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Randomized Phase 3 Trial of Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer and No Prior Chemotherapy

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Collection and assembly of data: The blinded database was held at a third-party contract clinical organization (CRO), and queries were issued by both the sponsor and the CRO staff.

Data analysis and interpretation: After the IDMC recommended unblinding, data analyses were performed by Youn Choi Park, Ph.D. and Thian Kheoh, Ph.D. and the results were reviewed by the authors.

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Abstract

Background—Abiraterone acetate, an androgen biosynthesis inhibitor, improves overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC) post-chemotherapy. Many mCRPC patients never receive chemotherapy and thus cannot benefit from abiraterone acetate; we evaluated this agent in mCRPC patients who had not received chemotherapy.

Methods—In this double-blind study, 1088 patients were randomized 1:1 to abiraterone acetate (1000 mg) plus prednisone (5 mg twice daily) or placebo plus prednisone. Co-primary end points were radiographic progression-free survival (rPFS) and OS. Secondary end points measured clinically relevant landmarks of mCRPC progression. Patient-reported outcomes included pain progression and quality of life.

Results—The study was unblinded after a planned interim analysis (IA) at 43% of OS events. Treatment with abiraterone acetate-prednisone resulted in a 57% reduction in the risk of radiographic progression or death (hazard ratio [HR], 0.43; 95% confidence interval [CI]: 0.35 to 0.52; P<0.001; 13% OS events IA) and an estimated 25% decrease in the risk of death (HR, 0.75; 95% CI: 0.61 to 0.93; P=0.009; 43% OS events IA). Secondary end points supported superiority of abiraterone acetate-prednisone: time to cytotoxic chemotherapy initiation, opiate use for cancer-related pain, prostate-specific antigen progression (all P<0.001) and performance status deterioration (P=0.005). Self-reported time to pain progression and patient functional status degradation favored abiraterone acetate-prednisone (P=0.05 and P=0.003). Grade 3/4 mineralocorticoid-related adverse events and liver function test abnormalities were more common with abiraterone acetate-prednisone.

Conclusions—Abiraterone acetate produces OS and rPFS benefits, as well as significant delays in clinical deterioration and initiation of chemotherapy, in mCRPC.

Keywords

Abiraterone acetate; prednisone; metastatic castration-resistant prostate cancer; androgen; CYP17

INTRODUCTION

Metastatic castration-resistant prostate cancer (mCRPC), defined by tumor growth despite a testosterone of <50 ng per deciliter (<1.7 nmol/liter), causes approximately 258,400 deaths annually worldwide.[1,2] Death in mCRPC patients, which typically occurs within 24 to 48 months of the onset of castration resistance, is commonly preceded by a sequence of landmark events associated with deterioration of overall health and worsening symptoms (Fig. 1 in the Supplementary Appendix).[3–7]

Among management options in mCRPC are a variety of second-line hormonal manipulations[8] that produce responses in many patients; however, none has been shown to delay progression or prolong life. Subsequently, a standard approach is docetaxel chemotherapy, which has a demonstrated survival benefit;[4] however, many patients with mCRPC never receive it.[9,10] A result of the limited penetrance of chemotherapy is the unmet need for a therapy that can effectively treat mCRPC and delay or prevent the landmark

events that characterize its morbidity.[2] One treatment, sipuleucel-T, an immunotherapy, is associated with a modest survival benefit in mCRPC but without tumor regression, symptom relief, or delays in disease progression.[11]

Abiraterone acetate is a first-in-class inhibitor of cytochrome P-450 c17, a critical enzyme in extragonadal and testicular androgen synthesis.[12–18] Abiraterone acetate plus low-dose prednisone improves survival in patients with mCRPC treated after docetaxel,[19] and has received regulatory approval for this indication. Phase 1 and 2 studies in chemotherapy-naïve mCRPC patients, however, demonstrated a high proportion of durable responses, suggesting that the benefits of abiraterone acetate may be optimized in this patient group.[20–22] In this randomized, phase 3 study, we evaluated the effects of abiraterone acetate-prednisone on radiographic progression-free survival (rPFS), overall survival (OS), pain progression, and clinically relevant measures of disease progression in patients with mCRPC who had not received chemotherapy or developed significant cancer-related symptoms.

METHODS

Patients

Patients (aged ≥18 years) with histologically- or cytologically-confirmed adenocarcinoma of the prostate were eligible provided they had prostate-specific antigen (PSA) progression according to Prostate Cancer Clinical Trials Working Group (PCWG2) criteria[2] or radiographic progression in soft tissue or bone with or without PSA progression, ongoing androgen deprivation with serum testosterone <50 ng per deciliter (<1.7 nmol/liter), prior therapy with an anti-androgen, an Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1, no symptoms or mild symptoms as defined by Brief Pain Inventory-Short Form (BPI-SF) scores of 0 to 1 and 2 to 3, respectively, and hematology and chemistry laboratory values that met predefined criteria. 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 Harmonization, and the Guidelines for Good Clinical Practice. All patients gave written informed consent.

STUDY DESIGN AND TREATMENT

In this multinational, double-blind, placebo-controlled study, patients were randomized in a 1:1 ratio to receive abiraterone acetate-prednisone or placebo-prednisone, respectively (henceforth referred to as “abiraterone” or “prednisone,” respectively). Patients were stratified according to baseline ECOG performance status grade (0 versus 1). Patients received abiraterone acetate 1 g (administered as four 250-mg tablets) or four placebo tablets orally once daily at least 1 hour before and 2 hours after a meal, and prednisone 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.

The co-primary efficacy end points were 1) rPFS based on independent review, defined as progression based upon any of the following: death from any cause, progression in soft tissue lesions measured by computed tomography (CT) or magnetic resonance imaging (MRI) as defined by modified Response Evaluation Criteria in Solid Tumors (RECIST), or progression by bone scan as adapted by PCWG2[2] (Table 1 in the Supplementary Appendix), and 2) OS defined as the time from randomization to death from any cause. Changes in PSA were not included in the rPFS definition. The prespecified secondary end points were time to opiate use for cancer-related pain, to initiation of cytotoxic chemotherapy, to ECOG performance status deterioration, and to PSA progression (based on PCWG2).[2] Other end points included rPFS by investigator review, PSA response rate, objective response rate, and

health-related quality of life (HRQOL) through patient-reported outcomes in time to pain progression (defined as a >30% increase from baseline in the average pain items of the BPI-SF sustained at two consecutive visits, without a decrease in analgesic use) and time to degradation in Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score (defined as the time interval from randomization to the first date a patient experiences a decrease of 10 points).

ASSESSMENTS

Efficacy assessments included: sequential radiographic imaging to assess rPFS (CT or MRI and bone scan) and PSA levels.[2] All patients underwent serial monitoring of blood chemistries, hematologic parameters, coagulation studies, serum lipids, and kidney function. Cardiac safety was monitored through serial electrocardiograms. Left ventricular ejection fraction was measured at baseline. Patient-reported outcomes were assessed at baseline and at every cycle using BPI-SF. FACT-P questionnaires were completed every third cycle.

STUDY OVERSIGHT

This study was designed by academic and sponsor-employed investigators. The lead academic author initially drafted this manuscript with sponsor input, and all coauthors subsequently provided input and approval. The blinded 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 analysis to an independent data monitoring committee (IDMC), whose members were invited by the sponsor. The IDMC monitored safety at regular intervals and evaluated efficacy and safety at interim analyses. At unblinding, analyses were performed by sponsor statisticians.

STATISTICAL ANALYSIS

The overall level of significance for the study was 0.05 allocated between the co-primary end points of rPFS (0.01) and OS (0.04). A single analysis was planned for the co-primary end point of rPFS based on the independent radiographic review, after 378 rPFS events, which would provide 91% power to detect a hazard ratio (HR) of 0.67 at a two-tailed level of significance of 0.01. For the co-primary end point of OS, 773 events were required to detect a HR of 0.80 at a two-tailed significance level of 0.04 with a power of 85%.

Three interim analyses were planned for OS, after approximately 15% (n=116) (in conjunction with the final rPFS analysis), 40% (n=311), and 55% (n=425) of the total events were observed and a final analysis was planned after 773 events. The group sequential design was utilized for the OS end point using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method (Table 2 in the Supplementary Appendix). Approximately 1000 patients were planned for the study. The primary statistical method of comparison for the time-to-event end points was the stratified log-rank test. Cox proportional hazards model was used to estimate the HR and its associated confidence interval (CI). The Hochberg procedure was used to adjust for multiplicity testing of the secondary efficacy end points.[23] The strength of association between rPFS and OS was evaluated using Spearman's correlation coefficient estimated through the Clayton copula.[24]

RESULTS

PATIENTS AND TREATMENT

From April 2009 to June 2010, 1088 patients were randomly assigned to receive abiraterone acetate-prednisone (n=546) or prednisone (n=542) (Fig. 2 in the Supplementary Appendix). Clinical cutoff date for the independent review of rPFS and the first OS interim analysis (IA) was December 20, 2010 (13% of OS events) and the clinical cutoff date for the second IA of

OS was December 20, 2011 (40% of OS events). Baseline demographic characteristics were well balanced between the two treatment groups (Table 1).

EFFICACY

Radiographic Progression-Free Survival—Based on the independent review, treatment with abiraterone resulted in a 57% reduction in the risk of radiographic progression or death compared with prednisone (HR, 0.43; 95% CI: 0.35 to 0.52; P<0.001) at the time of the first IA (Fig. 1A). At the time of the second IA of OS, the median rPFS based on investigator assessment was 16.5 months in the abiraterone group and 8.3 months (HR, 0.53; 95% CI: 0.45 to 0.62; P<0.001) in the prednisone group at a median follow-up of 22.2 months. The treatment effect of abiraterone on rPFS was consistently favorable (all HR <1.0) across all prespecified subgroups (Fig. 1B).

Overall Survival—The planned IA of OS was performed after 333 events (43% of total) were observed. More deaths were observed in the prednisone group than in the abiraterone group (186 [34%] versus 147 [27%]). The median OS had not been reached for the abiraterone group and was 27.2 months (95% CI, 26.0, NE) in the prednisone group. A 25% decrease in the risk of death in the abiraterone group (HR, 0.75; 95% CI, 0.61 to 0.93; P=0.009) (Fig. 1C) was observed indicating a strong trend toward improved survival with abiraterone, however, the prespecified boundary for significance (HR ≤ 0.67, P ≤ 0.008) was not reached at this number of events. The treatment effect of abiraterone on OS was consistently favorable (all HR <1.0) across all prespecified subgroups (Fig. 1D). rPFS was positively correlated with OS, with an estimated value of the correlation coefficient of 0.72. Based on the aggregate efficacy and safety data at the second IA the IDMC unanimously recommended unblinding in February 2012.

Secondary End Points—Secondary end points are summarized in Table 2. Abiraterone decreased the risk of deterioration in ECOG performance status score (≥1 grade) by 18% compared with prednisone (HR, 0.82; 95% CI, 0.71 to 0.94; P=0.005). The median time to deterioration in ECOG performance status score by ≥1 grade was 12.3 months in the abiraterone group and 10.9 months in the prednisone group (Fig. 2A). The median time to cytotoxic chemotherapy was 25.2 months in the abiraterone group and 16.8 months in the prednisone group (HR, 0.58; 95% CI, 0.49 to 0.69; P<0.001) (Fig. 2B). A statistically significant delay in the time to opiate use for cancer-related pain was observed (HR, 0.69; 95% CI, 0.57 to 0.83; P<0.001) favoring abiraterone (Fig. 2C). The median time to PSA progression was 11.1 months in the abiraterone group and 5.6 months in the prednisone group, a 51% reduction (HR, 0.49; 95% CI, 0.42 to 0.57; P<0.001) (Fig. 2D).

Other End Points—Time to pain progression was 26.7 months in the abiraterone group and 18.4 months in the prednisone group (HR, 0.82; 95% CI, 0.67 to 1.00; P<0.05) (Table 2). Time to degradation in FACT-P total score was 12.7 months in abiraterone-treated patients and 8.3 months in the prednisone group (HR, 0.78; 95% CI, 0.66 to 0.92; P=0.003). PSA response and objective response rates were significantly higher in the abiraterone group compared with the prednisone group (Table 2).

SAFETY

Adverse events (AEs) are summarized in Table 3. Grade 3 or 4 AEs were reported in 48% of patients in the abiraterone group versus 42% of patients in the prednisone group; serious AEs were reported in 33% versus 26% of patients, and AEs with an outcome of death were reported in 4% versus 2% of patients, respectively. Fatigue, arthralgia, and peripheral edema were among the AEs reported more frequently in the abiraterone group compared with the prednisone group. Grade 3 or 4 AEs classified as hepatotoxicity consisting primarily of

reversible transaminase elevation were reported in 8% of patients in the abiraterone group and 3% of patients in the prednisone group. No patient in either treatment group died from hepatotoxicity-related AEs.

The frequency of AEs resulting in treatment discontinuation was similar in the two treatment groups. Nineteen percent of patients in the abiraterone group and 12% of patients in the prednisone group had AEs leading to dose modification or interruption of investigational product. Across both treatment groups, the most frequently occurring AEs with an outcome of death were those related to disease progression (0.6% of patients in each group). The proportions of patients with grade 3 or 4 serious AEs were similar between the groups. AEs classified as cardiac disorders were reported in 19% of patients in the abiraterone group and 16% of patients in the prednisone group. The mineralocorticoid-related toxicities of hypertension, hypokalemia and fluid retention/edema were more common in the abiraterone group and were mostly grade 1 or 2 AEs.

DISCUSSION

In this multi-national, randomized, placebo-controlled study, abiraterone plus low-dose prednisone resulted in prolonged radiographic progression free survival (HR = 0.43) and delayed the time to initiation of opiate analgesia, treatment with cytotoxic chemotherapy, deterioration of performance status, PSA progression, onset of pain, and degradation of HRQOL. The PSA response proportion and time to disease progression in the current study are consistent with that observed in earlier phase 1/2 studies of abiraterone.[20–22] Additionally, a strong trend toward improved survival (HR = 0.75) was evident at 43% of the prespecified total number of events required for the final analysis. This broad and consistent pattern of benefit resulted in the unanimous decision of the IDMC to recommend unblinding and crossover of placebo patients to abiraterone treatment.

Despite the various therapies available for men with mCRPC, a need persists for effective non-toxic agents that can improve and maintain quality and duration of life while preventing the morbidity associated with disease progression.[25] Second-line hormonal manipulation with antiadrogens, diethylstilbesterol, and ketoconazole has long been utilized despite the absence of randomized clinical data to support its use.[8] The pattern of use persisted despite the availability of docetaxel and sipuleucel-T, where application of the former is limited by toxicity while the latter is limited by a lack of demonstrable antitumor activity, despite a survival benefit. The durable antitumor effect and safety profile observed with abiraterone confirms earlier experience that it can be utilized long-term without significant concern for life-threatening toxicity.[21,22] Taken together, these data strongly suggest that abiraterone merits consideration by clinicians as a new standard of care prior to chemotherapy in patients with mCRPC.

It has long been known that corticosteroids modulate mCRPC, and prednisone has been a comparator in randomized trials in the disease for decades.[4,7,19] The present data, from a randomized phase 3 study, now validate this approach by demonstrating that targeting persistent extragonadal androgen synthesis[26] leads to benefits that are superior to the standard prednisone comparator utilized in contemporary clinical trials. An additional notable finding is that the median OS of 27.2 months in the prednisone alone group is the longest survival prospectively observed in this patient population, possibly a consequence of anti-tumor activity of the prednisone control and impact of subsequent effective therapies.

In addition to a marked improvement in rPFS, treatment with abiraterone acetate was associated with a trend towards improved OS (HR, 0.75; P=0.009), accounting for a conservative allocation of α-level associated with an IA (Table 3 of the Supplementary

Appendix). Emblematic of the magnitude of the survival benefit of abiraterone acetate compared to prednisone are improvement trends in the OS of all pre-specified patient subgroups including older men and those with lower performance status, greater pain, and greater disease burden (Fig. 1D). Despite the high disease burden and proportion of patients with Gleason score ≥8 enrolled, the survival curves did not separate until after approximately 12 months; an observation ascribed to the low number of events observed and active prednisone comparator, and consistent with a low rate of death in an asymptomatic or mildly symptomatic mCRPC population.

Those deaths that did occur early in the course of the study may result from the presence of a proportion of patients harboring a tumor phenotype against which androgen modulation may have little effect. Although the effectiveness of post-study therapies including abiraterone acetate is not known, the prevalence of subsequent therapy was higher in the prednisone group compared to the abiraterone group (60% versus 44%, respectively; Table 4 in the Supplementary Appendix). The most common subsequent therapy was docetaxel in both groups.

The safety of abiraterone acetate observed in this study was similar to that previously reported in men with mCRPC and disease progression after docetaxel chemotherapy.[19] Compared with prior studies, no toxicities unique to this patient population were identified despite a longer duration of abiraterone-prednisone treatment. Liver function abnormalities (typically seen in the first 3 months of therapy) and cardiac toxicities were more common in the abiraterone-treated patients. Cardiac abnormalities tended to appear later. Most toxicities were manageable, as discontinuation of abiraterone therapy due to toxicity was rare.

In summary, the totality of data accumulated in the present study—including the co-primary end points of rPFS and OS, the clinically meaningful secondary end points such as time to opiate use for cancer pain and time until chemotherapy, patient-reported outcomes related to delay in time to pain progression and degradation of HRQOL, and PSA and radiographic responses—support the use of abiraterone acetate as a new standard of care for patients with chemotherapy-naïve, asymptomatic or minimally symptomatic mCRPC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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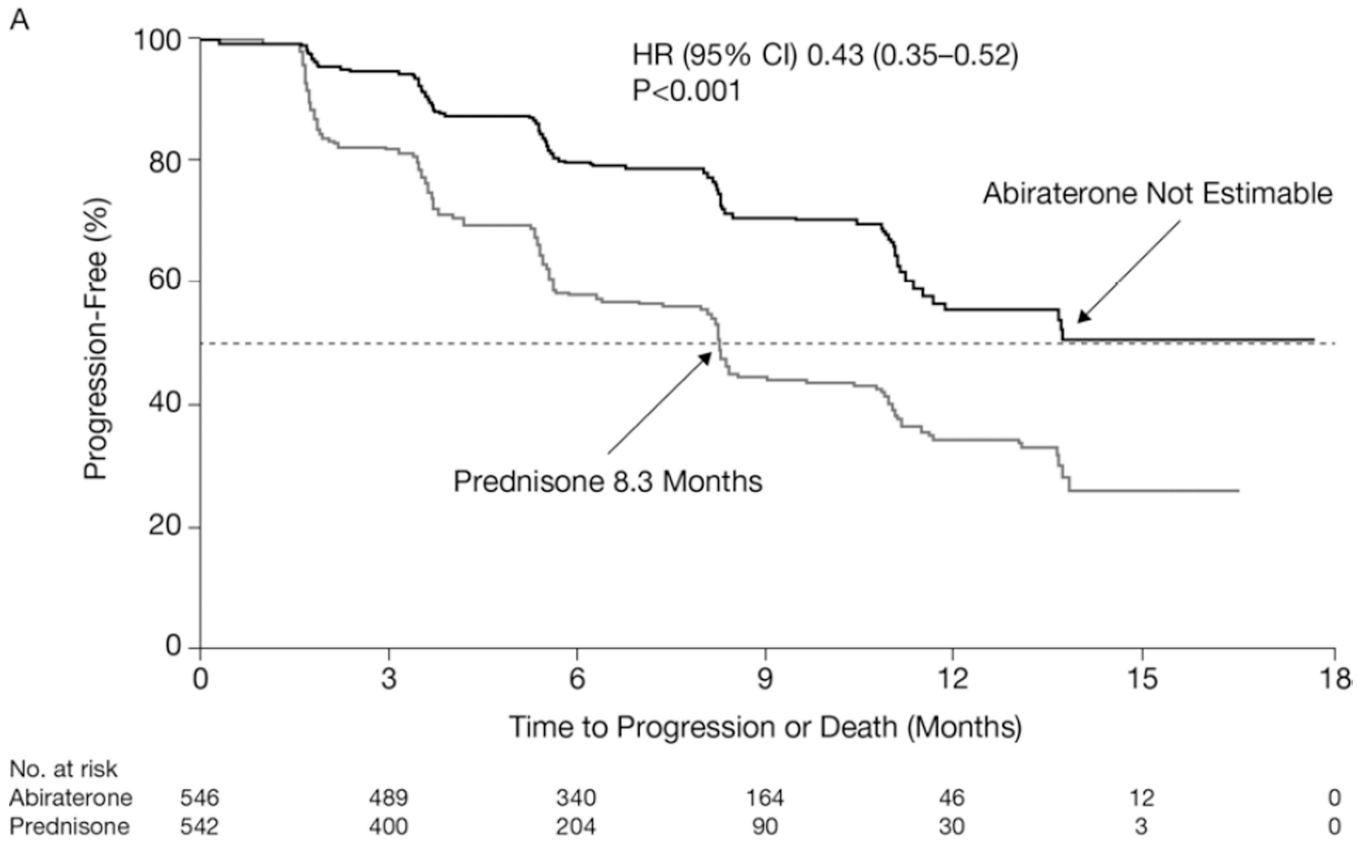

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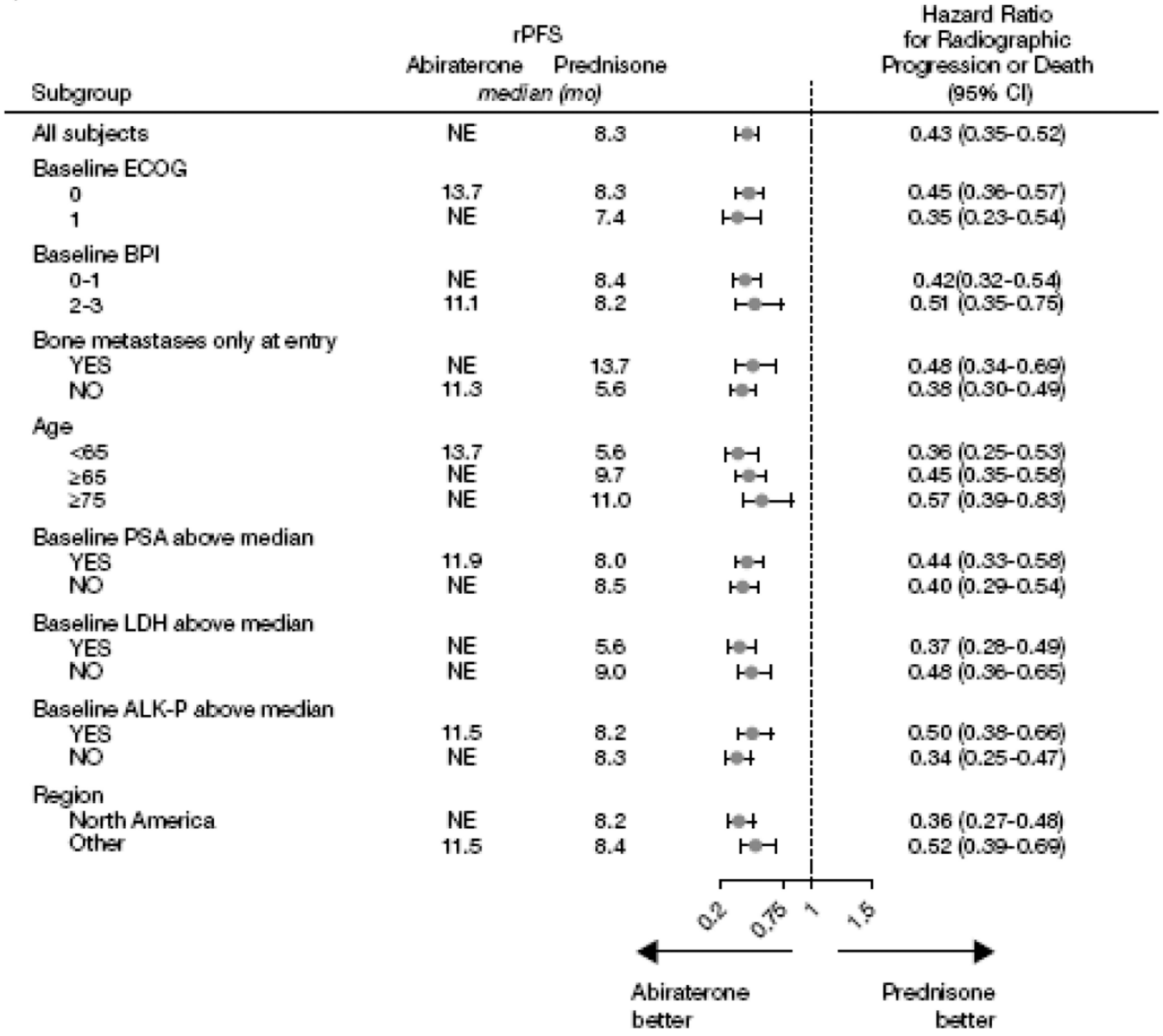

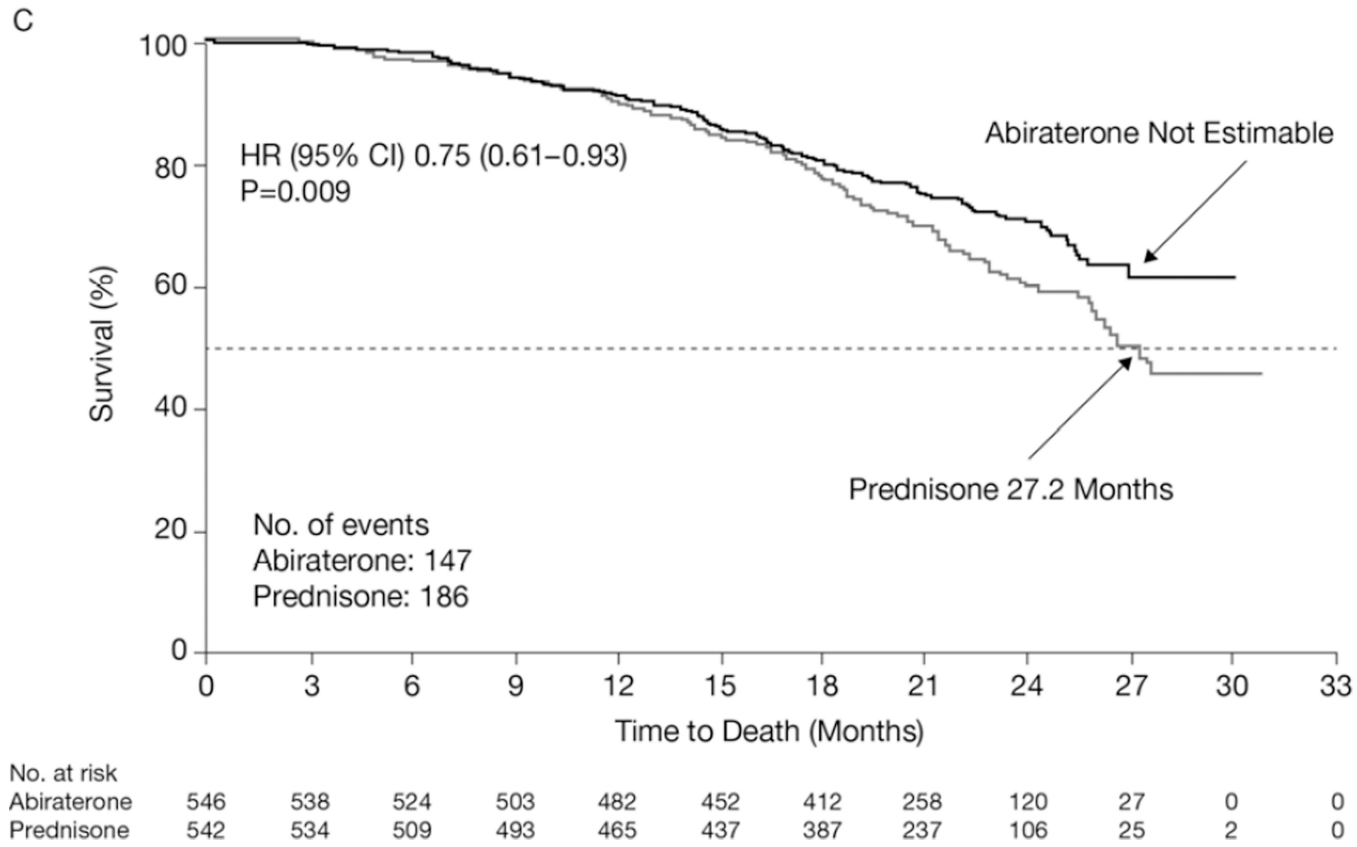

No. at risk												
Abiraterone	546	538	524	503	482	452	412	258	120	27	0	0
Prednisone	542	534	509	493	465	437	387	237	106	25	2	0

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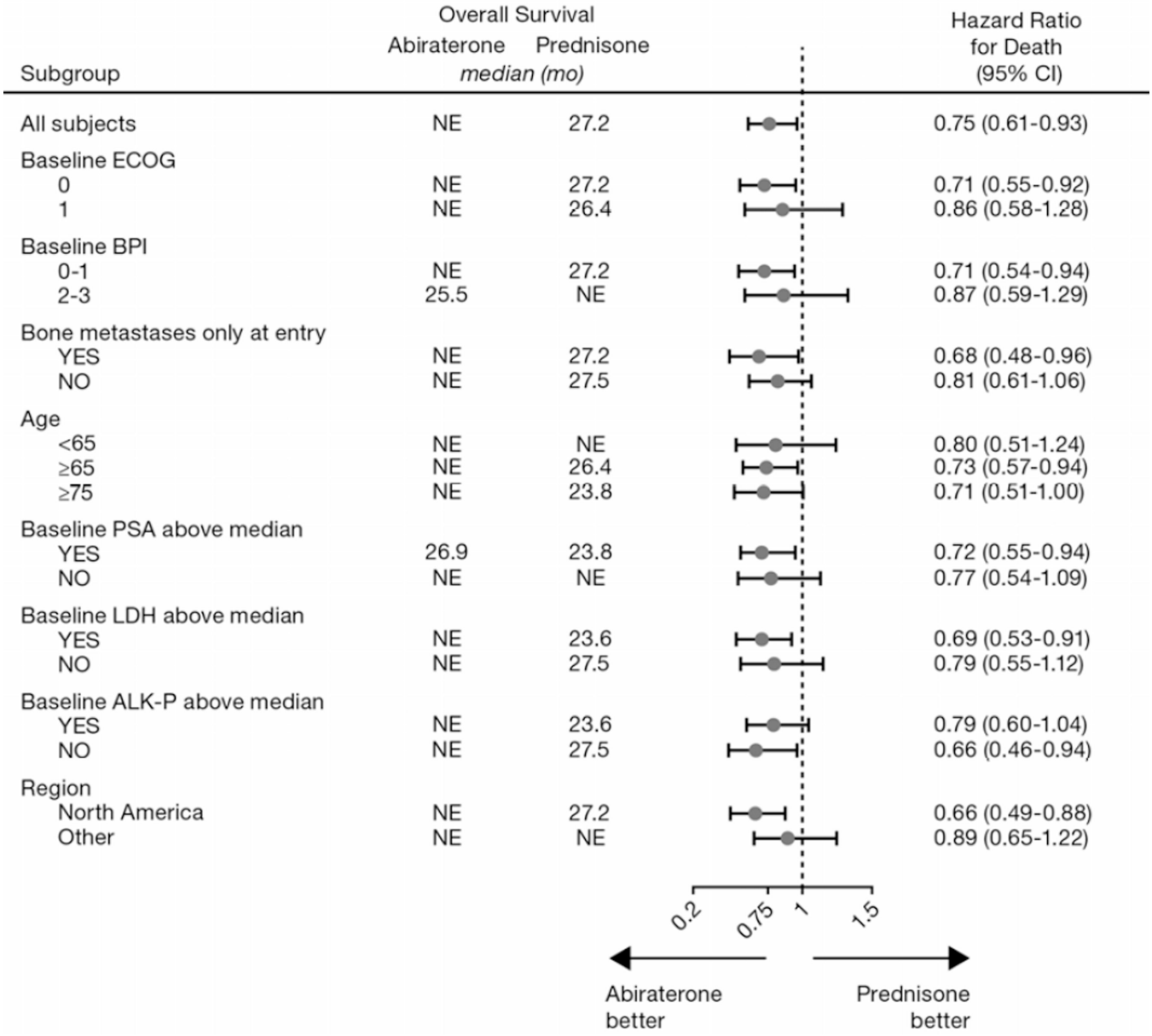


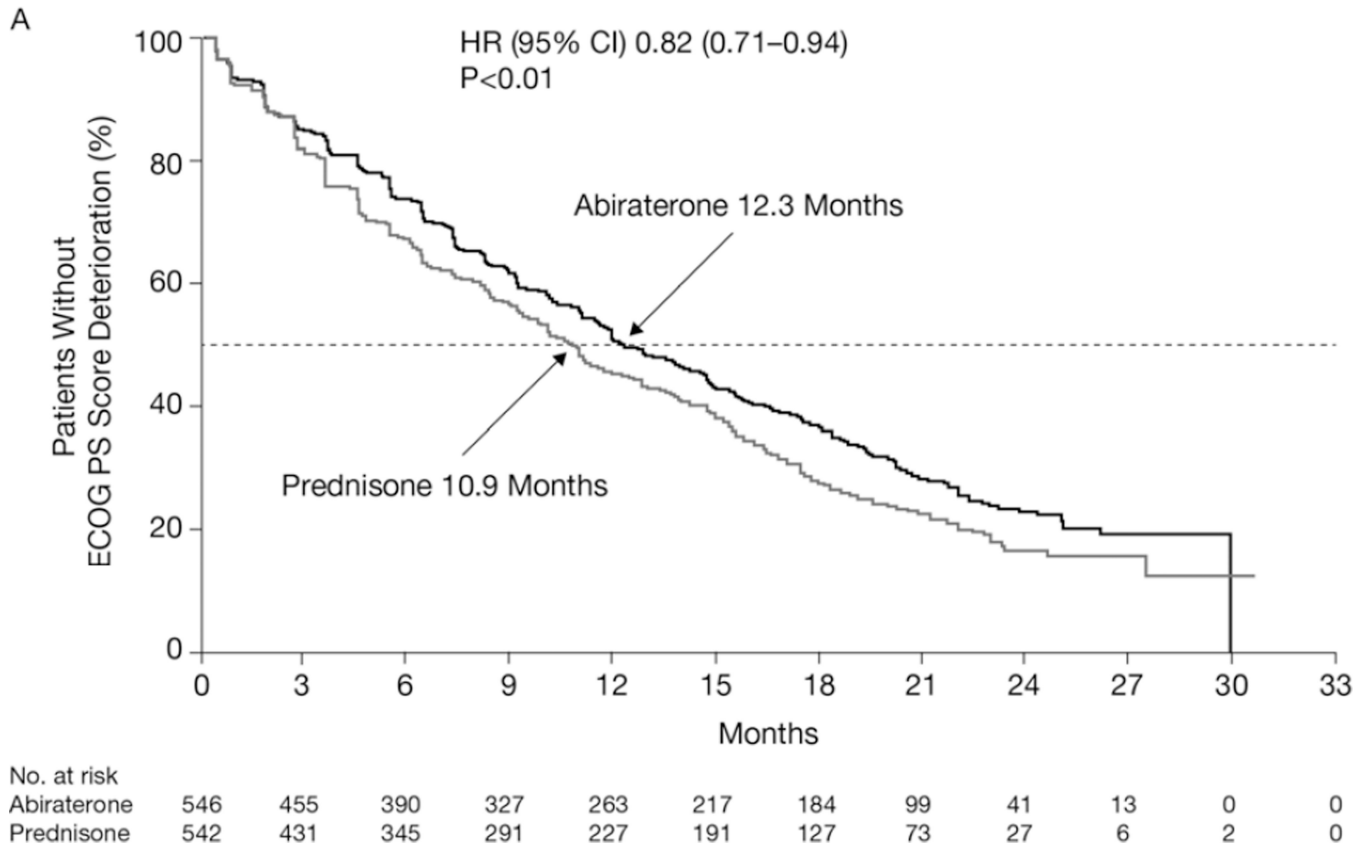
Figure 1. Kaplan-Meier Estimates of Radiographic Progression-Free Survival and Overall Survival and Forest Plots by Subgroup

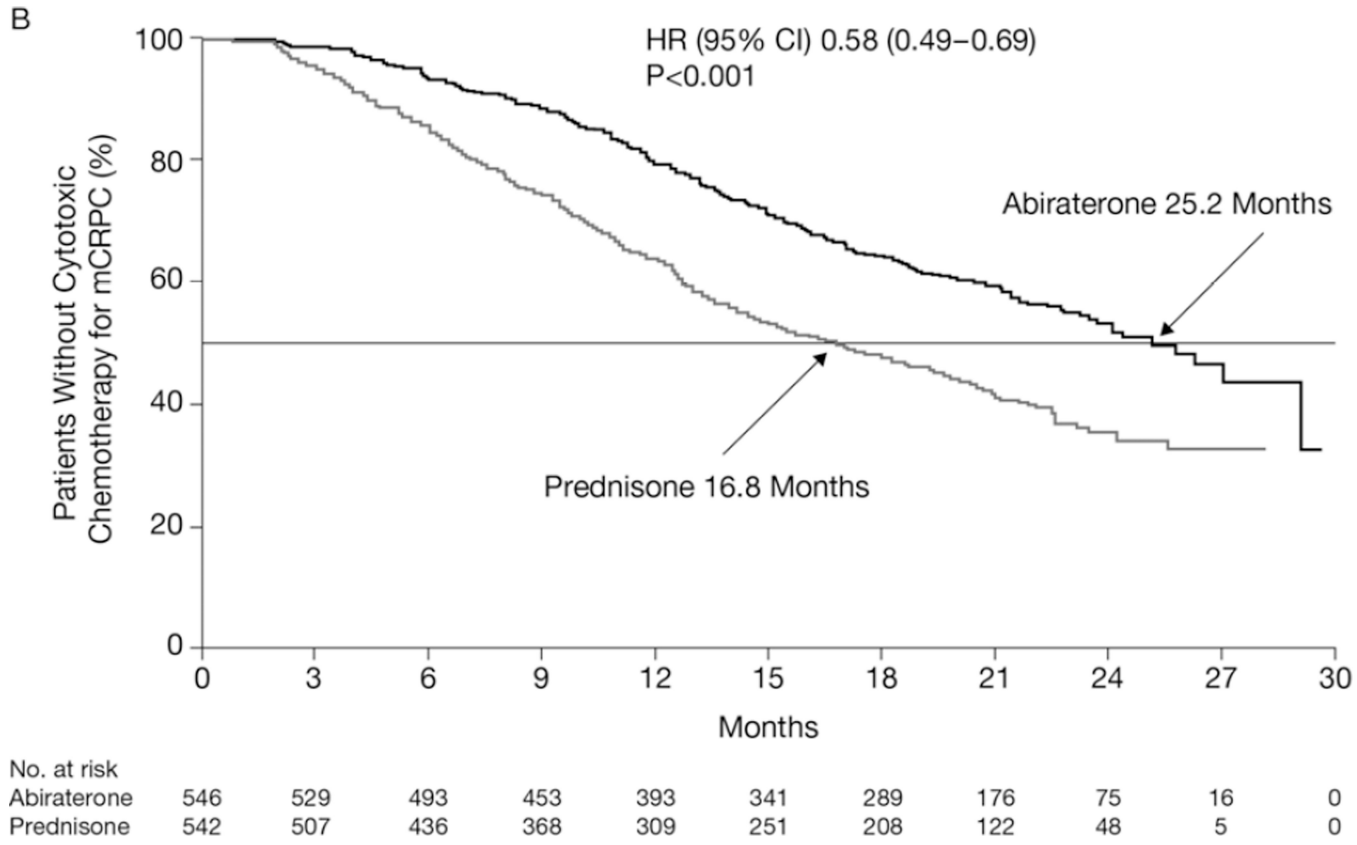
A. Radiographic Progression-free Survival

B. Radiographic Progression-free Survival in Prespecified Subgroups. ALK-P denotes alkaline phosphatase; BPI, Brief Pain Inventory; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NE, not evaluable; PSA, prostate-specific antigen. Note: Hazard ratio is based on a nonstratified proportional hazards model

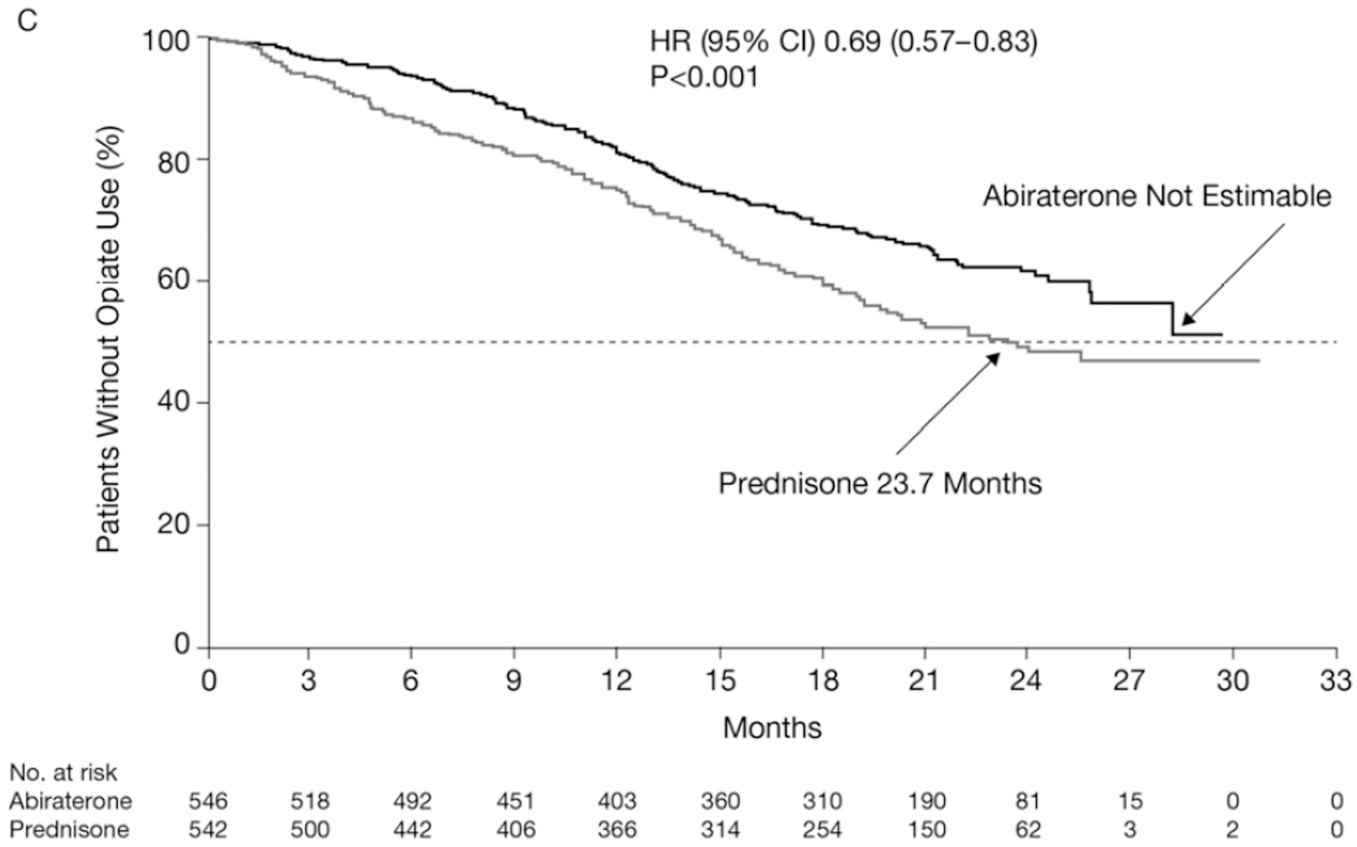
C. Overall Survival

D. Overall Survival in Prespecified Subgroups. Abbreviations as in panel B.





No. at risk											
Abiraterone	546	529	493	453	393	341	289	176	75	16	0
Prednisone	542	507	436	368	309	251	208	122	48	5	0



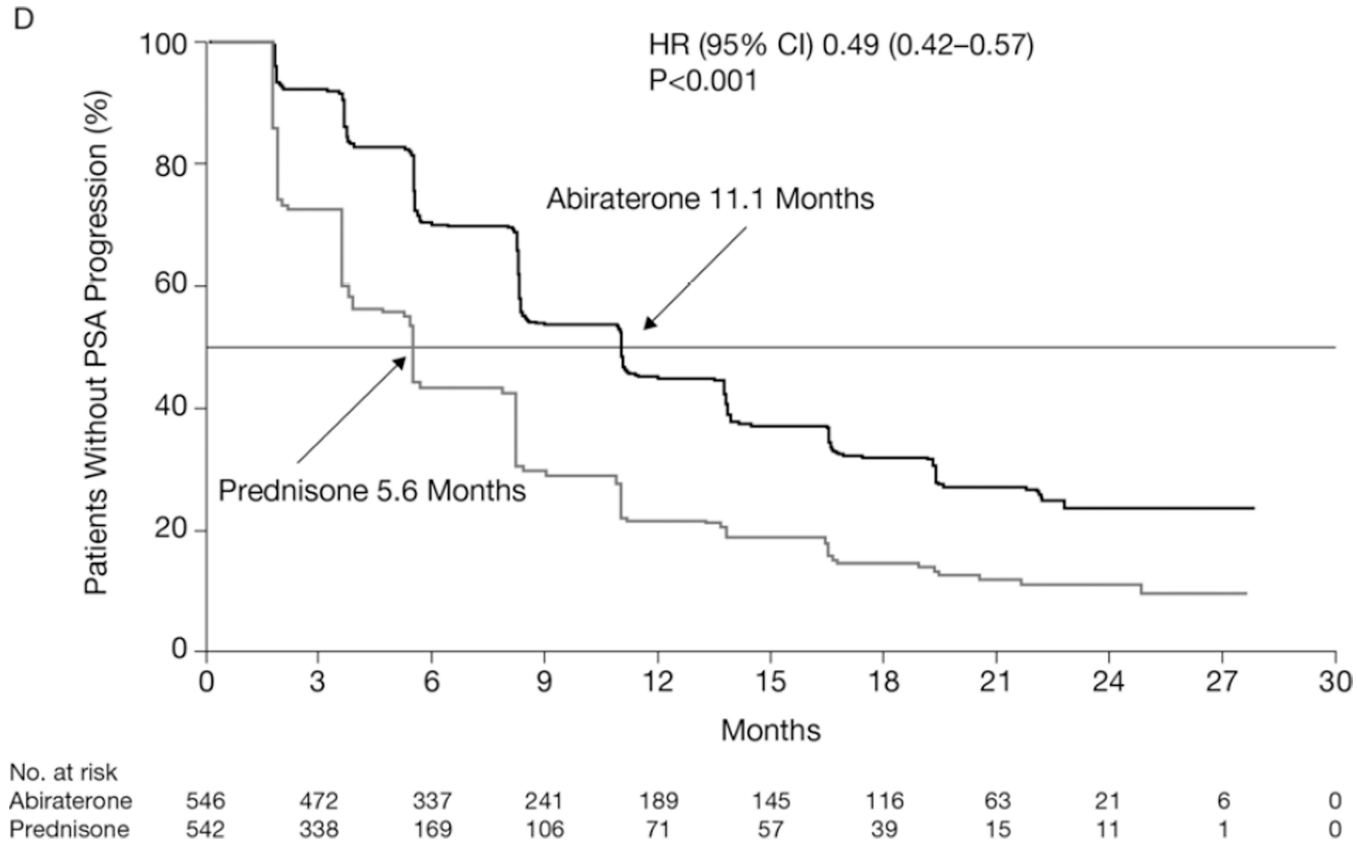


Figure 2. Secondary Exploratory Efficacy End Points

A. Time to Deterioration in Eastern Cooperative Oncology Group Performance Status Score by ≥1 Grade

B. Time to Initiation of Cytotoxic Chemotherapy

C. Time to Opiate Use for Prostate Cancer Pain

D. Time to Prostate-specific Antigen Progression

Table 1

Demographics and Baseline Disease Characteristics.

	Abiraterone (N = 546)	**Prednisone (N = 542)**
Age (yr)		
n	546	542
<65	135 (25%)	155 (29%)
65–69	112 (21%)	103 (19%)
70–74	114 (21%)	119 (22%)
≥75	185 (34%)	165 (30%)
Median	71.0	70.0
Range	44–95	44–90
Gleason score at initial diagnosis		
n	488	508
≤7	225 (46%)	254 (50%)
≥8	263 (54%)	254 (50%)
Previous cancer therapy		
n	544	542
Surgery	256 (47%)	244 (45%)
Radiotherapy	283 (52%)	303 (56%)
Hormonal	544 (100%)	542 (100%)
Other	82 (15%)	63 (12%)
PSA at initial diagnosis (ng/ml)		
n	470	454
Median	22.3	21.0
Range	0.4 – 5036.0	0.3 – 9726.3
Extent of disease		
n	542	540
Bone only	274 (51%)	267 (49%)
>10 bone metastases	264 (49%)	253 (47%)
Soft tissue or node	267 (49%)	271 (50%)
Other	4 (0.7%)	7 (1.3%)
Time from initial diagnosis to first dose (yr)		
n	542	540
Median	5.5	5.1
Range	0.0 – 28.0	0.0 – 28.0
Baseline PSA (ng/ml)		
n	546	539
Median	42.0	37.7
Range	0.0 – 3927.4	0.7 – 6606.4
Baseline alkaline phosphatase (IU/l)		
n	546	539

	Abiraterone (N = 546)	**Prednisone (N = 542)**
Median	93.0	90.0
Range	32 – 1927	21 – 3056
Baseline lactate dehydrogenase (U/l)		
n	543	536
Median	187.0	184.0
Range	60 – 871	87 – 781
Screening BPI-SF pain score (worst pain over last 24 hours)		
n	532	522
0–1	353 (66%)	336 (64%)
2–3	169 (32%)	170 (33%)
≥4	10 (2%)	16 (3%)
Median	0.0	0.0
Range	0–10	0–9
Median predicted survival (months) *	18.8	19.0

* Estimated using prognostic model for predicting survival in men with metastatic castrate-resistant prostate cancer.[27]

Table 2

Secondary and Prespecified Exploratory Efficacy End Points.

	Abiraterone (N = 546) Median, months	Prednisone (N = 542) Median, months	HR (95% CI)
Secondary end points			
Time to opiate use (cancer-related pain)	NE	23.7	0.69*** (0.57 to 0.83)
Time to initiation of cytotoxic chemotherapy	25.2	16.8	0.58*** (0.49 to 0.69)
Time to deterioration in ECOG performance score by ≥1 point	12.3	10.9	0.82** (0.71 to 0.94)
Time to PSA progression	11.1	5.6	0.49*** (0.42 to 0.57)
Exploratory end points			
Time to pain progression†	26.7	18.4	0.82* (0.67 to 0.99)
Time to functional status degradation by FACT-P total score	12.7	8.3	0.78** (0.66 to 0.92)
	Abiraterone (N=546)	**Prednisone (N=542)**	**RR (95% CI)**
PSA decline ≥50%‡	62%	24%	2.586*** (2.193 to 3.048)
	N = 220	**N = 218**	
RECIST: Defined objective response§	36%	16%	2.273*** (1.591 to 3.247)
Complete response	11%	4%	
Partial response	25%	12%	
Stable disease	61%	69%	
Progressive disease	2%	15%	

† Defined as a >30% increase from baseline pain measured by the average pain item in the Brief Pain Inventory-Short Form.

‡ Confirmed response and based on modified Prostate Cancer Working Group Criteria 2.

§ Patients with measureable disease at baseline.

CI denotes confidence interval, HR hazard ratio, NE not estimable, PSA prostate-specific antigen, RECIST, Response Evaluation Criteria in Solid Tumors, RR, relative risk.

* P<0.05,

** P<0.01,

*** P<0.001

Table 3

Adverse Events Reported During Treatment.

	Abiraterone (N = 542)	Prednisone (N = 540)
	Number (percent)	
Patients with AEs	537 (99)	524 (97)
Patients with grade 3/4 AEs	258 (48)	225 (42)
Patients with serious AEs	178 (33)	142 (26)
Patients with AEs leading to treatment discontinuation	55 (10)	49 (9)
Patients with AEs leading to death	20 (4)	12 (2)
AEs, all grades [*]		
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)
Pain in extremity	90 (17)	85 (16)
Cough	94 (17)	73 (14)
AEs of special interest [*†]		
Fluid retention/edema	149 (28)	127 (24)
Hypertension	117 (22)	71 (13)
Cardiac disorders [‡]	102 (19)	85 (16)
Hypokalemia	91 (17)	68 (13)
Hepatoxicity	97 (18)	59 (11)
Grade 3/4 AEs [§]		
Back pain	15 (3)	20 (4)
Fatigue	12 (2)	9 (2)
Anemia	11 (2)	9 (2)
Arthralgia	10 (2)	10 (2)
Bone pain	6 (1)	11 (2)
Urinary-tract infection	8 (2)	3 (<1)

[*] Incidence of ≥15% in either group

[†] AEs of special interest selected on the basis of the safety profile of phase 2 and phase 3 studies of abiraterone.

[‡] Cardiac disorders associated with abiraterone acetate treatment included ischemic heart disease, myocardial infarction, supraventricular tachyarrhythmias, ventricular tachyarrhythmias, cardiac failure, and possible arrhythmia related investigations, signs and symptoms.

[§] Incidence of ≥2% in either group.

AE denotes adverse event.