ORIGINAL ARTICLE

Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy

Charles J. Ryan, M.D., Matthew R. Smith, M.D., Ph.D., Johann S. de Bono, M.B., Ch.B., Ph.D., Arturo Molina, M.D., Christopher J. Logothetis, M.D., Paul de Souza, M.B., Ph.D., Karim Fizazi, M.D., Ph.D., Paul Mainwaring, M.D., Josep M. Piulats, M.D., Ph.D., Siobhan Ng, M.D., Joan Carles, M.D., Peter F.A. Mulders, M.D., Ph.D., Ethan Basch, M.D., Eric J. Small, M.D., Fred Saad, M.D., Dirk Schrijvers, M.D., Ph.D., Hendrik Van Poppel, M.D., Ph.D., Som D. Mukherjee, M.D., Henrik Suttmann, M.D., Winald R. Gerritsen, M.D., Ph.D., Thomas W. Flaig, M.D., Daniel J. George, M.D., Evan Y. Yu, M.D., Eleni Efstathiou, M.D., Ph.D., Allan Pantuck, M.D., Eric Winquist, M.D., Celestia S. Higano, M.D., Mary-Ellen Taplin, M.D., Youn Park, Ph.D., Thian Kheoh, Ph.D., Thomas Griffin, M.D., Howard I. Scher, M.D., and Dana E. Rathkopf, M.D., for the COU-AA-302 Investigators*

ABSTRACT

BACKGROUND

Abiraterone acetate, an androgen biosynthesis inhibitor, improves overall survival in patients with metastatic castration-resistant prostate cancer after chemotherapy. We evaluated this agent in patients who had not received previous chemotherapy.

METHODS

In this double-blind study, we randomly assigned 1088 patients to receive abiraterone acetate (1000 mg) plus prednisone (5 mg twice daily) or placebo plus prednisone. The coprimary end points were radiographic progression-free survival and overall survival.

RESULTS

The study was unblinded after a planned interim analysis that was performed after 43% of the expected deaths had occurred. The median radiographic progression-free survival was 16.5 months with abiraterone–prednisone and 8.3 months with prednisone alone (hazard ratio for abiraterone–prednisone vs. prednisone alone, 0.53; 95% confidence interval [CI], 0.45 to 0.62; P<0.001). Over a median follow-up period of 22.2 months, overall survival was improved with abiraterone–prednisone (median not reached, vs. 27.2 months for prednisone alone; hazard ratio, 0.75; 95% CI, 0.61 to 0.93; P=0.01) but did not cross the efficacy boundary. Abiraterone–prednisone showed superiority over prednisone alone with respect to time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, prostate-specific antigen progression, and decline in performance status. Grade 3 or 4 mineralocorticoid-related adverse events and abnormalities on liver-function testing were more common with abiraterone–prednisone.

CONCLUSIONS

Abiraterone improved radiographic progression-free survival, showed a trend toward improved overall survival, and significantly delayed clinical decline and initiation of chemotherapy in patients with metastatic castration-resistant prostate cancer. (Funded by Janssen Research and Development, formerly Cougar Biotechnology; ClinicalTrials.gov number, NCT00887198.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Ryan at the Genitourinary Medical Oncology Program, UCSF Helen Diller Family Comprehensive Cancer Center, 1600 Divisadero St., San Francisco, CA 94115, or at ryanc@medicine.ucsf.edu.

*Additional investigators in the COU-AA-302 study are listed in the Supplementary Appendix, available at NEJM.org.

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Metastatic castration-resistant prostate cancer, defined by tumor growth despite a testosterone level of less than 50 ng per deciliter (1.7 nmol per liter), causes approximately 258,400 deaths annually worldwide.[1,2] Death of patients with this condition, which typically occurs within 24 to 48 months after the onset of castration resistance, is commonly preceded by a sequence of landmark events associated with deterioration of overall health and worsening symptoms (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[3-7]

Among the treatment options for patients with metastatic castration-resistant prostate cancer who have not undergone chemotherapy are a variety of second-line hormonal manipulations[8] that produce responses in many patients; however, none of these options have been shown to delay progression or prolong life. Subsequent to such second-line therapy, a standard approach is docetaxel chemotherapy, which has a survival benefit,[4] although many patients with metastatic castration-resistant prostate cancer never receive it.[9,10] Owing to the limited use of chemotherapy in the management of metastatic castration-resistant prostate cancer, there is an unmet need for effective therapy that delays or prevents the landmark events that characterize the morbidity associated with this cancer.[2] One treatment, sipuleucel-T, an immunotherapy, is associated with a modest survival benefit but without tumor regression, symptom relief, or delay in disease progression.[11]

Abiraterone acetate is a first-in-class inhibitor of cytochrome P-450c17, a critical enzyme in extragonadal and testicular androgen synthesis.[12-18] Abiraterone plus low-dose prednisone improves survival in patients with metastatic castration-resistant prostate cancer who have already received docetaxel,[19] and the combination therapy has received regulatory approval for this indication. Phase 1 and 2 studies in patients who have not received chemotherapy, however, have shown a high proportion of durable responses, suggesting that the benefits of abiraterone may be optimal in this patient group.[20-22] In our randomized, phase 3 study, we evaluated the effects of abiraterone plus prednisone on radiographic progression-free survival, overall survival, increase in pain, and clinically relevant measures of disease progression in patients with progressive metastatic castration-resistant prostate cancer who had not received chemotherapy and in whom clinically significant cancer-related symptoms had not developed.

Methods

Study Oversight and Conduct

This study was designed by academic and sponsor-employed investigators. The lead academic author initially drafted the manuscript with sponsor input, and all coauthors subsequently provided input and approval. The sponsor provided funding for editorial assistance with an early draft of the manuscript. All authors made the decision to submit the manuscript for publication. The database was held at a third-party contract clinical research organization (CRO), and queries were issued by both the sponsor and the CRO staff. The independent CRO statistician provided the results of analysis to an independent data and safety monitoring committee, whose members were invited by the sponsor. The committee monitored safety at regular intervals and evaluated efficacy and safety at prespecified interim analyses. At the time of unblinding, analyses were performed by statisticians who were employees of the sponsor. The authors assume responsibility for the completeness and integrity of the data and the fidelity of the study to the protocol and statistical analysis plan (available at NEJM.org).

The review boards at all participating institutions approved the study, which was conducted according to the principles of the Declaration of Helsinki, the International Conference on Harmonisation, and the Guidelines for Good Clinical Practice. All patients provided written informed consent.

Patients

Eligibility criteria were an age of 18 years or older; metastatic, histologically or cytologically confirmed adenocarcinoma of the prostate; prostate-specific antigen (PSA) progression according to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria[2] or radiographic progression in soft tissue or bone with or without PSA progression; ongoing androgen deprivation with a serum testosterone level of less than 50 ng per deciliter (1.7 nmol per liter); an Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1 (asymptomatic or restricted in strenuous activity but ambulatory, respectively); no symp-

toms or mild symptoms, as defined according to the Brief Pain Inventory–Short Form (BPI-SF) (scores of 0 to 1 [asymptomatic] or 2 to 3 [mildly symptomatic], respectively); and hematologic and chemical laboratory values that met predefined criteria. Previous therapy with an antiandrogen was required. Patients with visceral metastases or patients who had received previous therapy with ketoconazole lasting more than 7 days were excluded.

STUDY DESIGN AND TREATMENT

In this multinational, double-blind, placebo-controlled study, patients were randomly assigned in a 1:1 ratio to receive abiraterone acetate plus prednisone or placebo plus prednisone. Patients were stratified according to the baseline ECOG performance status grade (0 vs. 1). Patients in the abiraterone–prednisone group received abiraterone at a dose of 1 g (administered as four 250-mg tablets), and patients in the prednisone-alone group received four placebo tablets once daily at least 1 hour before and 2 hours after a meal. All patients received prednisone at a dose of 5 mg orally twice daily. Safety and dosing compliance were evaluated during each study visit, at treatment discontinuation if applicable, and at the end-of-study visit.

END POINTS

The coprimary efficacy end points were radiographic progression-free survival and overall survival, defined as the time from randomization to death from any cause. Radiographic progression-free survival was determined by an independent radiologist who was unaware of study-group assignments, and dates of death were confirmed. Radiographic progression-free survival was defined as freedom from death from any cause; freedom from progression in soft-tissue lesions as measured with the use of computed tomography (CT) or magnetic resonance imaging (MRI), defined as "progressive disease" according to modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria; or progression on bone scanning according to criteria adapted from the PCWG2 (Table S1 in the Supplementary Appendix).[2] Changes in PSA level were not included in the definition of radiographic progression-free survival.

The prespecified secondary end points were times to opiate use for cancer-related pain, to initiation of cytotoxic chemotherapy, to a decline in ECOG performance status, and to PSA progression (on the basis of PCWG2 criteria).[2] Other end points included radiographic progression-free survival as measured by investigators (rather than a blinded review), PSA response rate (≥50% decline in PSA level from baseline), rate of objective response according to RECIST criteria, and health-related quality of life, as measured by means of patients' reports of pain and functional status. An increase in pain was defined as an increase in the baseline pain score at two consecutive visits by 30% or more, as measured by the average of the pain scores on the BPI-SF (range, 0 to 10, with higher scores indicating worse average pain), without a decrease in analgesic use. A decline in functional status was defined as a decline of 10 or more points in the Functional Assessment of Cancer Therapy–Prostate (FACT-P) total score at any visit (range, 0 to 156, with higher scores indicating better overall quality of life).

ASSESSMENTS

Efficacy assessments included sequential radiographic imaging to assess radiographic progression-free survival (CT or MRI and bone scanning) and measurement of PSA levels.[2] CT or MRI and bone scanning were performed every 8 weeks during the first 24 weeks and every 12 weeks thereafter. All patients underwent serial monitoring of blood chemical levels, hematologic values, coagulation studies, serum lipids, and kidney function. Cardiac safety was monitored by means of serial electrocardiography. The left ventricular ejection fraction was measured at baseline. Patient-reported outcomes were assessed at baseline and at every visit with the use of the BPI-SF. FACT-P questionnaires were completed every third visit.

STATISTICAL ANALYSIS

The overall level of significance for the study was 0.05, allocated between the coprimary end points of radiographic progression-free survival (0.01) and overall survival (0.04). A single analysis was planned for the coprimary end point of radiographic progression-free survival on the basis of a blinded review by the central radiologist after 378 progression-free events, which would provide a statistical power of 91% to detect a hazard

ratio of 0.67 at a two-tailed level of significance of 0.01. The results of subsequent analyses of this end point based on investigator assessment are also reported. For the coprimary end point of overall survival, 773 events were required to detect a hazard ratio of 0.80 at a two-tailed significance level of 0.04 with a statistical power of 85%.

Three interim analyses were planned for overall survival, with the first analysis planned after the observation of approximately 116 of the required 773 events (15%) (in conjunction with the independent review of radiographic progression-free survival), the second analysis planned after 311 events (40%), and the third analysis planned after 425 events (55%); a final analysis was planned for after 773 events had occurred (Table S2 in the Supplementary Appendix). The group-sequential design was used for the overall survival end point with the use of the O'Brien–Fleming boundaries as implemented by the Lan–DeMets alpha spending method (Table S3 in the Supplementary Appendix).

We planned to enroll approximately 1000 patients in the study. The primary statistical method of comparison for the time-to-event end points was the stratified log-rank test with stratification according to the baseline ECOG score. The Cox proportional-hazards model was used to estimate the hazard ratio and its associated confidence interval. The Hochberg procedure was used to adjust for multiplicity testing of the secondary efficacy end points.[23] The strength of association between radiographic progression-free survival and overall survival was evaluated by means of Spearman's correlation coefficient estimated with the use of the Clayton copula.[24]

RESULTS

PATIENTS AND TREATMENT

From April 2009 through June 2010, we randomly assigned 1088 patients to receive study treatment: abiraterone plus prednisone in 546 patients and placebo plus prednisone in 542 patients (Fig. S2 in the Supplementary Appendix). The clinical cutoff date for the blinded central radiologic review of radiographic progression-free survival and the first overall survival interim analysis was December 20, 2010 (at which time 13% of deaths had occurred), and the clinical cutoff date for the second interim analysis of overall survival was December 20, 2011 (at which time 43% of deaths had occurred). The median follow-up duration for all patients was 22.2 months. Baseline demographic characteristics were well balanced between the two study groups (Table S4 in the Supplementary Appendix).

PRIMARY END POINTS

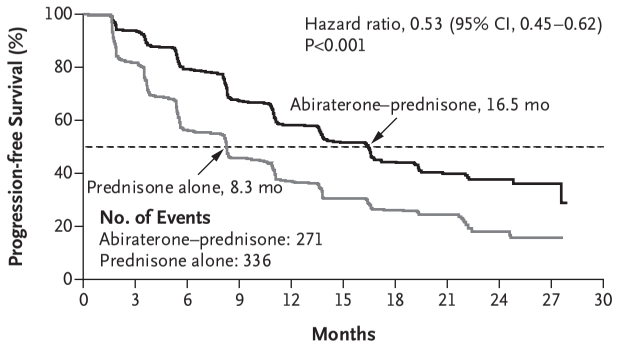
Radiographic Progression-free Survival

On the basis of the blinded central radiologic review, at the time of the first interim analysis, treatment with abiraterone plus prednisone, as compared with placebo plus prednisone, resulted in a 57% reduction in the risk of radiographic progression or death (median not reached vs. median of 8.3 months; hazard ratio for abiraterone–prednisone vs. prednisone alone, 0.43; 95% confidence interval [CI], 0.35 to 0.52; P<0.001). At the time of the second interim analysis, the median time to radiographic progression-free survival on the basis of investigator assessment was 16.5 months in the abiraterone–prednisone group and 8.3 months in the prednisone-alone group (hazard ratio, 0.53; 95% CI, 0.45 to 0.62; P<0.001) (Fig. 1A). The treatment effect of abiraterone on radiographic progression-free survival was consistently favorable (all hazard ratios, <1.0) across all prespecified subgroups (Fig. 1C).

Overall Survival

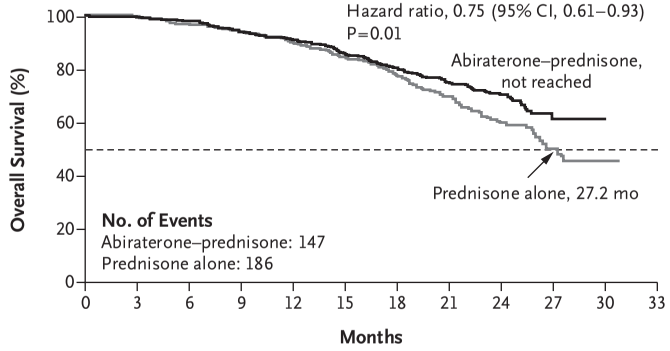
The planned interim analysis of overall survival was performed after 333 deaths (43% of 773 events) were observed. More deaths were observed in the prednisone-alone group than in the abiraterone–prednisone group (186 of 542 patients [34%] vs. 147 of 546 patients [27%]). Median overall survival was not reached for the abiraterone–prednisone group and was 27.2 months (95% CI, 26.0 to not reached) in the prednisone-alone group. There was a 25% decrease in the risk of death in the abiraterone–prednisone group (hazard ratio, 0.75; 95% CI, 0.61 to 0.93; P=0.01) (Fig. 1B), indicating a strong trend toward improved survival with abiraterone–prednisone; however, the prespecified boundary for significance (P≤0.001) was not reached at the observed number of events. The treatment effect of abiraterone on overall survival was consistently favorable (all hazard ratios, <1.0) across all prespecified subgroups (Fig. 1D). Radiographic progression-free survival was positively correlated with overall

A Radiographic Progression-free Survival



No. at Risk											
Abiraterone–prednisone	546	485	389	311	240	195	155	85	38	9	0
Prednisone alone	542	406	244	177	133	100	80	37	14	1	0

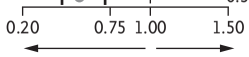
B Overall Survival



No. at Risk												
Abiraterone–prednisone	546	538	524	503	482	452	412	258	120	27	0	0
Prednisone alone	542	534	509	493	465	437	387	237	106	25	2	0

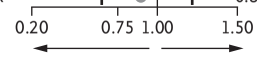
C Radiographic Progression-free Survival

Subgroup	Abiraterone–Prednisone (median, mo)	Prednisone Alone (median, mo)	Hazard Ratio (95% CI)
All patients	16.5	8.3	0.53 (0.45–0.62)
Baseline ECOG			
0	16.4	8.3	0.56 (0.47–0.67)
1	18.0	7.4	0.43 (0.30–0.61)
Baseline BPI-SF			
0–1	16.7	8.3	0.53 (0.43–0.65)
2–3	10.7	7.4	0.61 (0.44–0.83)
Bone metastases only at entry			
Yes	20.7	11.1	0.55 (0.42–0.71)
No	11.2	5.7	0.51 (0.41–0.62)
Age			
<65 yr	16.6	8.1	0.48 (0.35–0.66)
≥65 yr	16.5	8.3	0.55 (0.46–0.67)
≥75 yr	14.9	8.2	0.64 (0.48–0.84)
Baseline PSA above median			
Yes	12.8	5.8	0.54 (0.43–0.68)
No	19.4	10.2	0.48 (0.38–0.61)
Baseline LDH above median			
Yes	14.1	5.6	0.47 (0.38–0.60)
No	16.6	10.8	0.57 (0.45–0.71)
Baseline ALK-P above median			
Yes	13.6	5.6	0.54 (0.43–0.68)
No	19.4	9.7	0.48 (0.38–0.61)
Region			
North America	16.6	8.2	0.51 (0.40–0.63)
Other	16.3	8.3	0.56 (0.45–0.71)



D Overall Survival

Subgroup	Abiraterone–Prednisone (median, mo)	Prednisone Alone (median, mo)	Hazard Ratio (95% CI)
All patients	NR	27.2	0.75 (0.61–0.93)
Baseline ECOG			
0	NR	27.2	0.71 (0.55–0.92)
1	NR	26.4	0.86 (0.58–1.28)
Baseline BPI-SF			
0–1	NR	27.2	0.71 (0.54–0.94)
2–3	25.5	NR	0.87 (0.59–1.29)
Bone metastases only at entry			
Yes	NR	27.2	0.68 (0.48–0.96)
No	NR	27.5	0.81 (0.61–1.06)
Age			
<65 yr	NR	NR	0.80 (0.51–1.24)
≥65 yr	NR	26.4	0.73 (0.57–0.94)
≥75 yr	NR	23.8	0.71 (0.51–1.00)
Baseline PSA above median			
Yes	26.9	23.8	0.72 (0.43–0.94)
No	NR	NR	0.77 (0.38–1.09)
Baseline LDH above median			
Yes	NR	23.6	0.69 (0.53–0.91)
No	NR	27.5	0.79 (0.55–1.12)
Baseline ALK-P above median			
Yes	NR	23.6	0.79 (0.60–1.04)
No	NR	27.5	0.66 (0.46–0.94)
Region			
North America	NR	27.2	0.66 (0.49–0.88)
Other	NR	NR	0.89 (0.65–1.22)



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