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Platinum Priority – Prostate Cancer

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Updated Interim Efficacy Analysis and Long-term Safety of Abiraterone Acetate in Metastatic Castration-resistant Prostate Cancer Patients Without Prior Chemotherapy (COU-AA-302)

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Abstract

Background: Abiraterone acetate (an androgen biosynthesis inhibitor) plus prednisone is approved for treating patients with metastatic castration-resistant prostate cancer (mCRPC). Study COU-AA-302 evaluated abiraterone acetate plus prednisone versus prednisone alone in mildly symptomatic or asymptomatic patients with progressive mCRPC without prior chemotherapy.
Objective: Report the prespecified third interim analysis (IA) of efficacy and safety outcomes in study COU-AA-302.
Design, setting, and participants: Study COU-AA-302, a double-blind placebo-controlled study, enrolled patients with mCRPC from April 2009 to June 2010. A total of 1088 patients were stratified by Eastern Cooperative Oncology Group performance status (0 vs 1).
Intervention: Patients were randomised 1:1 to abiraterone 1000 mg plus prednisone 5 mg twice daily by mouth versus prednisone.
Outcome measurements and statistical analysis: Co–primary end points were radiographic progression-free survival (rPFS) and overall survival (OS). Median times to event outcomes were estimated using the Kaplan-Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were derived using the Cox model, and treatment comparison

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used the log-rank test. The O'Brien-Fleming Lan-DeMets α-spending function was used for OS. Adverse events were summarised descriptively.

Results and limitations: With a median follow-up duration of 27.1 mo, improvement in rPFS was statistically significant with abiraterone treatment versus prednisone (median: 16.5 vs 8.2 mo; HR: 0.52 [95% CI, 0.45–0.61]; $p < 0.0001$). Abiraterone improved OS (median: 35.3 vs 30.1 mo; HR: 0.79 [95% CI, 0.66–0.95]; $p = 0.0151$) but did not reach the prespecified statistical efficacy boundary (α-level: 0.0035). A post hoc multivariate analysis for OS using known prognostic factors supported the primary results (HR: 0.74 [95% CI, 0.61–0.89]; $p = 0.0017$), and all clinically relevant secondary end points and patient-reported outcomes improved. While the post hoc nature of the long-term safety analysis is a limitation, the safety profile with longer treatment exposure was consistent with prior reports.

Conclusions: The updated IA of study COU-AA-302 in patients with mCRPC without prior chemotherapy confirms that abiraterone delays disease progression, pain, and functional deterioration and has clinical benefit with a favourable safety profile, including in patients treated for ≥24 mo.

Trial registration: Study COU-AA-302, ClinicalTrials.gov number, NCT00887198.

Patient summary: The updated results of this ongoing study showed that disease progression was delayed in patients with advanced prostate cancer who were treated with abiraterone acetate and prednisone, and there was a continued trend in prolongation of life compared with patients treated with prednisone alone. Treatment with abiraterone acetate and prednisone was well tolerated by patients who were treated for >2 yr.

1. Introduction

Androgen deprivation therapy is the standard of care for advanced prostate cancer (PCa), but patients invariably progress to castration-resistant disease despite castration levels of serum testosterone (<50 ng/dl) [1,2]. Metastatic castration-resistant PCa (mCRPC) represents the lethal form of the disease, with, until recently, limited treatment options and a median survival of <2 yr [3]. Chemotherapy provides an overall survival (OS) benefit for patients with mCRPC [4–7], but newer treatments with fewer side-effects are now available that may be preferable options before chemotherapy. Building on an increased understanding of the continued relevance of the androgen receptor signalling pathway in mCRPC, targeting residual androgen production offers great promise as a well-tolerated and effective alternative to standard cytotoxic therapies [8–10].

Abiraterone acetate is the prodrug of abiraterone, a specific inhibitor of CYP17 that blocks extragonadal, testicular, and tumour androgen biosynthesis [9,11,12]. In patients with mCRPC who had received prior docetaxel chemotherapy, abiraterone acetate (henceforth *abiraterone*) plus low-dose prednisone improved median OS by 4.6 mo (hazard ratio [HR]: 0.74; 95% confidence interval [CI], 0.64–0.86; $p < 0.0001$) compared with placebo plus prednisone (henceforth *prednisone*) [13,14].

Study COU-AA-302 is evaluating the clinical benefit of abiraterone plus prednisone versus prednisone in mildly symptomatic or asymptomatic patients with progressive mCRPC without prior chemotherapy [15]. Based on a preplanned interim analysis (IA) [15], the independent data-monitoring committee reviewed the masked efficacy and safety outcomes and recommended that the study be unblinded and patients be allowed to cross over from the prednisone group to receive abiraterone. Subsequently, in December 2012, abiraterone therapy received expanded regulatory approval in the United States and Europe [16] to also treat patients with mCRPC prior to receiving chemotherapy. We report the results of the third IA (IA3), preplanned at 55% OS events (425 of 773), for study COU-AA-302 and provide an update of efficacy and long-term safety outcomes.

2. Patients and methods

COU-AA-302 (NCT00887198) is a phase 3, multinational, randomised, double-blind, placebo-controlled study being conducted at 151 sites in 12 countries. Patients were enrolled from April 2009 to June 2010; the study is ongoing. The review boards at all participating institutions approved the study, which was conducted according to the Declaration of Helsinki, the International Conference on Harmonisation, and the Guidelines for Good Clinical Practice. All patients gave written informed consent.

2.1. Patient population

The study design and primary and secondary efficacy end points have been previously described in detail for the second IA (IA2) [15] and are summarised in this paper. The study included male patients aged ≥18 yr with chemotherapy-naive mCRPC, who were medically or surgically castrated, had tumour progression, and were asymptomatic or mildly symptomatic, as defined by the Brief Pain Inventory–Short Form (asymptomatic with scores of 0 or 1 or mildly asymptomatic with scores of 2–3). Patients with visceral metastases or patients who had received previous therapy with ketoconazole for >7 d were excluded.

2.2. Study design

Patients were stratified by Eastern Cooperative Oncology Group performance status (ECOG-PS) score (0 vs 1) and randomised 1:1 to receive abiraterone acetate 1000 mg plus prednisone 5 mg twice daily by mouth or placebo plus prednisone.

2.3. Efficacy outcomes

The co–primary end points were radiographic progression-free survival (rPFS) and OS. OS was defined as time from randomisation to death from

any cause. The *rPFS* endpoint was defined as time from randomisation to radiographic progression, as previously described [15], or death. The prespecified secondary efficacy end points were time to opiate use for cancer pain, time to initiation of cytotoxic chemotherapy, time to deterioration in ECOG-PS, and time to prostate-specific antigen (PSA) progression based on Prostate Cancer Working Group 2 (PCWG2) criteria [17]. Exploratory end points included PSA response rate, defined as the proportion of patients achieving a PSA decline ≥50% according to PCWG2 criteria [17]. Patient-reported outcomes (PROs) related to pain and functional status were prespecified in the study protocol (Supplement).

2.4. Safety

Clinical assessments were conducted at prespecified visits and included medical history, vital sign measurements, body weight, physical examination, review of concomitant therapy and procedures, and review of adverse events (AEs) and serious AEs.

2.5. Statistical analyses

All randomised patients were included in the intent-to-treat population, regardless of treatment received, and were analysed according to the randomised treatment group. All patients who received study treatment were included in the safety population [18]. Three interim analyses were planned for the OS end point at approximately 15%, 40%, and 55% OS events. The data cut-off for the IA3 was 22 May 2012, and the actual analysis was conducted at 56% OS events (434 of 773 events).

Median time-to-event end points were estimated using the Kaplan-Meier product limit method, and the log-rank test was used to compare the treatment differences. The HR and associated 95% CIs were estimated by the Cox proportional hazards model [18]. A significance level of 0.04 (0.0035 for IA3) was allocated for the OS end point (three interim and a final) using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets α-spending function [19]. An exploratory multivariate analysis for OS using the Cox proportional hazards model, adjusting for known baseline prognostic factors, was performed. The incidence of grade 1/2 and 3/4 AEs was descriptively reported for patients with treatment exposure of <3, 12–15, and ≥24 mo to provide a safety overview at representative time points in the disease process across short- and long-term treatment duration. The cumulative incidence of selected AEs from time to first incidence of the AE is summarised graphically.

3. Results

A total of 1088 patients were randomised 1:1 to study treatments: 546 to abiraterone plus prednisone therapy and 542 to prednisone therapy. Patients were evenly matched between treatment groups, and baseline characteristics were consistent with asymptomatic/minimally symptomatic chemotherapy-naive mCRPC (Table 1) [15]. At IA3, the median follow-up duration of OS for the intent-to-treat population was 27.1 mo. The median treatment duration at IA3 was 13.8 mo (range: 0.3–34.9) for abiraterone and 8.3 mo (range: 0.1–32.4) for prednisone.

At the time of analysis, treatment was ongoing for 23% of the patients in the abiraterone group and 11% of the patients in the prednisone group, while treatment discontinuations because of AEs were low across treatment groups (8% vs 6%, respectively) (Supplemental Fig. 1). Most patients discontinued therapy because of disease progression (57% in the abiraterone group and 68% in the prednisone group); the majority went on to receive cytotoxic chemotherapy for unequivocal clinical progression, as defined per protocol. Subsequent therapy with docetaxel was common in the abiraterone group (44%) and the prednisone group (56%), while 7% and 14% of patients, respectively, received subsequent abiraterone plus prednisone treatment (Table 2).

Table 1 – Baseline patient characteristics

Characteristic	Abiraterone plus prednisone, *n* = 546	Prednisone alone, *n* = 542
Median age, yr (IQR)	71 (65–77)	70 (63–76)
Median time from initial diagnosis to first dose, yr (IQR)	5.5 (2.7–9.7)	5.1 (2.8–9.1)
Median PSA, ng/ml (IQR)	42.0 (16.1–116.0)	37.7 (14.9–95.3)
Gleason score (≥8) at initial diagnosis, no. (%)	263 (54)	254 (50)
Extent of disease, no. (%)		
Bone metastases	452 (83)	432 (80)
>10	264 (49)	253 (47)
Soft tissue or node*	267 (49)	271 (50)
Pain at screening (BPI-SF), no. (%)		
0–1	353 (66)	336 (64)
2–3	169 (32)	170 (33)
BPI-SF score, mean ± SD; median (IQR)	*n* = 539	*n* = 534
Pain intensity	0.8 ± 1.1; 0.5 (0–1.25)	0.8 ± 1.1; 0.5 (0–1.25)
Worst pain intensity	1.2 ± 1.7; 0 (0–2)	1.2 ± 1.6; 1 (0–2)
Pain interference	0.7 ± 1.3; 0 (0–0.9)	0.7 ± 1.2; 0.1 (0–1.0)
FACT-P total score	*n* = 527	*n* = 526
Mean ± SD	122.1 ± 17.0	122.6 ± 17.7
Median (IQR)	124.0 (112.0–134.7)	126.0 (112.0–137.0)

BPI-SF = Brief Pain Inventory–Short Form; FACT-P = Functional Assessment of Cancer Therapy–Prostate; IQR = interquartile range (25th and 75th quartiles); PSA = prostate-specific antigen; SD = standard deviation.
* Excludes visceral metastases.

Table 2 – Subsequent therapy for prostate cancer

	Abiraterone plus prednisone (*n* = 546), no. (%)	Prednisone alone (*n* = 542), no. (%)
Patients with selected subsequent therapy for mCRPC*	274 (50)	348 (64)
Docetaxel	239 (44)	304 (56)
Cabazitaxel	60 (11)	70 (13)
Ketoconazole	39 (7)	63 (12)
Abiraterone†	38 (7)	78 (14)
Sipuleucel-T	33 (6)	28 (5)

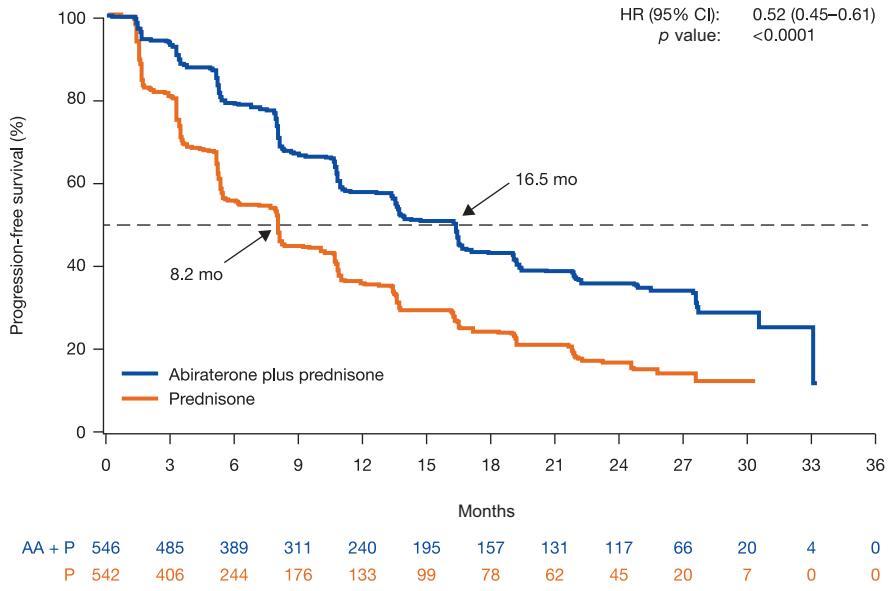
mCRPC = metastatic castration-resistant prostate cancer.
Table reports cumulative incidence of subsequent therapy regardless of sequence after study drug discontinuation to the third interim analysis clinical cut-off date of 22 May 2012.
* First patient crossover after unblinding on 7 May 2012.
† Prior to unblinding and crossover from the prednisone arm to the abiraterone arm.

3.1. Efficacy outcomes

Patients receiving abiraterone compared with prednisone had statistically significant improvement in rPFS ($p < 0.0001$), with a median time to disease progression

or death (per protocol definition) of 16.5 mo versus 8.2 mo, respectively (HR: 0.52; $p < 0.0001$) (Fig. 1A). This improvement was observed across all patient subgroups (Fig. 1B). The OS analysis favoured abiraterone therapy over prednisone (median: 35.3 vs 30.1 mo; HR: 0.79; $p = 0.0151$) but did not cross the prespecified statistical boundary with an α-level of 0.0035 (Fig. 2). An exploratory multivariate analysis adjusting for baseline prognostic factors supported an OS benefit for abiraterone versus prednisone (HR: 0.74; $p = 0.0017$) (Table 3). Baseline serum PSA, lactate dehydrogenase,

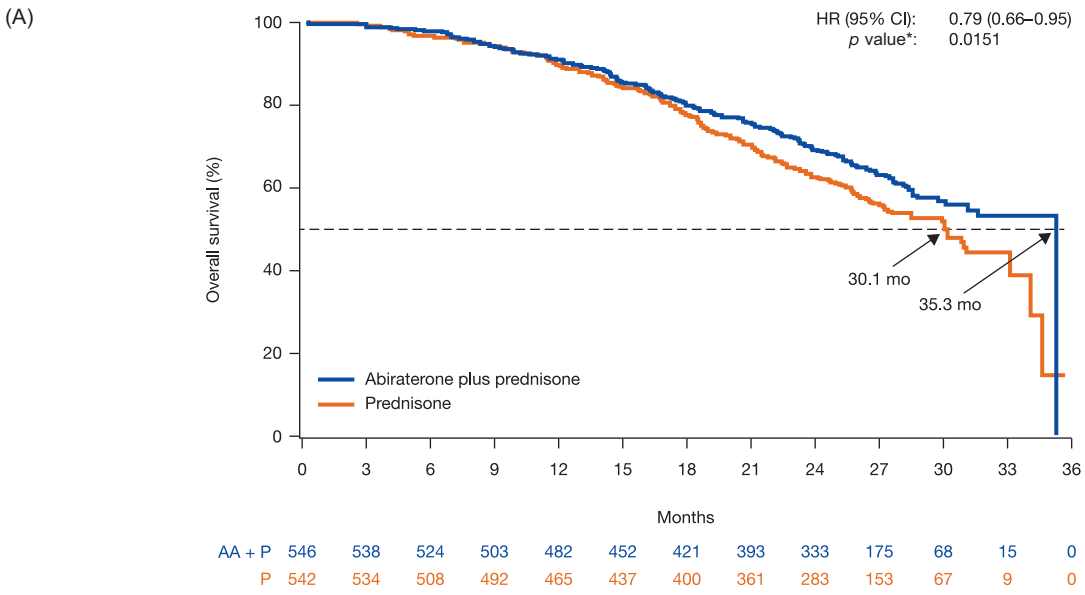
(A)



(B)

Variable	Subgroup	Median (mo) AA + P	Median (mo) P	HR	95% CI	Events/N AA + P	Events/N P
All patients	ALL	16.5	8.2	0.52	(0.45–0.61)	292/546	352/542
Baseline ECOG	0	16.4	8.3	0.55	(0.46–0.66)	233/416	269/414
	1	18.0	7.4	0.43	(0.31–0.61)	59/130	83/128
Baseline BPI	0–1	16.6	8.3	0.52	(0.42–0.63)	195/370	220/346
	2–3	10.7	7.4	0.60	(0.44–0.82)	74/129	94/147
Bone metastasis only at entry	YES	20.7	11.1	0.54	(0.42–0.70)	107/238	132/242
	NO	11.2	5.7	0.49	(0.41–0.60)	185/308	220/300
Age	<65	16.6	8.1	0.47	(0.35–0.64)	75/135	107/155
	≥65	16.5	8.3	0.55	(0.46–0.66)	217/411	245/387
	≥75	14.9	8.2	0.63	(0.48–0.83)	98/185	108/165
Baseline PSA above median	YES	12.8	5.8	0.54	(0.43–0.67)	168/282	167/260
	NO	19.4	10.2	0.46	(0.37–0.58)	124/264	185/282
Baseline LDH above median	YES	14.1	5.6	0.48	(0.38–0.60)	150/278	171/259
	NO	16.6	10.2	0.55	(0.44–0.69)	142/268	181/283
Baseline ALK-P above median	YES	13.6	5.6	0.55	(0.44–0.68)	163/279	161/256
	NO	19.4	9.7	0.47	(0.37–0.59)	129/267	191/286
Region	N.A.	16.6	8.2	0.49	(0.40–0.62)	154/297	177/275
	Other	16.3	8.3	0.56	(0.45–0.70)	138/249	175/267

Fig. 1 – Co–primary end point: (A,B) radiographic progression-free survival assessed by investigator review at prespecified interim analysis. (B) The size of the circle reflects the number of patients affected. For hazard ratio (HR) <1, the result favours abiraterone.
AA = abiraterone; ALK-P = alkaline phosphatase; BPI = Brief Pain Inventory; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; N.A. = North America; P = prednisone; PSA = prostate-specific antigen.



(B)

Favours abiraterone plus prednisone ← → Favours prednisone

Variable	Subgroup	Median (mo) AA + P	Median (mo) P	HR	95% CI	Events/N AA + P	Events/N P
All patients	ALL	35.3	30.1	0.79	(0.66–0.95)	200/546	234/542
Baseline ECOG	0	35.3	30.3	0.76	(0.60–0.95)	139/416	171/414
	1	28.3	26.4	0.89	(0.62–1.26)	61/130	63/128
Baseline BPI	0–1	35.3	31.0	0.74	(0.57–0.94)	117/370	136/346
	2–3	26.4	27.0	0.94	(0.68–1.31)	65/129	78/147
Bone metastasis only at entry	YES	35.3	31.0	0.70	(0.51–0.95)	72/238	93/241
	NO	30.2	30.0	0.86	(0.68–1.10)	128/308	141/301
Age	<65	35.3	34.1	0.82	(0.56–1.20)	48/135	60/155
	≥65	NE	30.1	0.78	(0.63–0.97)	152/411	174/387
	≥75	28.6	25.6	0.74	(0.55–1.00)	80/185	90/165
Baseline PSA above median	YES	28.6	25.7	0.78	(0.61–0.99)	124/282	140/260
	NO	35.3	33.2	0.78	(0.58–1.06)	76/264	94/282
Baseline LDH above median	YES	NE	24.3	0.68	(0.53–0.87)	114/278	139/259
	NO	35.3	34.7	0.93	(0.69–1.24)	86/268	95/283
Baseline ALK-P above median	YES	27.8	26.6	0.86	(0.67–1.10)	127/279	128/256
	NO	NE	31.0	0.67	(0.50–0.91)	73/267	106/286
Region	N.A.	35.3	30.2	0.72	(0.55–0.94)	104/297	120/275
	Other	NE	30.3	0.89	(0.68–1.17)	96/249	114/267

Fig. 2 – Co–primary end point: (A,B) overall survival. Prespecified significance level by the O'Brien-Fleming boundary = 0.0035. (B) The size of circle reflects the number of patients affected. For hazard ratio (HR) <1, the result favours abiraterone.
AA = abiraterone; ALK-P = alkaline phosphatase; BPI = Brief Pain Inventory; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; N.A. = North America; NE = not estimable; P = prednisone; PSA = prostate-specific antigen.

alkaline phosphatase, haemoglobin, bone metastasis, and age were significant prognostic factors ($p < 0.01$) (Table 3).

All secondary end points favoured abiraterone versus prednisone (Fig. 3). Abiraterone delayed the time to opiate use for cancer-related pain (HR: 0.71; $p = 0.0002$) and time to initiation of chemotherapy (HR: 0.61; $p < 0.0001$). Abiraterone also delayed the time to deterioration in ECOG-PS (HR: 0.83; $p = 0.005$) and PSA progression (HR: 0.50; $p < 0.0001$).

Table 3 – Exploratory multivariate analysis of overall survival

Parameter*	Hazard ratio (95% CI)	*p* value
Treatment (abiraterone plus prednisone vs prednisone alone)	0.74 (0.61–0.89)	0.002
ECOG score (1 vs 0)	1.17 (0.94–1.45)	0.2
Log (baseline serum PSA, ng/ml)	1.18 (1.10–1.27)	<0.0001
Log (baseline lactate dehydrogenase, IU/l)	3.07 (2.11–4.48)	<0.0001
Log (baseline alkaline phosphatase, IU/l)	1.33 (1.14–1.56)	0.0003
Baseline haemoglobin, g/dl	0.92 (0.85–0.99)	0.02
Bone metastasis only at baseline, yes vs no	0.69 (0.57–0.85)	0.0003
Age	1.02 (1.01–1.03)	0.0006

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; PSA = prostate-specific antigen.
Patients who are not deceased at time of analysis are censored on the last date they were known to be alive or lost to follow-up.
* Post hoc sensitivity analysis. Model dependent variable is overall survival, expressed as days from date of randomisation to death from any cause.

The PSA response rate (≥50%) was more than doubled with abiraterone (68% [374 of 546]) compared with prednisone (29% [156 of 542]) (Fig. 4).

3.2. Patient-reported outcomes

The baseline pain scores and functional status scores (see Supplement for definitions) were well balanced between study groups (Table 1). The compliance rates across treatment groups for completion of the Brief Pain Inventory–Short Form and Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaires were >95% each; compliance was defined as the number of completed questionnaires over the total expected. Following treatment, PRO scores showed a consistent pattern of delays in pain progression and in degradation of subscales of functional status for patients treated with abiraterone versus prednisone (Table 4). Patients receiving abiraterone had statistically significant improvement in pain interference ($p = 0.005$) versus prednisone, although the improvement in mean pain intensity ($p = 0.061$) was not significant (Table 4).

Using the prespecified ≥30% change from baseline in pain intensity as the minimal important difference, the worst pain intensity was not significantly different between treatment groups ($p = 0.113$) (Table 4). Abiraterone treatment did delay degradation in FACT-P total scores

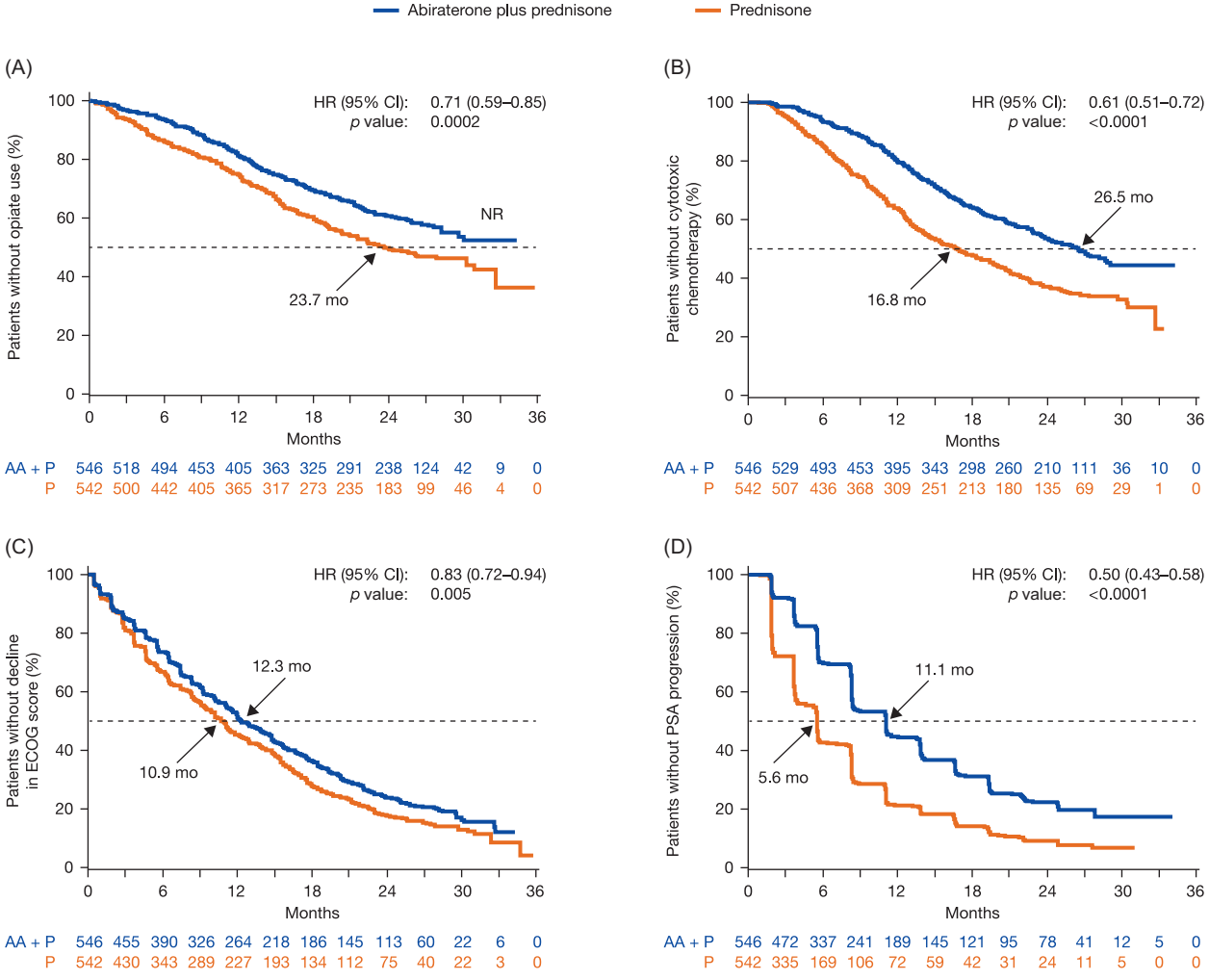


Fig. 3 – Secondary end points: (A) time to opiate use for cancer-related pain; (B) time to initiation of chemotherapy; (C) time to deterioration in the Eastern Cooperative Oncology Group (ECOG) score; (D) time to prostate-specific antigen (PSA) progression.
AA = abiraterone; CI = confidence interval; HR = hazard ratio; NR = not reached; P = prednisone.

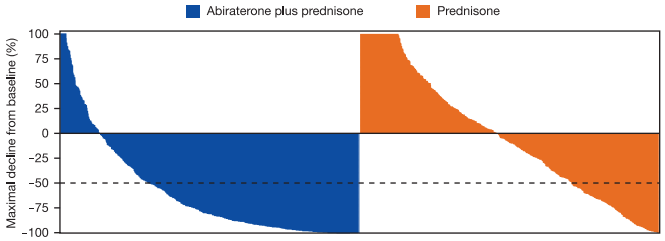


Fig. 4 – Maximal prostate-specific antigen (PSA) decline from baseline. A negative percentage indicates a decline in PSA. A positive percentage indicates that the patient never has a decline in PSA.

Table 4 – Patient-reported outcomes

PRO end points	Abiraterone plus prednisone, $n = 546$	Prednisone alone, $n = 542$	Hazard ratio* (95% CI)	p value†
Median time to pain progression, mo				
Mean pain intensity‡	26.7	18.4	0.83 (0.68–1.01)	0.06
Pain interference###	10.3	7.4	0.80 (0.68–0.93)	0.005
Worst pain intensity‡ (prespecified analysis)	25.8	20.3	0.85 (0.69–1.04)	0.1
Median time to functional status degradation, mo				
FACT-P total score‖	12.7	8.3	0.79 (0.67–0.93)	0.005
FACT general score¶	16.6	11.1	0.76 (0.64–0.91)	0.002
Prostate Cancer Subscale	11.1	5.8	0.72 (0.61–0.84)	<0.0001
Physical well-being	14.8	11.1	0.76 (0.64–0.91)	0.002
Functional well-being	13.3	8.4	0.77 (0.65–0.91)	0.002
Trial outcome index**	13.9	9.3	0.77 (0.65–0.91)	0.002
Social/family well-being	18.4	16.6	0.95 (0.78–1.15)	0.6
Emotional well-being	22.5	14.2	0.73 (0.61–0.89)	0.002

BPI-SF = Brief Pain Inventory–Short Form; CI = confidence interval; FACT = Functional Assessment of Cancer Therapy; FACT-P = Functional Assessment of Cancer Therapy–Prostate; PRO = patient-reported outcomes.
* Obtained from stratified proportional hazards model. Hazard ratio <1 favours abiraterone plus prednisone.
† Obtained from log-rank test stratified by Eastern Cooperative Oncology Group performance status (0 or 1).
‡ Progression: ≥30% increase from baseline in BPI-SF score without decreased analgesic usage score, at two consecutive visits.
Pain interference progression: an increase at any visit in the baseline BPI-SF pain interference score of one-half the baseline standard deviation of BPI-SF.
‖ Total score consists of FACT general and Prostate Cancer Subscale scores.
¶ FACT general score consists of physical well-being, social/family well-being, emotional well-being, and functional well-being subscales.
** Trial outcome index consists of physical well-being, functional well-being, and Prostate Cancer Subscale.

($p = 0.005$) and in the PCa-specific subscale scores ($p < 0.0001$) versus prednisone (Table 4). All other FACT-P subscales also favoured abiraterone versus prednisone, except the social/family well-being subscale ($p = 0.577$).

3.3. Safety

AEs are summarised in Table 5. The most frequently reported AEs (≥15% of patients in either group) were similar to those reported previously (Table 5) [15]. The most frequently reported grade 3/4 AEs in the abiraterone or prednisone treatment groups (reported in ≥3% of patients in either group) were alanine aminotransferase (ALT) increased (6% [30 of 542] vs 1% [4 of 540]), hypertension (4% [23 of 542] vs 3% [17 of 540]), back pain (3% [15 of 542] vs 4% [21 of 542]), hyperglycaemia (3% [14 of 542] vs 2% [11 of 540]), hypokalaemia (3% [14 of 542] vs 2% [10 of 542]), aspartate aminotransferase (AST) increased (3% [17 of 542] vs 1% [5 of 540]), and dyspnoea (3% [14 of 542] vs 1% [5 of 540]), respectively.

AEs leading to dose modifications or interruption of treatment occurred in 21% of patients receiving abiraterone (112 of 542) and in 12% of patients in the prednisone group (65 of 540) and included ALT increased, AST increased, hypertension, and vomiting. AEs leading to death occurred in 4% of patients in the abiraterone group (21 of 542) and 3% of patients in the prednisone group (16 of 540). Drug-related treatment-emergent AEs leading to death occurred in 1% of patients in each treatment group (6 patients each).

AEs of special interest included events related to mineralocorticoid excess (hypertension, hypokalaemia, fluid retention) based on the known mechanism of action of abiraterone. Grade 3 or 4 mineralocorticoid-related AEs and increases in ALT and AST were more common with abiraterone (Table 5). The grade 3 or 4 AEs of increased ALT and AST remained higher in the abiraterone group (6% [30 of 542] and 3% [17 of 542]) versus the prednisone group (1% [4 of 540] and 1% [5 of 540]), respectively. Grade 3 or 4 cardiac disorder AEs in the abiraterone versus the prednisone group were rare: arrhythmias (4% [21 of 542] vs 2% [11 of 540]), ischaemic heart disease (2% [11 of 542] vs 1% [8 of 540]), cardiac failure (1% [6 of 542] vs 0), and cardiac disorders of other causes (<1% each), respectively. Cardiac disorders that led to treatment discontinuation were also extremely

Table 5 – Safety overview and adverse events of special interest

	Abiraterone plus prednisone (n = 542), no. (%)		Prednisone alone (n = 540), no. (%)	
AEs (grade 1–4)	538 (99)		524 (97)	
Grade 3/4 AE	267 (49)		235 (44)	
Any serious AE	188 (35)		146 (27)	
AE leading to treatment discontinuation	58 (11)		53 (10)	
AE leading to death	21 (4)		16 (3)	
Common AEs (≥15% patients in either group)	**Grade 1–4, no. (%)**		**Grade 1–4, no. (%)**	
Fatigue	215 (40)		187 (35)	
Back pain	180 (33)		179 (33)	
Arthralgia	159 (29)		132 (24)	
Peripheral oedema	141 (26)		113 (21)	
Nausea	130 (24)		124 (23)	
Constipation	128 (24)		110 (20)	
Hot flush	123 (23)		99 (18)	
Diarrhoea	127 (23)		98 (18)	
Hypertension	118 (22)		73 (14)	
Bone pain	113 (21)		103 (19)	
Cough	98 (18)		74 (14)	
Hypokalaemia	93 (17)		69 (13)	
Pain in extremity	93 (17)		87 (16)	
Musculoskeletal pain	88 (16)		81 (15)	
Insomnia	79 (15)		62 (12)	
Muscle spasm	77 (14)		111 (21)	
AEs of special interest	**Grade 1–4, no. (%)**	**Grades 3/4, no. (%)**	**Grade 1–4, no. (%)**	**Grades 3/4, no. (%)**
Fatigue	215 (40)	13 (2)	187 (35)	10 (2)
Fluid retention	159 (29)	5 (1)	130 (24)	9 (2)
Hypertension	118 (22)	23 (4)	73 (14)	17 (3)
Cardiac disorders	110 (20)	36 (7)	92 (17)	19 (4)
Hypokalaemia	93 (17)	14 (3)	69 (13)	10 (2)
ALT increased	65 (12)	30 (6)	27 (5)	4 (1)
AST increased	60 (11)	17 (3)	26 (5)	5 (1)
Hyperglycaemia	47 (9)	14 (3)	43 (8)	11 (2)
Weight gain	28 (5)	0	39 (7)	0

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

rare and were reported in <1% of patients in each treatment group. In a post hoc analysis, the incidence of selected grade 3 or 4 AEs was low, despite longer abiraterone treatment exposure (Supplemental Fig. 2). The cumulative incidence of selected AEs (all grades) from the time of first event was similar across treatment groups (Supplemental Fig. 3).

4. Discussion

We present the updated efficacy and safety outcomes from the prespecified IA3, with longer treatment exposure and a greater number of death events—434 compared with 333 in the previous analysis [15]. With a longer follow-up of 27.1 mo, the current results confirm the clinical benefits of abiraterone versus prednisone in chemotherapy-naive patients with mCRPC, including significantly delayed time to disease progression (16.5 mo vs 8.2 mo; HR: 0.52; $p < 0.0001$). Abiraterone therapy improved OS compared with prednisone (median: 35.3 mo vs 30.1 mo; HR: 0.79; $p = 0.0151$), but this result did not cross the prespecified efficacy boundary for statistical significance, as defined by the O'Brian-Fleming boundary implemented by the Lan-DeMets α-spending function.

This study also used two primary end points and several clinically relevant secondary end points to establish efficacy and clinical benefit. Previous findings at IA2 of this study showed that rPFS, when assessed by investigator review, was consistently and robustly associated with OS, with a Spearman correlation coefficient of 0.72 between the two end points [15,20]. All secondary end points (time to opiate use for cancer-related pain, time to cytotoxic chemotherapy, time to ECOG-PS deterioration by at least one grade, time to PSA progression) remained consistent with the results of previous analyses [15] and demonstrated statistically significant differences in favour of treatment with abiraterone compared with prednisone.

Additionally, this study incorporated and reported prespecified, validated PRO measures to show that abiraterone treatment delayed pain progression and deterioration of functional status compared with prednisone, consistent with our previous IA2 report [21]. Along with previous explorations of PROs in patients with mCRPC following chemotherapy [22–24], the current data further confirm the value of addressing the concerns of patients and clinicians related to improvements in how the patient feels and functions during treatment.

Unmet needs for chemotherapy-naive patients with progressive mCRPC are low toxicity and effective treatments that can prolong life, delay disease progression, and maintain quality of life [25]. Second-line antiandrogens,

nonspecific adrenal androgen inhibitors, and oestrogen-based therapies are associated with PSA responses in some patients, but the effects of these agents on survival are unknown [25–27]. Sipuleucel-T, an immunotherapeutic drug, has demonstrated significant survival benefit over placebo for patients with mCRPC (median OS: 25.8 mo vs 21.7 mo; $p = 0.03$) [28], with no impact on disease progression (median: 3.7 mo vs 3.6 mo; $p = 0.63$) or post-therapy changes in PSA. Enzalutamide is approved in the United States and the European Union based on survival benefits in patients with mCRPC following chemotherapy [29], and positive results for chemotherapy-naive mCRPC were recently announced [30]. Radium 223 chloride is approved in the United States and Europe for patients with symptomatic bone mCRPC without visceral metastasis [31].

The most common subsequent therapy for patients who terminated the study was docetaxel in both study groups (44% for abiraterone; 56% for prednisone). As the data cut-off date for the current analysis (22 May 2012) was in proximity to the date of unblinding of the study, as recommended by the independent data-monitoring committee (7 May 2012), only three patients had crossed over from the prednisone group to receive abiraterone. Hence, the unblinding of the study is unlikely to have had a significant impact on the study results presented in this paper.

The safety findings of the updated results with longer follow-up are similar to those of the previous report [15], with mostly grade 1 or 2 AEs. Among AEs of special interest, only increased ALT or AST remained higher in the abiraterone group than in the prednisone group, similar to the previous observation [15]. Post hoc analyses of long-term safety did not reveal any new safety findings in patients with $\geq$24 mo of treatment exposure with abiraterone or with prednisone. Despite the limitation of a post hoc analysis, these results are particularly reassuring for clinicians who may be concerned about long-term side-effects of prolonged prednisone exposure.

5. Conclusions

In patients with asymptomatic and mildly symptomatic mCRPC without prior chemotherapy, treatment with abiraterone plus prednisone significantly delayed disease progression, time to opiate use, and initiation of chemotherapy, and it was associated with an increase in OS. Abiraterone also delayed functional decline and progression of pain interference compared with prednisone alone. No new safety signals were observed with $\geq$24 mo of treatment with abiraterone or with prednisone. With the follow-up duration now exceeding 27 mo, this ongoing study in patients with mCRPC provides more mature efficacy and safety follow-up outcomes. The observed continued benefits of prolonged rPFS, coupled with the improved maintenance of quality of life, are particularly important for chemotherapy-naive patients with mCRPC.

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Appendix A. Supplementary data

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