ORIGINAL ARTICLE

Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy

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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.)

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This article was published on December 10, 2012, and updated on January 17, 2013, at NEJM.org.

N Engl J Med 2013;368:138-48.
DOI: 10.1056/NEJMoa1209096

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

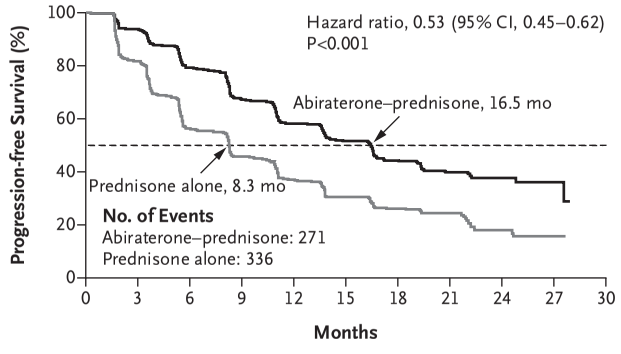
Radiographic Progression-free Survival

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

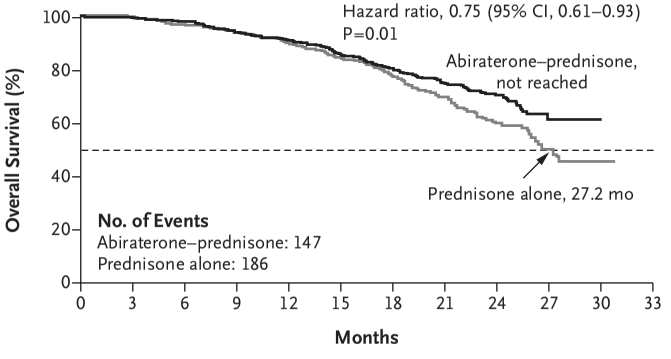
A Radiographic Progression-free Survival



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

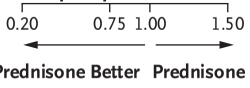


No. at Risk

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)

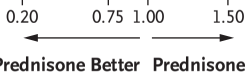


Figure 1 (facing page). Kaplan–Meier Estimates of Radiographic Progression-free Survival, Overall Survival, and Subgroup Analyses at the Second Interim Analysis.

Panels A and C show data for radiographic progression-free survival on the basis of investigator review, and Panels B and D show data for overall survival. The dashed line in Panels A and B indicates the median. In Panels C and D, the size of the circle reflects the number of patients affected. All analyses were performed with the use of a stratified log-rank test according to the baseline score on the Eastern Cooperative Oncology Group (ECOG) scale (a performance status grade of 0 indicates asymptomatic, and 1 restricted in strenuous activity but ambulatory). Scores on the Brief Pain Inventory–Short Form (BPI-SF) range from 0 to 10, with higher scores indicating worse average pain. ALK-P denotes alkaline phosphatase, LDH lactate dehydrogenase, and PSA prostate-specific antigen.

survival, with an estimated correlation coefficient of 0.72.

SECONDARY END POINTS

Prespecified secondary and exploratory efficacy end points are summarized in Table 1. Abiraterone–prednisone decreased the risk of decline (by ≥1 point) in ECOG performance-status score by 18%, as compared with prednisone alone (time to decline, 12.3 vs. 10.9 months; hazard ratio for decline, 0.82; 95% CI, 0.71 to 0.94; P=0.005) (Fig. 2A). The median time to the initiation of cytotoxic chemotherapy was 25.2 months in the abiraterone–prednisone group and 16.8 months in the prednisone-alone group (hazard ratio, 0.58; 95% CI, 0.49 to 0.69; P<0.001) (Fig. 2B). A significant delay in the time to opiate use for

Table 1. Prespecified Secondary and Exploratory Efficacy End Points.*

End Point	Abiraterone–Prednisone (N=546)	Prednisone Alone (N=542)	Value (95% CI)†	P Value
Secondary end points				
Median time to opiate use for cancer-related pain — mo	NR	23.7	0.69 (0.57–0.83)	<0.001
Median time to initiation of cytotoxic chemotherapy — mo	25.2	16.8	0.58 (0.49–0.69)	<0.001
Median time to decline in ECOG performance score by ≥1 point — mo	12.3	10.9	0.82 (0.71–0.94)	0.005
Median time to PSA progression — mo‡	11.1	5.6	0.49 (0.42–0.57)	<0.001
Exploratory end points§				
Median time to increase in pain — mo¶	26.7	18.4	0.82 (0.67–1.00)	0.049
Median time to functional-status decline measured as FACT-P total score — mo‖	12.7	8.3	0.78 (0.66–0.92)	0.003
Patients with decline of ≥50% in PSA level — %**	62	24	2.59 (2.19–3.05)††	<0.001
Patients with a RECIST response — %‡‡				
Defined objective response	36	16	2.27 (1.59–3.25)††	<0.001
Stable disease	61	69		
Progressive disease	2	15		

* Percentages may not sum to 100 because of rounding. CI denotes confidence interval, NR not reached, and PSA prostate-specific antigen.
† Values are hazard ratios unless otherwise specified.
‡ PSA progression was based on Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria.[2]
§ The exploratory analyses are reported with no adjustment for multiplicity.
¶ Increase in pain is defined as an increase in the baseline pain level by 30% or more, as measured by the average of the pain scores on the Brief Pain Inventory–Short Form (range, 0 to 10, with higher scores indicating worse average pain) at two consecutive visits, without a decrease in analgesic use.
‖ The time to a decline in functional status is defined as the months from randomization to the first date a patient has a decrease of 10 points or more on the Functional Assessment of Cancer Therapy–Prostate (FACT-P) instrument (range, 0 to 156, with higher scores indicating better overall quality of life).
** A decline of 50% or more in the PSA level was based on modified PCWG2 criteria.
†† Values are relative risks.
‡‡ Response Evaluation Criteria in Solid Tumors (RECIST) criteria were ascertained in patients with measurable disease at baseline: 220 in the abiraterone–prednisone group and 218 in the prednisone-alone group.

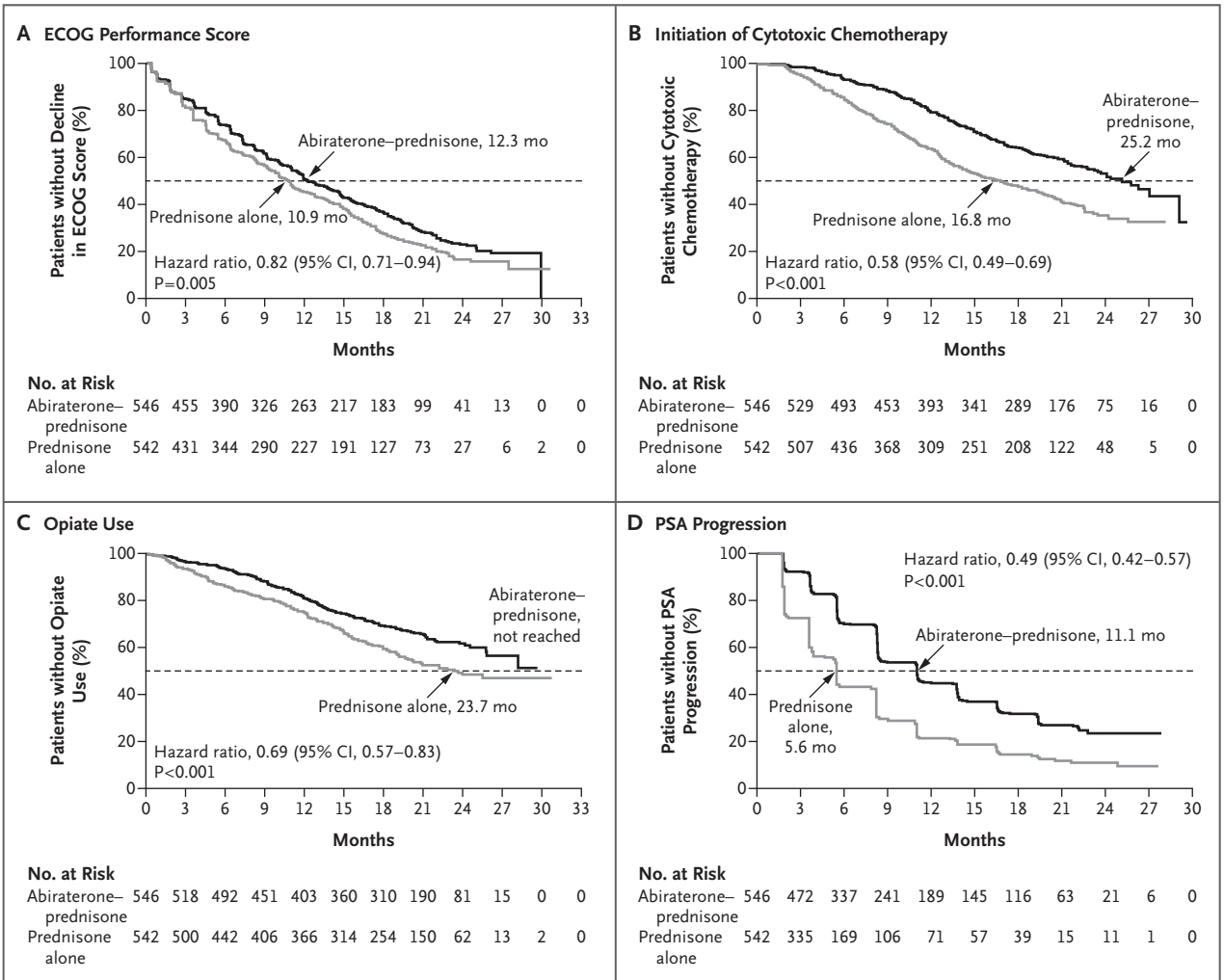


Figure 2. Secondary Efficacy End Points.

Shown are the time until a decline in the Eastern Cooperative Oncology Group (ECOG) score by one point or more (Panel A), the time until the initiation of cytotoxic chemotherapy (Panel B), the time until the use of opiates for pain from prostate cancer (Panel C), and the time until prostate-specific antigen (PSA) progression according to Prostate Cancer Clinical Trials Working Group 2 criteria[2] (Panel D). The dashed line indicates the median. All analyses were performed with the use of a stratified log-rank test according to the baseline ECOG score.

cancer-related pain was observed with abiraterone (not reached vs. 23.7 months; hazard ratio, 0.69; 95% CI, 0.57 to 0.83; P<0.001) (Fig. 2C). The median time to PSA progression was 11.1 months in the abiraterone–prednisone group and 5.6 months in the prednisone-alone group, a 51% reduction in risk (hazard ratio, 0.49; 95% CI, 0.42 to 0.57; P<0.001) (Fig. 2D). On the basis of aggregate efficacy and safety data from the second interim analysis, the data and safety monitoring committee unanimously recommended unblinding the study in February 2012.

OTHER END POINTS

The median time to increase in pain was 26.7 months among patients receiving abiraterone–prednisone and 18.4 months among those receiving prednisone alone (hazard ratio, 0.82; 95% CI, 0.67 to 1.00; P=0.049) (Table 1). The median time to a decline in the FACT-P total score was 12.7 months in the abiraterone–prednisone group and 8.3 months in the prednisone-alone group (hazard ratio, 0.78; 95% CI, 0.66 to 0.92; P=0.003). The rates of PSA response and objective response to therapy were significantly higher in the abir-

aterone–prednisone group than in the prednisone-alone group (Table 1).

SAFETY

Adverse events are summarized in Tables 2 and 3. Grade 3 or 4 adverse events were reported in 48% of patients in the abiraterone–prednisone group and 42% of patients in the prednisone-alone group; serious adverse events were reported in 33% and 26% of patients, and adverse events resulting in death were reported in 4% and 2% of patients, respectively. Fatigue, arthralgia, and peripheral edema were among the adverse events reported more frequently in the abiraterone–prednisone group than in the prednisone-alone group. Grade 3 or 4 adverse events classified as hepatotoxicity, consisting primarily of a reversible elevation in aminotransferase levels, were reported in 8% of patients in the abiraterone–prednisone group and 3% of patients in the prednisone-alone group. No patient in either study group died from hepatotoxicity-related adverse events.

The frequency of adverse events resulting in treatment discontinuation was similar in the two study groups. A total of 19% of patients in the abiraterone–prednisone group and 12% of patients in the prednisone-alone group had adverse events leading to dose modification or interruption of study treatment. In the two study groups, the most frequently occurring adverse events resulting in death were those related to disease progression (0.6% of patients in each group). The proportions of patients with grade 3 or 4 serious adverse events were similar in the two groups. Adverse events that were classified as cardiac disorders were reported in 19% of patients in the abiraterone–prednisone group and 16% of those in the prednisone-alone group. Mineralocorticoid-related toxic effects were more common in the abiraterone–prednisone group than in the prednisone-alone group, including hypertension (22% vs. 13%), hypokalemia (17% vs. 13%), and fluid retention or edema (28% vs. 24%), and were mostly grade 1 or 2 adverse events.

Table 2. Adverse Events.*

Adverse Event	Abiraterone–Prednisone (N=542)	Prednisone Alone (N=540)
	no. of patients (%)	
Any adverse event	537 (99)	524 (97)
Grade 3 or 4 adverse event	258 (48)	225 (42)
Any serious adverse event	178 (33)	142 (26)
Adverse event leading to treatment discontinuation	55 (10)	49 (9)
Adverse event leading to death*	20 (4)	12 (2)
Adverse event of grade 1–4 in ≥15% of patients in either group		
Fatigue	212 (39)	185 (34)
Back pain	173 (32)	173 (32)
Arthralgia	154 (28)	129 (24)
Nausea	120 (22)	118 (22)
Constipation	125 (23)	103 (19)
Hot flush	121 (22)	98 (18)
Diarrhea	117 (22)	96 (18)
Bone pain	106 (20)	103 (19)
Muscle spasm	75 (14)	110 (20)
Pain in extremity	90 (17)	85 (16)
Cough	94 (17)	73 (14)

* The most common adverse events leading to death were general disorders, including disease progression, a decline in physical health, and infections including pneumonia and respiratory tract infection.

Table 3. Adverse Events of Special Interest.*

Adverse Event	Abiraterone–Prednisone (N=542)		Prednisone Alone (N=540)	
	Grade 1–4	Grade 3 or 4	Grade 1–4	Grade 3 or 4
Fluid retention or edema	150 (28)	4 (<1)	127 (24)	9 (2)
Hypokalemia	91 (17)	13 (2)	68 (13)	10 (2)
Hypertension	118 (22)	21 (4)	71 (13)	16 (3)
Cardiac disorder†	102 (19)	31 (6)	84 (16)	18 (3)
Atrial fibrillation	22 (4)	7 (1)	26 (5)	5 (<1)
ALT increased	63 (12)	29 (5)	27 (5)	4 (<1)
AST increased	58 (11)	16 (3)	26 (5)	5 (<1)

* Adverse events of special interest were selected on the basis of the safety profile of phase 2 and phase 3 studies of abiraterone. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† Cardiac disorders included ischemic heart disease, myocardial infarction, supraventricular tachyarrhythmia, ventricular tachyarrhythmia, cardiac failure, and possible arrhythmia-related investigations, signs, and symptoms.

DISCUSSION

In our study involving men with metastatic castration-resistant prostate cancer, abiraterone plus low-dose prednisone resulted in prolonged radio-

graphic progression-free survival (median time to event, 16.5 months vs. 8.3 months; hazard ratio, 0.53), as compared with placebo plus prednisone. Patients receiving abiraterone also had an extended time until the initiation of opiate analgesia, treatment with cytotoxic chemotherapy, or a decline in performance status, as well as delays in PSA progression, onset of pain, and decline in health-related quality of life. The proportion of men in the abiraterone–prednisone group with a PSA response and the time to PSA progression are consistent with outcomes reported in earlier phase 1 or 2 studies of abiraterone.[20-22] In addition, a strong trend toward improved survival (hazard ratio, 0.75) was evident at the time at which 43% of the prespecified total number of events required for the final analysis had occurred. This consistent pattern of benefit resulted in the unanimous decision of the data and safety monitoring committee to recommend unblinding of the study and crossover of patients in the prednisone-alone group to abiraterone treatment.

Despite the various therapies available for men with metastatic castration-resistant prostate cancer, a need remains for effective nontoxic agents that can improve and maintain the quality and duration of life while preventing the morbidity associated with disease progression.[25] Second-line hormonal manipulation with antiandrogens, diethylstilbestrol, and ketoconazole has long been used on the sole basis of symptom relief and PSA-level response data.[8] This pattern of use has persisted despite the availability of two new agents with a survival benefit: docetaxel, the use of which is limited by toxic effects, and sipuleucel-T, the use of which is limited by a lack of demonstrable antitumor activity. The durable antitumor effect and safety profile of abiraterone confirms earlier experience that it can be used long term without concern for life-threatening toxic effects.[21,22]

Glucocorticoids have beneficial effects in patients with metastatic castration-resistant prostate cancer, and prednisone has been an active comparison agent in randomized trials for decades.[4,7,19] Our data show that targeting persistent extragonadal androgen synthesis[26] leads to benefits that exceed those with standard prednisone therapy used in current clinical trials. An additional notable finding is that the median overall survival of 27.2 months with prednisone alone is the longest survival prospectively observed in this patient population, possibly a consequence of antitumor activity of the prednisone control and the activity of subsequent effective therapies.

In addition to the marked improvement in radiographic progression-free survival, treatment with abiraterone was associated with a trend toward improved overall survival. Evidence of the magnitude of the survival benefit of abiraterone–prednisone, as compared with prednisone alone, was that treatment effects were consistently favorable across all prespecified patient subgroups, including older men and those with a decreased performance status, increased pain, and increased disease burden (Fig. 1D). The use of abiraterone after crossover among patients originally assigned to the prednisone-alone group may affect the ability to show statistical significance in subsequent analyses of overall survival. Despite the high disease burden and the proportion of patients with high-grade tumors (Gleason score, ≥8) who were enrolled, the survival curves did not separate until after approximately 12 months. This finding can be ascribed to the use of an active prednisone control and the low rate of early death in asymptomatic or mildly symptomatic patients with metastatic castration-resistant cancer.

Early deaths related to cancer may occur in patients with a tumor phenotype against which androgen modulation may have little effect. Although we do not know the effectiveness of therapies (including abiraterone) that were used after termination of the study treatment, the prevalence of subsequent therapy was higher in the prednisone-alone group than in the abiraterone–prednisone group (60% and 44%, respectively) (Table S5 in the Supplementary Appendix). The most common subsequent therapy in the two groups was docetaxel. Between-group disparities in subsequent therapies may be attributable to the greater number of patients in the abiraterone–prednisone group who continued to receive the drug, as compared with the prednisone-alone group: 166 of 542 patients (31%) in the abiraterone–prednisone group vs. 86 of 540 patients (16%) in the prednisone-alone group.

The safety of abiraterone in this study was similar to that previously reported in men with metastatic castration-resistant prostate cancer and disease progression after docetaxel chemotherapy.[19] No toxic effects unique to this patient population were identified (a finding that was consistent with previous studies), despite a longer

duration of abiraterone–prednisone treatment. Liver-function abnormalities (typically seen in the first 3 months of therapy) and cardiac toxic effects were more common in the abiraterone-treated patients than in the prednisone-alone group. Cardiac abnormalities tended to appear later. Discontinuation of therapy because of toxicity occurred in 10% of patients in the abiraterone–prednisone group and in 9% of patients in the prednisone-alone group.

In summary, the results show benefit from the use of abiraterone in patients with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer who have not received previous chemotherapy. These findings include increased rates of radiographic progression-free survival and overall survival, as well as clinically meaningful secondary end points, such as delays in the use of opiates for pain and chemotherapy and patient-reported outcomes related to health-related quality of life.

Presented in part at the annual meeting of the American Society of Clinical Oncology, Chicago, June 1–5, 2012 (abstract LBA4518).

Supported by Ortho Biotech Oncology Research and Development, a unit of Cougar Biotechnology (now Janssen Research and Development).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients who volunteered to participate in this study and the study site staff who cared for them, and Namit Ghildyal, Ph.D., an employee of the study sponsor, and Ira Mills, Ph.D., of Parexel, for editorial assistance with an earlier draft of the manuscript.

APPENDIX

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