td>9.7</td>
<td></td>
</tr>
<tr>
<td>≥ 65</td>
<td>NE</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>≥ 75</td>
<td>NE</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>Baseline PSA above median</td>
<td>11.9</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline LDH above median</td>
<td>5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline ALK-P above median</td>
<td>11.5</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td>NE</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11.5</td>
<td>8.4</td>
<td></td>
</tr>
</tbody>
</table>


*Independent review Dec 2010 interim analysis.

Pred, prednisone
Majority of New Lesions at week 8 were NOT Confirmed as Progression

Adapted PCWG2 rPFS criteria identified a substantial level of false protocol-defined progression at 8 weeks

- Abiraterone: \((\frac{92}{108}) = 85\%\)
- Prednisone: \((\frac{74}{121}) = 61\%\)
Bone Scan “Improvement” Occurred in a minority of those with “Flare”

<table>
<thead>
<tr>
<th>↓Bone lesions (post 8-week bone scan), n = 47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone (n = 33)</td>
</tr>
<tr>
<td>Prednisone (n = 14)</td>
</tr>
</tbody>
</table>

- Adapted PCWGFW rPFS criteria also uncovered patients who showed PD at 8 weeks with a reduction in identified lesions on their post 8-week bone scan
  - **Abiraterone**: 31% (33/108)
  - **Prednisone**: 12% (14/121)

- Intensity of lesions was not considered

PD, progressive disease.
rPFS Was Highly Consistent Between Independent and Investigator Reviews

• Agreement between independent and investigator assessment on rPFS event status was observed (abiraterone group, 430/546 [79%]; prednisone group, 414/542 [76%])*  

IND, independent review; INV, investigator review

*based on the IND 2010 – INV 2010 analysis.
## Consistency of rPFS Analyses

<table>
<thead>
<tr>
<th>Review</th>
<th>Interim Analysis</th>
<th>Abiraterone Median (mos)</th>
<th>Prednisone Median (mos)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rPFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IND</td>
<td>Dec 2010</td>
<td>NR</td>
<td>8.3</td>
<td>0.43 (0.35-0.52)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>IND*</td>
<td>Dec 2010</td>
<td>12</td>
<td>7.9</td>
<td>0.42 (0.35-0.51)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>INV</td>
<td>Dec 2010</td>
<td>13.7</td>
<td>8.3</td>
<td>0.49 (0.41-0.60)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>INV</td>
<td>Dec 2011</td>
<td>16.5</td>
<td>8.3</td>
<td>0.53 (0.45-0.62)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>Dec 2011†</td>
<td>NR</td>
<td>27.2</td>
<td>0.75 (0.61-0.93)</td>
<td>0.0097</td>
</tr>
</tbody>
</table>

*Including investigator assessment of unequivocal clinical progression.
†Prespecified alpha level 0.0008.
Strong Trend in OS Primary End Point\textsuperscript{1}

![Graph showing survival rates for Abiraterone and Prednisone over time to death (months).]

<table>
<thead>
<tr>
<th></th>
<th>Abiraterone (median, mos)</th>
<th>Prednisone (median, mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>0.75 (0.61-0.93)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.0097</td>
<td></td>
</tr>
</tbody>
</table>

Abiraterone (median, mos): NR
Prednisone (median, mos): 27.2
HR (95% CI): 0.75 (0.61-0.93)
P value: 0.0097

Data cutoff 12/20/2011.
Prespecified significance level by O’Brien-Fleming Boundary = 0.0008.

Positive Association of rPFS With OS

Association of rPFS and OS at Dec 2011 Interim Analysis*

<table>
<thead>
<tr>
<th>Spearman Rho (r)</th>
<th>Level of Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>Negatively associated</td>
</tr>
<tr>
<td>0</td>
<td>No association</td>
</tr>
<tr>
<td>1</td>
<td>Positively associated</td>
</tr>
</tbody>
</table>

*Per Spearman’s correlation coefficient estimated through Clayton copula.
Conclusions

• COU-302 was the first phase 3 study to require confirmatory scans for rPFS
  – Occurs q8w during first 24 weeks; q12w thereafter
  – Optimizes and tests PCWG2 criteria
  – Reduced likelihood of early discontinuation due to false positive bone scan or rising PSA

• The present rPFS results establish consistency between independent and investigator reviewers
  – Attests to validity of rPFS as an outcome measure
Conclusions (cont)

- Robust association between rPFS and OS provides possible support for use of rPFS adapted from PCWG2 criteria as
  - Outcome measure of OS
  - Primary/co-primary end point in phase 3 mCRPC studies
  - Merits validation in further phase III studies in mCRPC
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