

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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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 plus prednisone ($N = 546$) or placebo plus prednisone ($N = 542$). The coprimary 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 abiraterone acetate arm {HR, 0.43 [95% confidence interval (CI) 0.35–0.52]; $P < 0.0001$ }. A prespecified interim analysis demonstrated an improvement in OS favoring the abiraterone acetate 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 abiraterone acetate. Full approval was granted on the basis of 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 use 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 abiraterone acetate for patients with mCRPC who had received prior chemotherapy containing docetaxel. *Clin Cancer Res*; 19(24); 6650–6. ©2013 AACR.

Introduction

Despite significant therapeutic advances over the last decade, prostate cancer remains the second leading cause of cancer-related deaths in men in the United States (1). Two cytotoxic chemotherapy drugs improve survival in patients with metastatic castration-resistant prostate cancer (mCRPC), docetaxel (2–4) and cabazitaxel (5, 6). Although 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 is a 17 α -hydroxylase/C17,20-lyase (CYP17) inhibitor that acts on extragonadal testosterone production. The inhibition of CYP17 in 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 abiraterone acetate (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

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COU-AA-301 trial: a randomized, double-blind, placebo-controlled, multicenter phase III trial in 1,195 patients with mCRPC who had previously received docetaxel-based chemotherapy. Patients were randomly allocated (2:1) to receive either 1,000 mg of abiraterone acetate ($N = 797$) 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 prespecified interim analysis, there was a statistically and clinically significant improvement in OS favoring the abiraterone acetate arm [HR, 0.65; 95% confidence interval (CI), 0.54–0.77; $P < 0.0001$]. The median OS durations were 14.8 months and 10.9 months in the abiraterone acetate 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, interest has been expressed 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 the PCWG-2 criteria form the basis for measurement of radiographic progression-free survival (rPFS) in most contemporary mCRPC studies, including the COU-AA-302 trial (14).

In June 2012, the FDA received a supplemental new drug application (sNDA) for the use of abiraterone acetate in chemotherapy-naïve patients with mCRPC. This sNDA was the first regulatory submission for the treatment of mCRPC that used rPFS as a primary efficacy endpoint. The FDA review of this application is summarized in this report.

Chemistry

Abiraterone acetate is the active ingredient of Zytiga and is chemically designated as (3 β)-17-(3-pyridinyl)androst-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, nonhygroscopic, 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 *in vivo* to abiraterone, which irreversibly inhibits cytochrome P450 17 α -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.

Nonclinical toxicology studies conducted in rats and monkeys resulted in toxicities in the reproductive system

likely related to the pharmacologic activity of abiraterone acetate. These findings suggest that abiraterone acetate 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 abiraterone acetate on the eyes cannot be excluded as no cataracts were observed in monkeys after 39 weeks of abiraterone acetate 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.

Embryo–fetal developmental toxicology studies and carcinogenicity studies were not necessary for the proposed indication. Abiraterone and abiraterone acetate 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, abiraterone acetate was below detectable levels in more than 99% of plasma samples. The median time to maximum abiraterone concentrations (T_{max}) is 2 hours and the terminal half-life (mean \pm SD) is 12 ± 5 hours. A significant food effect has been observed for abiraterone acetate. In a single-dose healthy volunteer study, abiraterone C_{max} and $AUC_{0-\infty}$ (systemic exposure) increased up to 17- and 10-fold, respectively, in a fed state as compared with a fasted state. No food should be consumed for at least 2 hours before, and for at least 1 hour after abiraterone acetate 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 ($AUC_{0-\infty}$) was observed in subjects with mild ($n = 8$) and moderate ($n = 8$) baseline hepatic impairment, respectively, when compared with 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) by approximately 3-fold. Therefore, coadministration of abiraterone acetate 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 III clinical trial that randomly allocated

(1:1) 1,088 asymptomatic or mildly symptomatic patients with mCRPC to either 1,000 mg of abiraterone acetate 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 prostate-specific antigen (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 that 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 of 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 used 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 coprimary efficacy endpoints were OS and rPFS. OS 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 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 with baseline is observed <12 weeks from randomization and is confirmed by a second bone scan taken ≥ 6 weeks later showing additional ≥ 2 new lesions (a total of ≥ 4 new lesions compared with baseline); or
 - (b) the first bone scan with ≥ 2 new lesions compared with 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 with baseline).

Tumor assessments included CT/MRI and bone scan obtained every two cycles (cycle length, 28 days) during

the first six cycles and every three cycles thereafter. Scans were read by one independent reader per modality for the entire patient case and no adjudication was required.

Prespecified 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 two-sided α of 0.05, which was split between the coprimary 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 three interim analyses and one 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 α spending function was used in the OS hypothesis testing. Secondary endpoints were compared between treatment groups according to the Hochberg test procedure at an overall two-sided 0.05 level of significance.

The intent-to-treat 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

The trial enrolled 1,088 patients from 151 study centers in the United States, Europe, Australia, and Canada. U.S. sites accounted for 43% of accrual. Patient demographics were balanced between the treatment arms. Patients were predominantly 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 to 1 in 69% of patients on the abiraterone acetate arm and 65% of placebo patients. Key disease characteristics were well balanced. The median PSA was 40 ng/mL, 52% of patients had a Gleason score of ≥ 8 , and 81% had bone metastases.

Efficacy Results

The results for the coprimary efficacy endpoints are presented in Table 1. There was a statistically significant improvement in rPFS favoring the abiraterone acetate arm with an HR 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 abiraterone acetate arm. The rPFS benefit was seen across all

eight prespecified subgroups analyzed. Agreement of rPFS events between investigator and independent review was balanced between the arms at approximately 78%. The rPFS analysis results by the 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 HR of 0.75 favored the abiraterone acetate arm (95% CI, 0.61–0.93; $P = 0.01$). However, this result did not cross the predefined O'Brien-Fleming boundary for statistical significance. On the basis of these data, the IDMC unanimously recommended unblinding the treatment and allowing subjects in the placebo group to cross over to receive abiraterone acetate. The prespecified third interim analysis of OS was submitted to the FDA during the review and demonstrated persistence of the survival trend (Fig. 1) favoring abiraterone acetate, with a median OS of 35.3 months versus 30.1 months in the abiraterone acetate 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 abiraterone acetate arm. Fourteen percent of the placebo arm and 7% of patients on the abiraterone

acetate arm had received continued or subsequent abiraterone acetate.

All prespecified secondary endpoints showed statistically significant improvements in favor of abiraterone acetate (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 III, placebo-controlled clinical trials (COU-AA-302 and -301) as well as postmarketing 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 abiraterone acetate. The median treatment duration was 13.8 months versus 8.3 months in the abiraterone acetate and placebo arms, respectively. The majority of the common adverse reactions were grade 1 or 2. Ten percent of patients taking abiraterone acetate experienced an adverse event leading to treatment discontinuation compared with

Table 1. Primary endpoint results for COU-AA-302

	Abiraterone acetate (N = 546)	Placebo (N = 542)
Radiographic progression-free survival (rPFS), per independent radiologic review		
PFS events	150 (28%)	251 (46%)
Progression by bone scan only	57	79
Progression by CT/MRI only	66	115
Progression by both bone scan and CT/MRI	18	46
Death without progression	9	11
Censored	396 (72%)	291 (54%)
Median rPFS in months (95% CI)	NR (11.7–NR)	8.3 (8.1–8.5)
P value ^a	<0.0001	
HR (95% CI) ^b	0.43 (0.35–0.52)	
Overall survival (OS)		
Second 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 ^c	
HR (95% CI) ^b	0.75 (0.61–0.93)	
Updated third 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 ^d	
HR (95% CI) ^b	0.79 (0.66–0.96)	

Abbreviation: NR, not reached.

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

^bHR is derived from a stratified proportional hazards model. HR < 1 favors abiraterone.

^cResult did not meet the O'Brien-Fleming boundary for a significance of 0.0008.

^dResult did not meet the O'Brien-Fleming boundary for a significance of 0.0035.

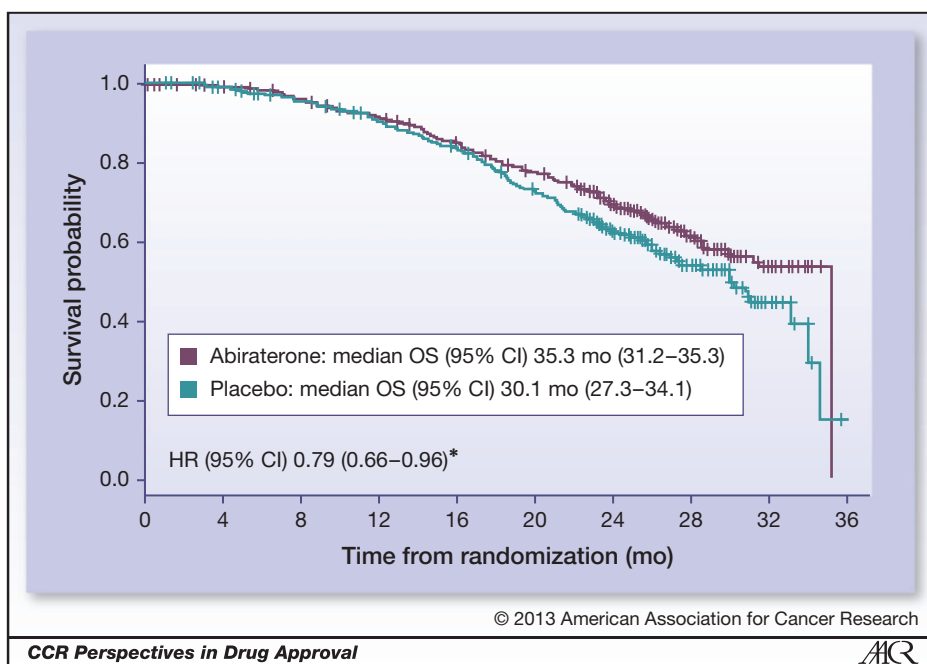


Figure 1. COU-AA-302 Kaplan-Meier overall survival curves (third interim analysis). *, Results did not meet predefined O'Brien-Fleming boundary for statistical significance.

8% for placebo. The most common reason for treatment discontinuation in the abiraterone acetate arm was a hepatic adverse event (2.2%). The incidence of grade 3 or higher alanine aminotransferase (ALT) was 6.1% versus 0.7% in the abiraterone acetate and placebo arms, respectively. Consistent with abiraterone acetate's mechanism of action, mineralocorticoid excess occurred more commonly in the abiraterone acetate 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.

Combined phase III and postmarketing safety data

Combining the COU-AA-301 and -302 phase III clinical trial data provided a safety dataset of 1,333 patients receiving abiraterone acetate (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 ($\geq 10\%$) 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 III data, cardiac failure occurred more commonly in patients treated with abiraterone acetate compared with patients on

Table 2. Prespecified secondary endpoint results for COU-AA-302

	Abiraterone acetate (N = 546)	Placebo (N = 542)
Time to opiate use for cancer pain		
Events, n (%)	183 (34%)	235 (43%)
Median, mo (95% CI)	NR (28.3–NR)	23.7 (20.2–NR)
HR (95% CI) and P value	0.69 (0.57–0.83); P = 0.0001	
Time to initiation of cytotoxic chemotherapy		
Events, n (%)	220 (40%)	298 (55%)
Median, mo (95% CI)	25.2 (23.3–NR)	16.8 (14.6–19.4)
HR (95% CI) and P value	0.58 (0.49–0.69); P < 0.0001	
Time to ECOG performance status deterioration		
Events, n (%)	390 (71%)	411 (76%)
Median, mo (95% CI)	12.3 (11.3–14.3)	10.9 (9.5–11.8)
HR (95% CI) and P value	0.82 (0.71–0.94); P = 0.005	
Time to PSA progression		
Events, n (%)	339 (62%)	381 (70%)
Median, mo (95% CI)	11.1 (8.5–11.2)	5.6 (5.4–5.6)
HR (95% CI) and P value	0.49 (0.42–0.57); P < 0.0001	

the placebo arm (2.1% vs. 0.7%). Grade 3–4 cardiac failure occurred in 1.6% of patients taking abiraterone acetate and led to five treatment discontinuations and two 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 abiraterone acetate arm based on the combined phase III data. The results about cardiac failure were included in the safety section of the FDA label.

Hepatic toxicity was also reviewed over the cumulative safety database. No cases met Hy's law for drug-induced liver injury in randomized clinical studies, but two cases were reported in the postmarketing period as of September 2013. No drug-related hepatic deaths were reported. A review of postmarketing 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

Although 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, abiraterone acetate was an approved drug based on a statistically and clinically significant improvement in OS in the postdocetaxel setting and there was a trend in improved OS favoring abiraterone acetate in the COU-AA-302 chemotherapy-naïve trial. Second, the absolute and relative magnitude of effect on rPFS was large and was seen across prespecified subgroup analyses. Third, internal consistency was demonstrated by multiple key secondary endpoints, including two endpoints that 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 on the basis of data from two large placebo-controlled clinical trials, as well as postmarketing safety surveillance data.

Accurately measuring radiographic progression in mCRPC is challenging when compared with other solid tumor malignancies. This is, in large part, because prostate cancer metastases are located in bone in approximately 80% to 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 abiraterone acetate 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 add 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 three times more commonly with bone scans when compared with 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 intrareviewer 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. Although this uncertainty does not preclude the use of rPFS as a primary or coprimary endpoint, it must be taken into account during the benefit–risk assessment of a regulatory submission.

In summary, FDA review of the sNDA for abiraterone acetate concluded that treatment with abiraterone acetate 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-

Table 3. Interpretation of follow-up bone scans by number of baseline lesions

	<5 Lesions		5–9 Lesions		10–20 Lesions		>20 Lesions	
	N = 2,131 scans		N = 591 scans		N = 549 scans		N = 728 scans	
NOT PD	2,009	94.3%	518	87.6%	451	82.1%	534	73.4%
PD	114	5.3%	60	10.2%	69	12.6%	56	7.7%
UNK	8	0.4%	13	2.2%	29	5.3%	138	19.0%

Abbreviations: PD, progression of disease; UNK, unknown, radiologist unable to make a determination.

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reported pain data can provide added evidence of clinical benefit. Regardless of the primary endpoint selected, an analysis of OS should be included in any clinical trial intended to support regulatory approval in patients with CRPC.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: P.G. Kluetz, Y.-M. Ning, R. Pazdur

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y.-M. Ning

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References

- Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013;63:11–30.
- Dagher R, Li N, Abraham S, Rahman A, Sridhara R, Pazdur R. Approval summary: docetaxel in combination with prednisone for the treatment of androgen-independent hormone-refractory prostate cancer. *Clin Cancer Res* 2004;10:8147–51.
- Petrylak DP, Tangen CM, Hussain MH, Lara PN, Jones JA, Taplin ME, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;351:1513–20.
- Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502–12.
- Food and Drug Administration [Internet]. FDA label for cabazitaxel. [cited 2013 Sep 12]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/201023s003lbl.pdf.
- de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010;376:1147–54.
- Yuan X, Cai C, Chen S, Chen S, Yu Z, Balk SP. Androgen receptor functions in castration-resistant prostate cancer and mechanisms of resistance to new agents targeting the androgen axis. *Oncogene*. 2013 Jul 10. [Epub ahead of print].
- Tsao CK, Galsky MD, Small AC, Yee T, Oh WK. Targeting the androgen receptor signalling axis in castration-resistant prostate cancer (CRPC). *BJU Int* 2012;110:1580–8.
- Attard G, Reid AH, Auchus RJ, Hughes BA, Cassidy AM, Thompson E, et al. Clinical and biochemical consequences of CYP17A1 inhibition with abiraterone given with and without exogenous glucocorticoids in castrate men with advanced prostate cancer. *J Clin Endocrinol Metab* 2012;97:507–16.
- Food and Drug Administration [Internet]. FDA medical review of abiraterone acetate. [cited 2013 Sep 12]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist.
- de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364:1995–2005.
- Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2012;13:983–92.
- Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol* 1999;17:3461–7.
- Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008;26:1148–59.
- Atkinson TM, Mendoza TR, Sit L, Passik S, Scher HI, Cleeland C, et al. The Brief Pain Inventory and its "pain at its worst in the last 24 hours" item: clinical trial endpoint considerations. *Pain Med* 2010;11:337–46.
- Food and Drug Administration [Internet]. FDA label for abiraterone acetate [cited 2013 Sep 12]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202379s005lbl.pdf.
- Dawson NA, McLeod DG. The assessment of treatment outcomes in metastatic prostate cancer: changing endpoints. *Eur J Cancer* 1997;33:560–5.
- Ryan CJ, Shah S, Efstathiou E, Smith MR, Taplin ME, Bubley GJ, et al. Phase II study of abiraterone acetate in chemotherapy-naïve metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. *Clin Cancer Res* 2011;17:4854–61.