U.S. FDA Approval Summary: Abiraterone Acetate

**CCR Perspectives in Drug Approval**

Abiraterone Acetate in Combination with Prednisone for the Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer:

U.S. Food and Drug Administration Drug Approval Summary

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**U.S. FDA Approval Summary: Abiraterone Acetate**

**Abstract**

On December 10, 2012, the U.S. Food and Drug Administration granted full approval for a modified indication for abiraterone acetate (ZYTIGA® Tablets, Janssen Biotech, Inc.) in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). The approval was based on clinical trial COU-AA-302 which randomly allocated asymptomatic or mildly symptomatic patients with chemotherapy-naïve mCRPC and no visceral metastases to either abiraterone acetate (AA) plus prednisone (N = 546) or placebo plus prednisone (N = 542). The co-primary endpoints were radiographic progression-free survival (rPFS) and overall survival (OS). The median rPFS was 8.3 months in the placebo arm and had not yet been reached in the AA arm [HR 0.43 (95% CI: 0.35, 0.52), p < 0.0001]. A pre-specified interim analysis demonstrated an improvement in OS favoring the AA arm [HR 0.79 (95% CI: 0.66, 0.96)] but did not cross the O'Brien-Fleming boundary for statistical significance. Safety data confirmed the known adverse reaction profile of AA. Full approval was granted based on a large magnitude of effect on rPFS, a favorable trend in OS, and internal consistency across multiple secondary endpoints and exploratory patient-reported pain data. This is the first drug approval for mCRPC to utilize rPFS as the primary endpoint. Importantly, this approval was granted in the context of a prior statistically significant OS benefit that formed the basis of the original April 28, 2011 approval of AA for patients with mCRPC who had received prior chemotherapy containing docetaxel.

**Introduction**

Despite significant therapeutic advances over the last decade, prostate cancer remains the second leading cause of cancer death in men in the United States. [1] Two cytotoxic chemotherapy drugs improve survival in patients with metastatic CRPC; docetaxel [2-4] and cabazitaxel. [5, 6] While effective, treatment with these cytotoxic drugs is associated with significant toxicity including neutropenia, severe hypersensitivity reactions, neuropathy and mucositis, as well as the inconvenience of intravenous administration.

In addition to traditional cytotoxic agents, therapies with alternative mechanisms of action have recently been developed. Available data indicate that prostate cancer can remain dependent on activation of the androgen-receptor signaling pathway despite maintenance of castrate levels of serum testosterone, making this pathway important for mCRPC drug development. [7, 8] Abiraterone acetate (AA) is a 17α-hydroxylase/C17,20-lyase (CYP17) inhibitor which acts on extra-gonadal testosterone production. The inhibition of CYP17 in
U.S. FDA Approval Summary: Abiraterone Acetate

the adrenal gland can lead to increased levels of steroids with mineralocorticoid effects, which may result in mineralocorticoid-related side effects including hypokalemia, hypertension and fluid retention/edema. These effects can be mitigated by the use of concomitant prednisone. [9]

On April 28, 2011, the U.S. Food and Drug Administration (FDA) granted initial approval for AA (Zytiga® Tablets, Janssen Biotech, Inc.) for use in combination with prednisone for the treatment of patients with mCRPC who have received prior chemotherapy containing docetaxel.[10] Approval was based on findings from the COU-AA-301 trial: A randomized, double-blind, placebo-controlled, multicenter Phase 3 trial in 1195 patients with mCRPC who had previously received docetaxel-based chemotherapy. Patients were randomly allocated (2:1) to receive either 1000 mg of AA (N=797) or placebo (N=398) orally once daily. All patients received prednisone 5 mg orally twice daily. The primary endpoint was overall survival (OS). At the pre-specified interim analysis, there was a statistically and clinically significant improvement in OS favoring the AA arm (hazard ratio [HR] = 0.65; 95% CI: 0.54, 0.77; p< 0.0001). The median OS was 14.8 months and 10.9 months in the AA and placebo arms, respectively. [11] This benefit was maintained in the final OS analysis. [12]

With the exception of GnRH analogues, all recent drug approvals for the treatment of mCRPC have demonstrated a statistically significant improvement in OS. As the number of available therapies has increased, there has been interest in identifying alternative primary efficacy endpoints. The first attempt at a standard definition for radiographic progression in mCRPC was developed in 1999 by Bubley and colleagues and is known as the Prostate Cancer Working Group 1 (PCWG-1) criteria.[13] The PCWG updated its criteria in 2008, and it is the PCWG-2 criteria that form the basis for measurement of rPFS in most contemporary mCRPC studies, including the COU-AA-302 trial.[14]

In June of 2012, the FDA received a supplemental new drug application (sNDA) for the use of AA in chemotherapy-naïve patients with mCRPC. This sNDA was the first regulatory submission for the treatment of mCRPC that utilized rPFS as a primary efficacy endpoint. The FDA review of this application is summarized in this report.
U.S. FDA Approval Summary: Abiraterone Acetate

Chemistry

Abiraterone acetate is the active ingredient of Zytiga® and is chemically designated as (3β)-17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate. Its molecular formula is C_{26}H_{33}NO_{2} with a molecular weight of 391.55. It is a white to off-white, non-hygroscopic, lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. Zytiga® is provided as an oval-shaped 250 mg tablet debossed with “AA250” on one side.

Pharmacology and Toxicology

Abiraterone acetate is a prodrug converted \textit{in vivo} to abiraterone which irreversibly inhibits cytochrome P450 17α-hydroxylase/C17,20-lyase (CYP17). CYP17 is expressed in testicular, adrenal and prostatic tumor tissues and is required for androgen biosynthesis. Inhibition of CYP17 by abiraterone leads to further decreases in serum testosterone concentrations in patients who have already undergone surgical or medical castration. CYP17 is a dual function enzyme; as conversion of progestins into androgens is inhibited, the production of mineralocorticoids is increased.

Non-clinical toxicology studies conducted in rats and monkeys resulted in toxicities in the reproductive system likely related to the pharmacological activity of AA. These findings suggest that AA may impair reproduction or fertility in humans. In rats, cataracts developed in a dose-dependent manner at the end of the 26-week treatment period and were irreversible after treatment discontinuation. The mechanism underlying the cataract formation is unclear, but a species-specific effect of AA on the eyes cannot be excluded since no cataracts were observed in monkeys following 39 weeks of AA treatment. In monkeys, the liver was one of the major target organs of toxicity as evidenced by bile duct/oval cell hyperplasia and increases in alkaline phosphatase and total bilirubin. These toxicities were observed after 13 or 39 weeks of treatment.
U.S. FDA Approval Summary: Abiraterone Acetate

Embryo-fetal developmental toxicology studies and carcinogenicity studies were not necessary for the proposed indication. Abiraterone and AA were not mutagenic or clastogenic when tested in *in vitro* or *in vivo* genetic toxicology studies.

**Clinical Pharmacology**

Abiraterone acetate is converted *in vivo* to abiraterone. In clinical trials, AA was below detectable levels in > 99% of plasma samples. The median time to maximum abiraterone concentrations (T\text{max}) is 2 hours and the terminal half-life (mean ± SD) is 12 ± 5 hours. A significant food effect has been observed for AA. In a single dose healthy volunteer study, abiraterone C\text{max} and AUC\text{0-∞} (systemic exposure) increased up to 17- and 10-fold, respectively, in a fed as compared to a fasted state. No food should be consumed for at least two hours before, and for at least one hour after AA administration.

Following oral administration of $^{14}$C-abiraterone acetate, 88% of the radioactive dose was recovered in feces (5% in urine). A 1.1- and 3.6-fold increase in exposure (AUC\text{0-∞}) was observed in subjects with mild (n=8) and moderate (n=8) baseline hepatic impairment, respectively, when compared to subjects with normal hepatic function (n=8). Therefore, a dose of 250 mg once daily is recommended in patients with moderate hepatic impairment. Abiraterone acetate should not be used in patients with severe hepatic impairment, as it has not been studied in these patients.

Abiraterone is metabolized by SULT2A1 (predominant) and CYP3A4 enzymes. It has two major inactive metabolites that each account for approximately 43% of exposure. Abiraterone is a CYP2D6 inhibitor that increases the AUC of dextromethorphan (CYP2D6 substrate) approximately 3-fold. Therefore, co-administration of AA with substrates of CYP2D6 that have a narrow therapeutic index (e.g., thioridazine) should be avoided.

**Study COU-AA-302: Chemotherapy-Naïve mCRPC**

**Study Design**

COU-AA-302 was a placebo-controlled, double-blind, international phase 3 clinical trial which randomly allocated (1:1) 1,088 asymptomatic or mildly symptomatic patients with...
U.S. FDA Approval Summary: Abiraterone Acetate

mCRPC to either 1000 mg of AA once daily (N=546) or placebo once daily (N=542). Patients on both arms received concomitant prednisone 5 mg twice daily. Patient randomization was stratified by Eastern Cooperative Group (ECOG) performance status (0 vs. 1). Patients had documented disease progression by PSA and/or radiographic scans despite castrate levels of testosterone (< 50 ng/dL). Patients were required to have a score of ≤ 3 on item 3 of the Brief Pain Inventory-Short Form (BPI-SF), a 0-10 scale which asks patients to classify their worst pain in the last 24 hours.[15] Patients with moderate or severe pain, opiate use for cancer pain within the last 4 weeks, or liver or other visceral organ metastases were excluded. Additional key exclusion criteria included prior use of cytotoxic chemotherapy, biologic therapy or ketoconazole for prostate cancer or a history of adrenal gland or pituitary dysfunction. Treatment was to be continued until radiographic progression, unequivocal clinical progression, unacceptable toxicity or investigator or patient decision. Unequivocal clinical progression was defined as initiation of cytotoxic chemotherapy, radiation or surgical treatment for cancer, pain requiring chronic opioids, or ECOG performance status decline to 3 or more. Treatment was not discontinued for increasing PSA values alone.

An independent data monitoring committee (IDMC) was utilized to monitor safety during the study and to evaluate efficacy and safety results at the time of the protocol-specified interim analyses.

Study endpoints

The co-primary efficacy endpoints were OS and rPFS. Overall survival was defined as the time interval from the date of randomization to the date of death, regardless of cause. Radiographic PFS was defined as the time from randomization to death from any cause or the occurrence of any one of the following, as determined by an Independent Radiology Committee (IRC):

1. Progression of soft tissue lesions measured by computed tomography (CT) or magnetic resonance imaging (MRI) as defined by modified RECIST criteria OR;
2. Progression on bone scan defined as either:
   a. The first bone scan with ≥ 2 new lesions compared to baseline is observed < 12 weeks from randomization and is confirmed by a second bone scan.
U.S. FDA Approval Summary: Abiraterone Acetate

taken ≥6 weeks later showing an additional ≥ 2 new lesions (a total of ≥ 4 new lesions compared to baseline); OR

b. The first bone scan with ≥ 2 new lesions compared to baseline is observed ≥ 12 weeks from randomization and the new lesions are verified on the next bone scan ≥ 6 weeks later (a total of ≥ 2 new lesions compared to baseline).

Tumor assessments included CT/MRI and bone scan obtained every 2 cycles (cycle length 28 days) during the first 6 cycles and every 3 cycles thereafter. Scans were read by one independent reader per modality for the entire patient case and no adjudication was required.

Pre-specified secondary endpoints included time to first opiate use for cancer pain, time to initiation of cytotoxic chemotherapy, time to deterioration in ECOG performance score by ≥ 1 point and time to PSA progression based on PCWG-2 criteria[14]. In addition, patient reported outcome (PRO) pain data were obtained on day 1 of each 28-day cycle and at the end of treatment using the BPI-SF instrument.

Statistical Plan

The overall significance level was controlled at a 2-sided alpha of 0.05, which was split between the co-primary endpoints rPFS (0.01) and OS (0.04). A single rPFS analysis was planned after the occurrence of 378 rPFS events. The analysis of OS used a group sequential testing design with 3 interim analyses and 1 final analysis planned after 15%, 40%, 55% and 100% (final) of the total death events had occurred, respectively. The primary analysis of rPFS was planned to coincide with the first interim analysis of OS. To maintain an overall significance level of 0.04, a Lan-DeMets implementation of the O’Brien-Fleming alpha spending function was used in the OS hypothesis testing. Secondary endpoints were compared between treatment groups according to Hochberg's test procedure at an overall 2-sided 0.05 level of significance.

The intent-to-treat (ITT) population of all randomized patients, regardless of the actual treatment received, was used for all efficacy analyses. The safety population consisted of all patients who received at least one dose of study drug or placebo.

Patient Baseline Characteristics
U.S. FDA Approval Summary: Abiraterone Acetate

The trial enrolled 1,088 patients from 151 study centers in the U.S., Europe, Australia and Canada. U.S. sites accounted for 43% of accrual. Patient demographics were balanced between the treatment arms. Patients were predominately Caucasian (95%) with a median age of 70 years. The ECOG performance status was 0 for 76% of patients, and 1 for 24% of patients. The majority of patients were classified as asymptomatic with a baseline pain assessment of 0-1 in 69% of patients on the AA arm and 65% of placebo patients. Key disease characteristics were well balanced. The median PSA was 40 ng/mL, 52% of patients had Gleason Score of $\geq 8$ and 81% had bone metastases.

Efficacy Results

The results for the co-primary efficacy endpoints are presented in Table 1. There was a statistically significant improvement in rPFS favoring the AA arm with a hazard ratio of 0.43 (95% CI: 0.35, 0.52; p<0.0001). The median time to radiographic progression or death was 8.3 months in the placebo arm and had not been reached in the AA arm. The rPFS benefit was seen across all eight pre-specified subgroups analyzed. Agreement of rPFS events between investigator and independent review was balanced between the arms at approximately 78%. The rPFS analysis results by investigator and IRC were consistent. Multiple sensitivity analyses, including adding unequivocal clinical progression as an event, were supportive of the primary rPFS analysis.

At the second interim analysis of OS conducted at 43% of events, the hazard ratio of 0.75 favored the AA arm (95% CI: 0.61, 0.93; p= 0.01). However, this result did not cross the pre-defined O’Brien-Fleming boundary for statistical significance. Based on this data, the IDMC unanimously recommended unblinding the treatment and allowing subjects in the placebo group to cross over to receive AA. The pre-specified third interim analysis of OS was submitted to the FDA during the review and demonstrated persistence of the survival trend (}
U.S. FDA Approval Summary: Abiraterone Acetate

Figure 1 Legend

Figure 1) favoring AA, with a median OS of 35.3 months versus 30.1 months in the AA and placebo-containing arms, respectively (HR 0.79; 95% CI: 0.66, 0.96). At the time of this interim analysis of OS there was no significant imbalance in subsequent cancer-directed therapies that would favor the AA arm. Fourteen percent of the placebo arm and 7% of patients on the AA arm had received continued or subsequent AA.

All pre-specified secondary endpoints showed statistically significant improvements in favor of AA (Table 2). Exploratory analyses of time to pain progression using PRO pain scores were supportive of the time to initiation of opiate pain medication. The cumulative patient compliance rate for completion of the PRO pain instrument was 95% or higher at any given point during treatment.

Safety Results

This sNDA review benefited from analysis of a large safety database consisting of two randomized, phase 3, placebo-controlled clinical trials (COU-AA-302 and -301) as well as post-marketing safety surveillance databases from both the applicant and the FDA.

COU-AA-302 (Chemotherapy-Naïve Patients):
The COU-AA-302 trial data confirmed the known toxicity profile of AA. The median treatment duration was 13.8 months versus 8.3 months in the AA and placebo arms, respectively. The majority of the common adverse reactions were Grade 1 or 2. Ten percent of patients taking AA experienced an adverse event leading to treatment discontinuation compared with 8% for placebo. The most common reason for treatment discontinuation in the AA arm was a hepatic adverse event (2.2%). The incidence of grade 3 or higher ALT was 6.1% versus 0.7% in the AA and placebo arms, respectively. Consistent with AA’s mechanism of action, mineralocorticoid excess occurred more commonly in the AA arm. Hypokalemia (17.2%), hypertension (21.6%) and fluid retention/edema (25.1%) events were largely grade 1-2 with grade 3 events occurring at an incidence of 2.8%, 3.9% and 0.4%, respectively. Adrenocortical insufficiency was seen in two patients on each arm.
U.S. FDA Approval Summary: Abiraterone Acetate

Combined Phase 3 and Post-Marketing Safety Data:

Combining the COU-AA-301 and -302 phase 3 clinical trial data provided a safety dataset of 1,333 patients receiving AA (1,000 mg daily) and 934 receiving placebo. All patients received 5 mg of prednisone by mouth twice daily. The most common adverse drug reactions (≥10%) reported in the two randomized clinical trials were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion. In the combined phase 3 data, cardiac failure occurred more commonly in patients treated with AA compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking AA and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group. There was not an appreciable increase in the reporting of arrhythmias or cardiac ischemia in the AA arm based on the combined phase 3 data. The results regarding cardiac failure were included in the safety section of the FDA label.

Hepatic toxicity was also reviewed over the cumulative safety database. There were no cases meeting Hy’s Law for drug-induced liver injury in randomized clinical studies, but 2 cases were reported in the post-marketing period as of September 2013. There were no drug-related hepatic deaths reported. Review of post-marketing surveillance data did not reveal any new safety signals at the time of the sNDA review. Tables of adverse drug reactions and laboratory abnormalities can be found in the updated FDA-approved label for abiraterone acetate. [16]

Discussion

While an improvement in asymptomatic rPFS alone may not have been sufficient evidence for regular approval, there were several key components of this application that increased the FDA's confidence that the observed improvement in rPFS was likely to be predictive of meaningful clinical benefit. First, AA was an approved drug based on a statistically and clinically significant improvement in OS in the post-docetaxel setting and there was a trend in improved OS favoring AA in the COU-AA-302 chemotherapy-naïve trial. Second, the absolute and relative magnitude of effect on rPFS was large and was seen across pre-specified subgroup analyses. Third, internal consistency was demonstrated by multiple key
U.S. FDA Approval Summary: Abiraterone Acetate

secondary endpoints including two endpoints which were considered clinically meaningful to patients; the time to opiate use for cancer pain and the time to initiation of cytotoxic chemotherapy. In addition, PRO pain data were captured with high compliance in this large blinded clinical trial, and time to pain progression analyzed using multiple definitions was supportive of clinical benefit. Finally, the toxicity profile was felt to be favorable and well described based on data from two large placebo-controlled clinical trials, as well as post-marketing safety surveillance data.

Accurately measuring radiographic progression in mCRPC is challenging when compared to other solid tumor malignancies. This is in large part because prostate cancer metastases are located in bone in approximately 80-90% of patients, and the interpretation of bone scans is limited by poor resolution, variations in technique and false positive findings.[17] Because lesions seen on bone scan are not considered measurable using current technology, bone scan progression relies on the appearance of new lesions which may be complicated by the potential for transient increases in bone scan uptake seen early in treatment, the so-called “flare phenomena”. This effect has been reported to occur with AA and is taken into account in the PCWG-2 progression criteria.[18] While mitigating false positive progression from bone scan flare, PCWG-2 criteria necessarily adds significant complexity to the interpretation of radiographic progression events in mCRPC.

Highlighting the challenges with bone scan interpretation, the FDA review revealed that in COU-AA-302, radiologic reviewers documented image quality issues 3 times more commonly with bone scans when compared to CT/MRI studies. In addition, the likelihood of the radiologist being unable to make a progression determination by bone scan (progression or not progression) increased to as high as 19% of all follow up bone scans as the number of baseline bone lesions increased (Table 3). Importantly, the extent of bone metastases at baseline was balanced between the arms. Interestingly, inter- and intra-reviewer agreement was higher for bone scans than for CT/MRI, although these results were from a small subset of patients. How these differences in PCWG-2 progression affect the overall ability of rPFS to predict meaningful clinical benefit such as OS in mCRPC is uncertain. While this uncertainty does not preclude the use of rPFS as a primary or co-
U.S. FDA Approval Summary: Abiraterone Acetate

primary endpoint, it must be taken into account during the benefit:risk assessment of a regulatory submission.

In summary, FDA review of the sNDA for AA concluded that treatment with AA offers a favorable risk-benefit profile for patients with mCRPC regardless of docetaxel use. The degree to which radiographic PFS predicts meaningful benefit in mCRPC remains unclear and requires further study. Approval based on this endpoint will rely on a large absolute and relative magnitude of effect as well as internal consistency among carefully selected key secondary endpoints in the context of an acceptable safety profile. Adequately captured patient-reported pain data can provide added evidence of clinical benefit. Regardless of the primary endpoint selected, an analysis of overall survival should be included in any clinical trial intended to support regulatory approval in CRPC patients.

Reference List


U.S. FDA Approval Summary: Abiraterone Acetate


U.S. FDA Approval Summary: Abiraterone Acetate
Tables and Figures:

Table 1: Primary Endpoint Results for COU-AA-302

<table>
<thead>
<tr>
<th>Radiographic Progression Free Survival (rPFS), per Independent Radiologic Review</th>
<th>Abiraterone Acetate (N=546)</th>
<th>Placebo (N=542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS Events</td>
<td>150 (28%)</td>
<td>251 (46%)</td>
</tr>
<tr>
<td>Progression by bone scan only</td>
<td>57</td>
<td>79</td>
</tr>
<tr>
<td>Progression by CT/MRI only</td>
<td>66</td>
<td>115</td>
</tr>
<tr>
<td>Progression by both bone scan and CT/MRI</td>
<td>18</td>
<td>46</td>
</tr>
<tr>
<td>Death without progression</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Censored</td>
<td>396 (72%)</td>
<td>291 (54%)</td>
</tr>
<tr>
<td>Median rPFS in months (95% CI)</td>
<td>NR (11.7, NR)</td>
<td>8.3 (8.1, 8.5)</td>
</tr>
<tr>
<td>p value a</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI) b</td>
<td>0.43 (0.35, 0.52)</td>
<td></td>
</tr>
</tbody>
</table>

Overall Survival (OS)

2nd Interim OS Analysis

| Deaths (%) | 147 (27%) | 186 (34%) |
| Median OS in months (95% CI) | NR | 27.2 (25.9, NR) |
| p value a | 0.01* | |
| Hazard ratio (95% CI) b | 0.75 (0.61, 0.93) | |

Updated 3rd Interim OS Analysis

| Deaths (%) | 200 (37%) | 234 (43%) |
| Median OS in months (95% CI) | 35.3 (31.2, 35.3) | 30.1 (27.3, 34.1) |
| p value a | 0.015** | |
| Hazard ratio (95% CI) b | 0.79 (0.66, 0.96) | |

NR – Not Reached

* Result did not meet the O’Brien-Fleming boundary for significance of 0.0008.
** Result did not meet the O’Brien-Fleming boundary for significance of 0.0035.

a P-value is derived from a log-rank test stratified by ECOG performance status score (0 vs 1).

b Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors abiraterone.
# U.S. FDA Approval Summary: Abiraterone Acetate

Table 2: Pre-specified Secondary Endpoint Results for COU-AA-302

<table>
<thead>
<tr>
<th>Time to Endpoints</th>
<th>Abiraterone Acetate (N=546)</th>
<th>Placebo (N=542)</th>
<th>Hazard Ratio (95% CI) and p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to Opiate Use for Cancer Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events n (%)</td>
<td>183 (34%)</td>
<td>235 (43%)</td>
<td></td>
</tr>
<tr>
<td>Median in Months (95% CI)</td>
<td>NR (28.3, NR)</td>
<td>23.7 (20.2, NR)</td>
<td>0.69 (0.57, 0.83); p=0.0001</td>
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<tr>
<td><strong>Time to Initiation of Cytotoxic Chemotherapy</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Events n (%)</td>
<td>220 (40%)</td>
<td>298 (55%)</td>
<td></td>
</tr>
<tr>
<td>Median in Months (95% CI)</td>
<td>25.2 (23.3, NR)</td>
<td>16.8 (14.6, 19.4)</td>
<td>0.58 (0.49, 0.69); p&lt;0.0001</td>
</tr>
<tr>
<td><strong>Time to ECOG Performance Status Deterioration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events n (%)</td>
<td>390 (71%)</td>
<td>411 (76%)</td>
<td></td>
</tr>
<tr>
<td>Median in Months (95% CI)</td>
<td>12.3 (11.3, 14.3)</td>
<td>10.9 (9.5, 11.8)</td>
<td>0.82 (0.71, 0.94); p=0.005</td>
</tr>
<tr>
<td><strong>Time to PSA Progression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events n (%)</td>
<td>339 (62%)</td>
<td>381 (70%)</td>
<td></td>
</tr>
<tr>
<td>Median in Months (95% CI)</td>
<td>11.1 (8.5, 11.2)</td>
<td>5.6 (5.4, 5.6)</td>
<td>0.49 (0.42, 0.57); p&lt;0.0001</td>
</tr>
</tbody>
</table>
U.S. FDA Approval Summary: Abiraterone Acetate

Table 3: Interpretation of Follow-up Bone Scans by Number of Baseline Lesions

<table>
<thead>
<tr>
<th></th>
<th>&lt;5 Lesions</th>
<th>5-9 Lesions</th>
<th>10-20 Lesions</th>
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<tr>
<td>NOT PD</td>
<td>2009</td>
<td>591</td>
<td>549</td>
<td>728</td>
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<tr>
<td>PD</td>
<td>114</td>
<td>60</td>
<td>69</td>
<td>56</td>
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<tr>
<td>UNK</td>
<td>8</td>
<td>13</td>
<td>29</td>
<td>138</td>
</tr>
</tbody>
</table>

PD: Progression of Disease, UNK: Unknown, radiologist unable to make a determination.

Figure 1 Legend

Figure 1: COU-AA-302 Kaplan-Meier Overall Survival Curves (3rd Interim Analysis). * Results did not meet predefined O’Brien-Fleming boundary for statistical significance.
Abiraterone: Median OS (95% CI) 35.3 mo. (31.2, 35.3)
Placebo: Median OS (95% CI) 30.1 mo. (27.3, 34.1)
HR (95% CI) 0.79 (0.66, 0.96)
Clinical Cancer Research

Abiraterone Acetate in Combination with Prednisone for the Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer: U.S. Food and Drug Administration Drug Approval Summary


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