Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study

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Summary

Background Abiraterone acetate plus prednisone significantly improved radiographic progression-free survival compared with placebo plus prednisone in men with chemotherapy-naive castration-resistant prostate cancer at the interim analyses of the COU-AA-302 trial. Here, we present the prespecified final analysis of the trial, assessing the effect of abiraterone acetate plus prednisone on overall survival, time to opiate use, and use of other subsequent therapies.

Methods In this placebo-controlled, double-blind, randomised phase 3 study, 1088 asymptomatic or mildly symptomatic patients with chemotherapy-naive prostate cancer stratified by Eastern Cooperative Oncology performance status (0 *vs* 1) were randomly assigned with a permuted block allocation scheme via a web response system in a 1:1 ratio to receive either abiraterone acetate (1000 mg once daily) plus prednisone (5 mg twice daily; abiraterone acetate group) or placebo plus prednisone (placebo group). Coprimary endpoints were radiographic progression-free survival and overall survival analysed in the intention-to-treat population. The study is registered with ClinicalTrials.gov, number NCT00887198.

Findings At a median follow-up of 49·2 months (IQR 47·0–51·8), 741 (96%) of the prespecified 773 death events for the final analysis had been observed: 354 (65%) of 546 patients in the abiraterone acetate group and 387 (71%) of 542 in the placebo group. 238 (44%) patients initially receiving prednisone alone subsequently received abiraterone acetate plus prednisone as crossover per protocol (93 patients) or as subsequent therapy (145 patients). Overall, 365 (67%) patients in the abiraterone acetate group and 435 (80%) in the placebo group received subsequent treatment with one or more approved agents. Median overall survival was significantly longer in the abiraterone acetate group than in the placebo group (34·7 months [95% CI 32·7–36·8] *vs* 30·3 months [28·7–33·3]; hazard ratio 0·81 [95% CI 0·70–0·93]; p=0·0033). The most common grade 3–4 adverse events of special interest were cardiac disorders (41 [8%] of 542 patients in the abiraterone acetate group *vs* 20 [4%] of 540 patients in the placebo group), increased alanine aminotransferase (32 [6%] *vs* four [<1%]), and hypertension (25 [5%] *vs* 17 [3%]).

Interpretation In this randomised phase 3 trial with a median follow-up of more than 4 years, treatment with abiraterone acetate prolonged overall survival compared with prednisone alone by a margin that was both clinically and statistically significant. These results further support the favourable safety profile of abiraterone acetate in patients with chemotherapy-naive metastatic castration-resistant prostate cancer.

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Introduction

An overarching feature of the recent management of metastatic castration-resistant prostate cancer is the use of sequential therapies. Before 2010, the only approved systemic treatment associated with improved overall survival was docetaxel.[1,2] Over the past 4 years, five therapeutics with demonstrated survival benefit in randomised clinical studies have become available, and are commonly used in sequence.[3–11] Given the chronicity and heterogeneity of metastatic castration-resistant prostate cancer, administration of such subsequent therapies may confound the measurement of the effect of a particular treatment on overall survival.

Abiraterone acetate is a prodrug of abiraterone, an orally available inhibitor of the cytochrome P450 c17 enzyme complex critical to androgen production. Oral abiraterone acetate plus prednisone demonstrated a significant improvement in survival, compared with placebo plus prednisone, for patients with metastatic castration-resistant prostate cancer with progression of

disease after administration of chemotherapy.[5,6] In chemotherapy-naive patients, abiraterone acetate plus prednisone delayed radiographic progression, prevented the onset of symptoms, and preserved quality of life, compared with placebo plus prednisone.[9,10,12] However, at the interim analyses, overall survival results did not cross the prespecified efficacy boundary for statistical significance as defined by O'Brien and Fleming.[13]

Here, we present the final overall survival analysis of the COU-AA-302 trial of abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive patients with metastatic castration-resistant prostate cancer.

Methods

Study design and participants

The patient population for this multinational, double-blind, randomised, placebo-controlled phase 3 trial has been described previously.[9,10] Briefly, patients aged 18 years or over with histologically or cytologically confirmed adenocarcinoma of the prostate, prostate-specific antigen (PSA) progression according to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria, or radiographic progression in soft tissue or bone with or without PSA progression, ongoing androgen deprivation therapy with a serum testosterone level of less than 50 ng/dL (1·7 nmol/L), an Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1, with Brief-Pain Inventory-Short Form scores of 0–1 (asymptomatic) or 2–3 (mildly symptomatic), previous anti-androgen therapy followed by documented PSA progression after discontinuing the anti-androgen, and haematological and chemical laboratory values that met predefined criteria were eligible. Patients with visceral metastases or patients who had received previous therapy with ketoconazole for more than 7 days were excluded. The review boards at all participating institutions approved the study, conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation. All patients provided written informed consent to participate in the study.

Randomisation and masking

Patients were randomly assigned with a permuted block allocation scheme in a 1:1 ratio to receive either abiraterone acetate and prednisone (abiraterone acetate group), or placebo plus prednisone (placebo group). Patients were stratified according to baseline ECOG performance status (0 *vs* 1). After review of the second interim analysis results, the independent data monitoring committee recommended unblinding of the study and crossover of patients in the placebo group to receive abiraterone acetate plus prednisone. Eligibility criteria for patients receiving placebo plus prednisone who crossed over to abiraterone acetate and prednisone were instituted for ethical reasons. placebo plus prednisone group and in long-term follow-up, investigator assessment that abiraterone acetate therapy would be safe and beneficial, not currently receiving prostate cancer therapy other than luteinising hormone-releasing hormone analogues, no concomitant administration of cytotoxic chemotherapy, and ECOG performance status of 0, 1, or 2.

Procedures

Patients in the abiraterone acetate group received abiraterone acetate (Patheon, Mississauga, Canada) at a dose of 1000 mg (administered as four 250 mg tablets) and prednisone at a dose of 5 mg orally twice daily, while those in the placebo group received four placebo tablets once daily with the same dose of prednisone as in the experimental group. The planned duration for study treatment was until radiographic progression of disease, clinical progression, or both, or if the patient had unresolved adverse events, initiated new anticancer treatment, was lost to follow-up, or withdrew informed consent for treatment. Overall survival follow-up was for 60 months or until the patient died, was lost to follow-up, or withdrew consent for the study follow-up. Patients were allowed only two dose reductions for abiraterone acetate, the first to three tablets (750 mg) daily and, if indicated, a second to two tablets (500 mg) daily. The most common triggers for dose reduction were to restart dosing (referring to restarting of dosing after a patient had an adverse event; 31 [6%] patients in the abiraterone acetate group and eight [2%] patients in the placebo group) and adverse events or toxicity (six [1%] patients in the abiraterone acetate group and one [<1%] in the placebo group).

Radiographic assessments with CT or MRI and bone scanning were done every 8 weeks during the first 24 weeks and every 12 weeks thereafter. Clinical safety assessments included laboratory monitoring of blood chemical levels, haematological values, coagulation studies, serum lipids, kidney function, and PSA at baseline and prespecified visits.

Outcomes

The coprimary endpoints were radiographic progression-free survival and overall survival. Overall survival has been reported previously in interim analyses,[9,10] and the analysis of radiographic progression-free survival requiring 378 events was fully matured as reported previously.[9] The focus of this report is an update of overall survival from the final analysis and the secondary endpoint of time to opiate use for cancer-related pain. Long-term safety data are also reported.

Statistical analysis

A final analysis was planned when 773 death events had occurred. The group-sequential design was used for the overall survival endpoint with O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending

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See Online for appendix

Kaplan-Meier method, where patients were censored at death. The primary statistical method of comparison for the time-to-event endpoints was the stratified log-rank test stratified by baseline ECOG score. The Cox proportional-hazards model was used to estimate the hazard ratio (HR) and its associated CI. A planned sensitivity analysis to adjust for crossover effect via the iterative parameter estimate (IPE) method[14] was done to estimate the true treatment effect under an accelerated failure time model. The IPE method retains all patients in the treatment groups to which they were originally randomised. By conditioning on having observed patient switch times, the IPE method iteratively estimates the treatment effect by discounting the survival times of crossover patients so that they are comparable to the survival times of non-crossover patients, assuming the experimental group is always receiving effective treatment while the control group is receiving the same effective treatment at the start of crossover or subsequent therapy. An exploratory multivariate analysis for overall survival evaluated the potential effect of important prognostic factors on the treatment effect. Based on multivariate analysis at the second interim analysis, the following significant (univariate, $p<0{\cdot}01$) prognostic factors were included in the Cox regression model: ECOG performance status score, baseline serum PSA, baseline lactate dehydrogenase, baseline alkaline phosphatase, baseline haemoglobin, bone metastasis at baseline, and age. Efficacy analyses compared the randomised abiraterone acetate and placebo treatment groups. Data for exposure and safety analyses are reported by treatment received (ie, for patients assigned to the abiraterone acetate group who received abiraterone acetate plus prednisone, and patients assigned to the placebo group who received placebo plus prednisone); for patients assigned to the placebo group who later crossed over to abiraterone acetate, safety data from before crossover were used.

We used SAS version 9.1 for all key analyses. The study is registered with ClinicalTrials.gov, number NCT00887198.

Role of the funding source

Employees of the funder participated in the development of the trial design, data monitoring, data collection, data analysis, data interpretation, and writing of the manuscript. The first manuscript draft was initially written by the lead academic author (CJR) with sponsor input and editorial assistance funding. All coauthors subsequently provided input and approval to submit for publication. The authors assume responsibility for the completeness and integrity of the data, the study fidelity to the protocol, and statistical analysis. CJR had full access to all of the data and the final responsibility to submit for publication.

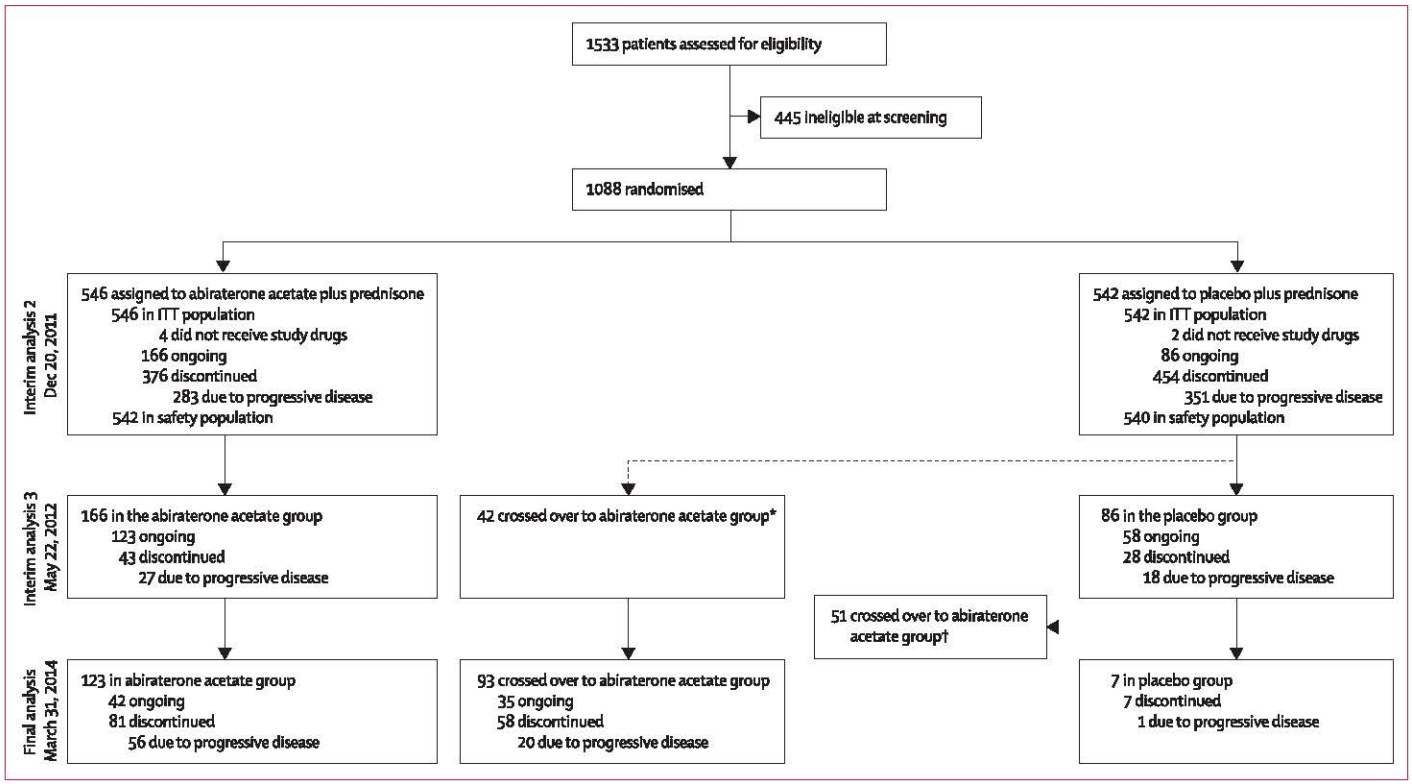

Figure 1: **Trial profile**

After interim analysis 2, the protocol was amended to allow patients receiving placebo plus prednisone (amendment 2) or those who were discontinued from placebo plus prednisone but continuing

	Abiraterone acetate group (n=546)	Placebo group (n=542)
Patients with subsequent therapy	365 (67%)	435 (80%)
Abiraterone acetate	69 (13%)	238 (44%)
Cabazitaxel	100 (18%)	105 (19%)
Docetaxel	311 (57%)	331 (61%)
Enzalutamide	87 (16%)	54 (10%)
Ketoconazole	42 (8%)	68 (13%)
Radium-223	20 (4%)	7 (1%)
Sipuleucel-T	45 (8%)	32 (6%)

Data are n (%).

Table 1: **Subsequent therapy for prostate cancer**

	Number of expected deaths (% of expected)	HR (95% CI)	p value
Interim analysis 1*	98 (13%)	1·08 (0·73–1·61)	0·69
Interim analysis 2†	333 (43%)	0·75 (0·61–0·93)	0·0097
Interim analysis 3‡	434 (56%)	0·79 (0·66–0·95)	0·015
Final analysis§	741 (96%)	0·81 (0·70–0·93)	0·0033

HR=hazard ratio. *Efficacy boundary HR 0·34, nominal significance level α<0·0001. †Efficacy boundary HR 0·67, nominal significance level α=0·0008. ‡Efficacy boundary HR 0·75, nominal significance level α=0·0035. §Efficacy boundary HR 0·86, nominal significance level α=0·038.

Table 2: **Overall survival at interim analysis 1, interim analysis 2, interim analysis 3, and final analysis**

Results

1088 patients were randomly assigned to receive study treatment between April 28, 2009, and June 23, 2010 (figure 1); treatment groups were well balanced.[9,10] The clinical cutoff date for the preplanned final analysis was March 31, 2014. At the time of the final analysis, treatment was ongoing for 42 (8%) patients in the abiraterone acetate group and for no patients in the placebo group. At the final analysis, 238 (44%) patients from the placebo group had subsequently received abiraterone acetate plus prednisone (table 1). Of these 238 patients, 93 crossed over from receiving prednisone to abiraterone acetate plus prednisone per the protocol amendment, with the remaining 145 patients receiving abiraterone acetate plus prednisone as subsequent therapy, independent of study amendments. Of the 93 patients who crossed over per the protocol amendment, 51 crossed over directly from one group to the other; 42 patients had discontinued prednisone alone and may have received subsequent prostate cancer therapy before receiving abiraterone acetate plus prednisone. The most common reason for discontinued treatment was disease progression (366 [68%] patients in the abiraterone acetate group and 370 [69%] in the placebo group); adverse events were the second most common reason (50 [9%] and 33 [6%]; appendix). Drug-related adverse events leading to treatment discontinuation occurred in 35 (7%) of 542 patients in the abiraterone acetate group and 23 (4%) of 540 patients in the placebo group. At the time of the final analysis, the median duration of treatment was

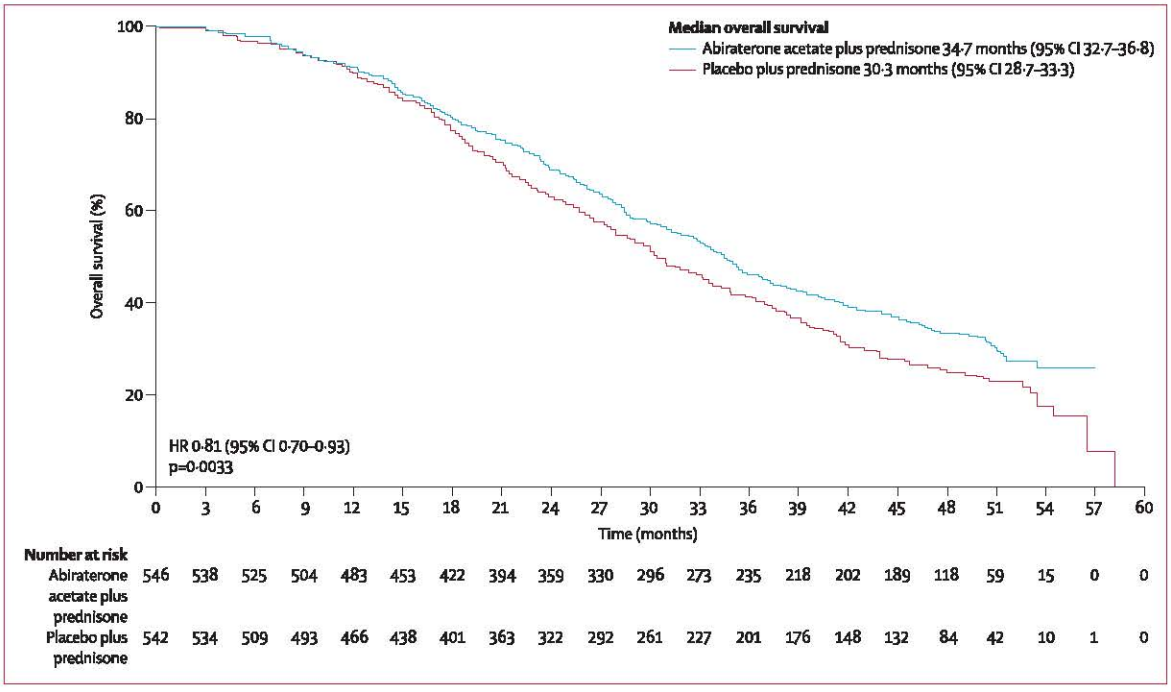

Figure 2: Kaplan-Meier curve of overall survival

	Median (months)		Hazard ratio (95% CI)	Events/N	
	Abiraterone acetate plus prednisone	Placebo plus prednisone		Abiraterone acetate plus prednisone	Placebo plus prednisone
All patients	**34·7 (32·7–36·8)**	**30·3 (28·7–33·3)**	**0·81 (0·70–0·93)**	**354/546**	**387/542**
Baseline ECOG					
0	35·4 (33·7–39·0)	32·0 (29·9–35·0)	0·79 (0·66–0·93)	261/416	292/414
1	27·9 (24·6–34·4)	26·4 (22·3–30·5)	0·87 (0·65–1·16)	93/130	95/128
Baseline BPI-SF					
0–1	38·1 (35·0–41·9)	33·4 (30·1–37·3)	0·77 (0·64–0·93)	223/370	233/346
2–3	26·4 (24·4–28·8)	27·4 (22·8–30·9)	0·97 (0·75–1·27)	100/129	120/147
Bone metastasis only at entry					
Yes	38·9 (34·9–45·2)	34·1 (30·1–39·1)	0·78 (0·62–0·97)	147/238	162/241
No	31·6 (27·8–34·5)	29·0 (26·0–30·9)	0·83 (0·69–1·00)	207/308	225/301
Age (years)					
<65	34·5 (31·5–41·7)	30·2 (27·9–36·9)	0·78 (0·59–1·03)	89/135	111/155
≥65	34·7 (31·2–36·8)	30·8 (27·3–33·6)	0·81 (0·69–0·96)	265/411	276/387
≥75	29·3 (26·1–34·5)	25·9 (21·4–30·0)	0·79 (0·61–1·10)	125/185	125/165
Baseline PSA above median					
Yes	28·5 (26·4–32·5)	25·8 (23·1–28·4)	0·86 (0·71–1·04)	208/282	206/260
No	43·1 (36·7–50·0)	34·4 (31·2–38·4)	0·72 (0·58–0·90)	146/264	181/282
Baseline LDH above median					
Yes	31·2 (27·3–34·3)	24·8 (21·5–28·6)	0·74 (0·61–0·90)	192/278	203/259
No	38·3 (34·5–44·2)	35·8 (32·7–38·8)	0·85 (0·69–1·05)	162/268	184/283
Baseline ALK-P above median					
Yes	28·6 (26·4–32·3)	26·8 (23·2–31·7)	0·92 (0·76–1·11)	211/279	201/256
No	44·5 (37·4–50·4)	33·2 (30·0–37·6)	0·68 (0·55–0·85)	143/267	186/286
Region					
North America	37·0 (33·5–40·6)	31·2 (28·7–34·9)	0·74 (0·61–0·91)	184/297	198/275
Other	33·2 (28·5–35·4)	30·1 (27·2–33·6)	0·90 (0·73–1·11)	170/249	189/267

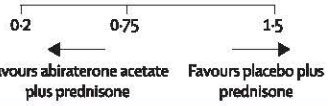

Figure 3: **Subgroup analyses of overall survival**
ECOG=Eastern Cooperative Oncology Group. BPI-SF=brief pain inventory—short form. PSA=prostate-specific antigen. LDH=lactate dehydrogenase. ALK-P=alkaline phosphatase. Efficacy analyses were done in the intention-to-treat populations (ie, all patients assigned to abiraterone acetate or placebo), irrespective of subsequent crossover.

13·8 months (IQR 8·3–27·4) with abiraterone acetate plus prednisone and 8·3 months (IQR 3·8–16·6) with placebo and prednisone. Dose reductions occurred in 38 (7%) of 542 patients in the abiraterone acetate group and 10 (2%) of 540 patients in the placebo group. Subsequent therapy was commonly used in both groups (table 1). Docetaxel was the most common subsequent therapy (table 1).

Three interim analyses and a final analysis were planned, with early analyses not crossing the prespecified efficacy boundary (table 2). With a median follow-up of 49·2 months (IQR 47·0–51·8), the final analysis of overall survival was performed after 741 deaths (96% of 773 expected deaths). The final analysis was done at this juncture due to the slowing down of the death events at the planned analysis time point and additional death events were not expected to alter the conclusion at 100% of expected deaths. Fewer deaths occurred in the abiraterone acetate group than in the placebo group (354 [65%] of 546 patients *vs* 387 [71%] risk of death in the abiraterone acetate group compared with the placebo group (hazard ratio [HR] 0·81, 95% CI 0·70–0·93; p=0·0033; figure 2, table 2). Median overall survival was 34·7 months (95% CI 32·7–36·8) in the abiraterone acetate group and 30·3 months (28·7–33·3) in the placebo group. The effect of abiraterone acetate was consistent across all prespecified subgroups (figure 3). After adjusting for the crossover effect using the IPE method, the risk of death was still lower in the abiraterone acetate group than in the placebo group, and the decrease was greater than without the adjustment (HR 0·74, 95% CI 0·60–0·88).

In a multivariate analysis correcting for variations in baseline prognostic factors, treatment with abiraterone acetate plus prednisone resulted in a significantly decreased risk of death compared with placebo plus prednisone (HR 0·79, 95% CI 0·68–0·91; p=0·0013). Baseline PSA, lactate dehydrogenase, alkaline phosphatase, haemoglobin, bone metastases, and age were all significant prognostic factors for overall survival

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