Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study

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Summary

Background Abiraterone acetate improved overall survival in metastatic castration-resistant prostate cancer at a preplanned interim analysis of the COU-AA-301 double-blind, placebo-controlled phase 3 study. Here, we present the final analysis of the study before crossover from placebo to abiraterone acetate (after 775 of the prespecified 797 death events).

Methods Between May 8, 2008, and July 28, 2009, this study enrolled 1195 patients at 147 sites in 13 countries. Patients were eligible if they had metastatic castration-resistant prostate cancer progressing after docetaxel. Patients were stratified according to baseline Eastern Cooperative Oncology Group (ECOG) performance status, worst pain over the past 24 h on the Brief Pain Inventory-Short Form, number of previous chemotherapy regimens, and type of progression. Patients were randomly assigned (ratio 2:1) to receive either abiraterone acetate (1000 mg, once daily and orally) plus prednisone (5 mg, orally twice daily) or placebo plus prednisone with a permuted block method via an interactive web response system. The primary endpoint was overall survival, analysed in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT00638690.

Findings Of the 1195 eligible patients, 797 were randomly assigned to receive abiraterone acetate plus prednisone (abiraterone group) and 398 to receive placebo plus prednisone (placebo group). At median follow-up of 20·2 months (IQR 18·4–22·1), median overall survival for the abiraterone group was longer than in the placebo group (15·8 months [95% CI 14·8–17·0] *vs* 11·2 months [10·4–13·1]; hazard ratio [HR] 0·74, 95% CI 0·64–0·86; p<0·0001). Median time to PSA progression (8·5 months, 95% CI 8·3–11·1, in the abiraterone group *vs* 6·6 months, 5·6–8·3, in the placebo group; HR 0·63, 0·52–0·78; p<0·0001), median radiologic progression-free survival (5·6 months, 5·6–6·5, *vs* 3·6 months, 2·9–5·5; HR 0·66, 0·58–0·76; p<0·0001), and proportion of patients who had a PSA response (235 [29·5%] of 797 patients *vs* 22 [5·5%] of 398; p<0·0001) were all improved in the abiraterone group compared with the placebo group. The most common grade 3–4 adverse events were fatigue (72 [9%] of 791 patients in the abiraterone group *vs* 41 [10%] of 394 in the placebo group), anaemia (62 [8%] *vs* 32 [8%]), back pain (56 [7%] *vs* 40 [10%]), and bone pain (51 [6%] *vs* 31 [8%]).

Interpretation This final analysis confirms that abiraterone acetate significantly prolongs overall survival in patients with metastatic castration-resistant prostate cancer who have progressed after docetaxel treatment. No new safety signals were identified with increased follow-up.

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Introduction

Androgen-deprivation therapy is the standard of care for advanced prostate cancer.[1,2] Although most men initially respond to castration with treatment with luteinising hormone-releasing analogues or bilateral orchiectomy, progression eventually occurs, and the median overall survival after chemotherapy is consistently less than 2 years in patients with metastatic disease.[3,4] Incontrovertible evidence now exists that tumour progression after androgen-deprivation therapy, previously thought to be androgen-independent or hormone-refractory, commonly remains hormone driven.[5–9] Postulated mechanisms of resistance include increased intratumoral steroid synthesis, increased expression of androgen receptor, splice variants of androgen receptor, and mutations leading to increased androgen receptor ligand promiscuity.[9] This disease state is consequently more precisely described as castration-resistant prostate cancer.[5,9] All patients ultimately progress to metastatic castration-resistant prostate cancer.[1] Patients who fail primary androgen-deprivation therapy are often treated with secondary hormonal therapies, including second-line anti-androgens, antiandrogen withdrawal, glucocorticoids,

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See Online for appendix

oestrogens, and ketoconazole. None of these treatments, however, have been assessed in definitive phase 3 trials and therefore, none have shown significant benefit in overall survival.[1] Docetaxel was the first systemic therapy to show an improvement in overall survival in patients with metastatic castration-resistant prostate cancer, but patients invariably die of progressive disease.[10,11] Recently, sipuleucel-T and cabazitaxel were approved for castration-resistant prostate cancer treated before and after chemotherapy on the basis of survival benefits in phase 3 trials.[12,13]

Abiraterone acetate is a selective inhibitor of androgen biosynthesis that potently and irreversibly blocks CYP17, a crucial enzyme in testosterone and oestrogen synthesis, resulting in virtually undetectable serum and intratumoral androgens[14,15] and antitumour activity in both chemotherapy-naive and chemotherapy-treated patients with metastatic castration-resistant prostate cancer.[16–19] In the prespecified interim analysis of the present phase 3 study of men with metastatic castration-resistant prostate cancer who had disease progression after docetaxel chemotherapy, treatment with abiraterone acetate plus prednisone was associated with median survival of 14·8 months versus 10·9 months for men treated with placebo plus prednisone.[20] The most common adverse events were associated with increased concentrations of mineralocorticoids and included hypokalaemia, fluid retention, and hypertension, which were mitigated by administration of prednisone as concomitant treatment. At the time of the initial analysis, 552 participants in the trial had died.[20]

On the basis of these results, on Aug 25, 2010, the Independent Data Monitoring Committee (IDMC) recommended that the study be unmasked and the study protocol amended to allow all remaining patients in the placebo group to receive treatment with abiraterone acetate if they met prespecified criteria for crossover treatment.[20] We describe the final analysis of the COU-AA-301 study at 775 death events, before crossover of patients from placebo to abiraterone acetate.

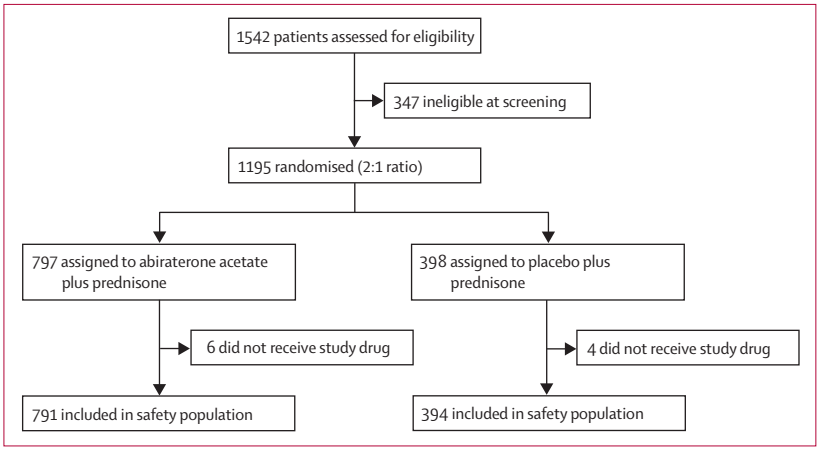

Figure 1: **Trial profile**

Methods

Patients

Full details of the COU-AA-301 study are provided in the initial report.[20] Briefly, in this phase 3, multinational, double-blind, randomised placebo-controlled trial, we enrolled patients from 147 sites in 13 countries. Men with histologically or cytologically confirmed metastatic castration-resistant prostate cancer were eligible if they had had previous treatment with docetaxel and a maximum of two previous chemotherapies; prostate-specific antigen (PSA) progression according to Prostate Cancer Working Group criteria (PCWG),[21,22] or radiographic progression in soft tissue or bone with or without PSA progression; ongoing androgen deprivation to maintain serum testosterone concentration lower than 50 ng/dL (<2·0 nmol/L by radioimmunoassay); Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; and haematology and chemistry laboratory values that met predefined criteria, including albumin concentration higher than 3·0 g/L. The review boards at all participating institutions approved the study, which was done according to the Declaration of Helsinki, the International Conference on Harmonisation, and the Guidelines for Good Clinical Practice. All patients gave written informed consent.

Randomisation and masking

Patients were randomly assigned to receive either abiraterone acetate plus prednisone (abiraterone group) or placebo plus prednisone (placebo group) in a 2:1 ratio. Patients who met the protocol eligibility criteria were randomly assigned to treatment in a blinded manner by permuted block method via an interactive web response system using a randomisation schedule generated by an external vendor. Patients were stratified according to baseline ECOG performance status (0–1 *vs* 2); worst pain over the past 24 h on the Brief Pain Inventory-Short Form (BPI-SF; 0–3 for absent *vs* 4–10 for present); number of previous chemotherapy regimens (one *vs* two); and type of progression (PSA progression only *vs* radiographic progression with or without PSA progression). The study sponsor, study personnel, patients, and members of IDMC remained masked to treatment assignment until completion of study.

Procedures

The study compared the combination of abiraterone acetate (1000 mg), taken once daily, plus prednisone (5 mg), taken twice daily, with placebo plus prednisone in previously treated men with metastatic castration-resistant prostate cancer progressing after docetaxel. Abiraterone acetate, or placebo, was given once daily as

four tablets of 250 mg. Prednisone was given twice daily as one tablet of 5 mg. Clinical and efficacy assessments included the following: medical history; vital sign measurements; bodyweight; physical examination; review of concomitant therapy and procedures; review of adverse events and serious adverse events, including laboratory test adverse events; blood chemistry, haematology, coagulation, and serum lipids studies; urinalysis; electrocardiogram; measurement of cardiac ejection fraction; PSA concentration; radiographic imaging; and BPI-SF; use of analgesic drugs; Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire; fatigue assessed by the Brief Fatigue Inventory instrument; and information of use of medical resources.

Statistical analysis

The primary endpoint was overall survival, defined as the time from randomisation to death from any cause, and analysed in the intention-to-treat population. Secondary endpoints were prespecified and were (1) the proportion of patients achieving a decrease in PSA of 50% or higher from the pretreatment baseline PSA value confirmed after 4 weeks or more by a further PSA assessment (PSA response rate); (2) time to PSA progression (TTPP), defined as a 25% increase over the nadir PSA value; (3) radiographic progression-free survival, defined as soft-tissue disease progression by modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria (target lesion ≥2·0 cm; complete response was the disappearance of all target lesions; partial response was a decrease of at least 30% in the sum of the largest diameter of target lesions taking as reference the baseline sum of the largest diameters; stable disease was neither a sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease taking as reference the baseline sum of the largest diameters; progressive disease was an increase of at least 20% in the sum of largest diameter of target lesions, taking as reference the smallest largest diameter recorded since the start of treatment or the appearance of one or more new lesions, or progression on bone scans with two or more new lesions not consistent with tumour flare, confirmed on a second scan 6 weeks later or more that shows at least one additional new lesion).[20] We did post-hoc exploratory analyses of the overall survival benefit of abiraterone acetate plus prednisone on the basis of previous timing of docetaxel administration, duration of docetaxel treatment, and reason for discontinuation of docetaxel.

The planned sample size of about 1158 patients was needed to provide 85% power with a two-sided significance level of 0·05 to detect an HR of 0·80. The assumed median survival for abiraterone acetate was 15 months, and 12 months for placebo. The study required a total of 797 death events. We used a group

	Abiraterone acetate plus prednisone	Placebo plus prednisone
Age (years)		
Median (range)	69 (42–95)	69 (39–90)
≥75 years	220/797 (28%)	111/397 (28%)
Disease location		
Bone	709/797 (89%)	357/397 (90%)
Node	361/797 (45%)	164/397 (41%)
Liver	90/797 (11%)	30/397 (8%)
BPI-SF score for pain*		
Number of patients	792	394
Median score (range)	3·0 (0–10)	3·0 (0–10)
Number of previous cytotoxic chemotherapy regimens		
1	558/797 (70%)	275/398 (69%)
2	239/797 (30%)	123/398 (31%)
ECOG performance status		
0 or 1	715/797 (90%)	353/398 (89%)
2	82/797 (10%)	45/398 (11%)
Prostate-specific antigen		
Number of patients	788	393
Median (range), ng/mL	128·8 (0·4–9253·0)	137·7 (0·6–10114·0)
Gleason score at initial diagnosis		
≤7	341/697 (49%)	161/350 (46%)
≥8	356/697 (51%)	189/350 (54%)
PSA at initial diagnosis (ng/mL)		
Number of patients	619	311
Median (range)	27·0 (0·1–16 065·9)	35·5 (1·1–7378·0)
Previous cancer therapy		
Surgery	429/797 (54%)	193/398 (49%)
Radiotherapy	570/797 (72%)	285/398 (72%)
Hormonal	796/797 (100%)	396/398 (100%)
Other†	797/797 (100%)	398/398 (100%)
Extent of disease‡		
Viscera, not otherwise specified	1 (0%)	0 (0%)
Lungs	103 (13%)	45 (11%)
Prostate mass	60 (8%)	23 (6%)
Other viscera	46 (6%)	21 (5%)
Other tissue	40 (5%)	20 (5%)
Baseline haemoglobin (g/L)		
Number of patients	779	389
Median (range)	118 (73–161)	118 (72–165)
Baseline LDH (ng/mL)		
Number of patients	783	386
Median (range)	223·0 (84–3373)	237·5 (123–5125)

Data are n/N (%) unless otherwise indicated. BPI-SF=Brief Pain Inventory-Short Form. ECOG=Eastern Cooperative Oncology Group. PSA=prostate-specific antigen. LDH=lactate dehydrogenase. *The BPI-SF rates pain on a scale of 0–10, with 0–3 indicating that clinically significant pain is absent and 4–10 indicating that clinically significant pain is present; the scores shown are for the worst pain over the previous 24 h. †Including chemotherapy. ‡Data are for the extent of disease in specific and relevant organs and therefore the numbers do not add up to 797 and 398.

Table 1: **Baseline and disease characteristics of patients**[20]

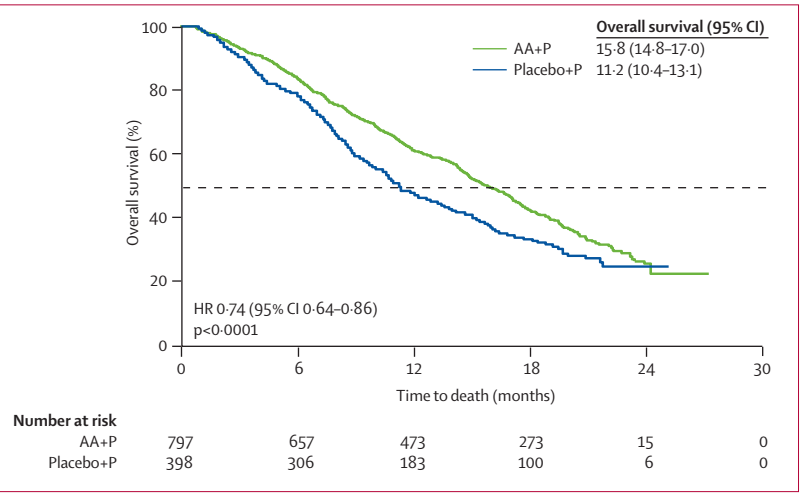

Figure 2: **Overall survival**
HR=hazard ratio. AA=abiraterone acetate. P=prednisone.

	Hazard ratio (95% CI)	p value
Treatment (abiraterone acetate+prednisone *vs* placebo+prednisone)	0·76 (0·66–0·88)	0·0003
ECOG score (0–1 *vs* 2)	0·46 (0·37–0·57)	<0·0001
Pain (absent *vs* present)	0·68 (0·59–0·78)	<0·0001
Previous chemotherapy regimens (1 *vs* 2)	0·75 (0·64–0·87)	0·0002
Progression category (PSA only *vs* radiographic)*	0·75 (0·64–0·88)	0·0005

ECOG=Eastern Cooperative Oncology Group. PSA=prostate-specific antigen. Patients who were not deceased at the time of analysis were censored on the last date the patient was known to be alive or lost to follow-up. Every test was done at significance level of 0·05. *Progression occurred before study entry; radiographic progression was with or without PSA progression.

***Table 2:* Overall survival by stratification factors—multivariate analysis (intention-to-treat population)**

sequential trial design incorporating the Lan-DeMets α-spending method with the O'Brien-Fleming boundary. One interim analysis was planned after the reporting of 534 death events (67% of 797 total events), and a final analysis was to be done after 797 events were observed. We used the stratified log-rank test to compare the treatment differences, whereas we used the Cox proportional hazards model to obtain the estimated HR and its associated 95% CIs for both the primary overall survival analyses and by stratification factors. We tested for homogeneity at a 0·1 significance level. We also did a multivariate analysis using the Cox model and sensitivity analyses for overall survival with the non-stratified log-rank test. We reported the relative risk (treatment:control) along with the associated 95% CIs for dichotomous outcomes; we assessed the statistical inference using the χ^2 statistic and used the Fisher's exact test if the expected counts in some cells were small. We did subgroup analyses adjusted by baseline stratification factors to assess whether or not treatment effects were consistent across the subgroups analysed. We analysed secondary endpoints using the Hochberg's test procedure to adjust for multiple testing. Statistical analyses were done with the SAS software package (version 9.2; SAS Institute, Cary, NC, USA). This study is registered with ClinicalTrials.gov, NCT00638690.

Role of the funding source

Employees of Janssen Research & Development participated in trial design, data collection, data analysis, data interpretation, and writing of the report. The sponsor of the study was involved in the design of the trial and provided grants to trial sites and had no other involvement in conduct of trial. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Patients were enrolled between May 8, 2008, and July 28, 2009. The clinical cutoff date for the analyses presented here was Sept 20, 2010. Overall, 1195 patients were randomly assigned to receive either abiraterone acetate plus prednisone or placebo plus prednisone (figure 1). With a median follow-up of 12·8 months (IQR 10·9–14·4) at the time of data cutoff for the interim analysis, 552 death events had occurred. The present analysis was done at a median follow-up of 20·2 months (IQR 18·4–22·1 months). At this time, 775 death events (97% of prespecified 797 death events) had occurred before unblinding and patient crossover from the placebo group to the abiraterone group.

Baseline demographics and disease characteristics, including presence of clinically significant pain, were balanced between the treatment groups (table 1). All patients had received at least one previous cytotoxic chemotherapy regimen containing docetaxel, with 30% of patients in the abiraterone group (239 of 797 patients) and 31% of patients in the placebo group (123 of 398 patients) having had two distinct previous lines of chemotherapy. Docetaxel followed by a treatment break and additional docetaxel as a monotherapy, or in combination with other agents, counted as single previous chemotherapy regimen. Most patients (559 [70%] of 797 patients in the abiraterone group and 273 [69%] of 398 patients in the control group) had radiographic progression, with or without PSA progression, before trial entry. 1066 (90%) of 1195 patients had bone metastasis (709 [89%] patients in the abiraterone group and 357 [90%] patients in the placebo group), with 253 (32%) of the 791 patients in the abiraterone group and 99 (25%) of the 398 patients in the placebo group having visceral metastases. At the cutoff date for this analysis, 125 (16%) patients in the abiraterone group and 18 (5%) patients in the placebo

group were still on study. The median duration of drug exposure and median number of treatment cycles were longer for the abiraterone group (7·4 months [range 0·2–25·6] and eight cycles [1–28]) than for the placebo group (3·6 months [0·1–24·9] and four cycles [1–27]).

Median overall survival was 15·8 months (95% CI 14·8–17·0) in the abiraterone group compared with 11·2 months (10·4–13·1) in the placebo group (hazard ratio [HR] 0·74, 95% CI 0·64–0·86; p<0·0001; figure 2). As the proportional hazards requirement was not met, the hazard ratio should be interpreted with caution. The treatment effect of abiraterone acetate on overall survival was noted in multivariate analysis including baseline stratification factors as covariates (table 2).

We did prespecified subgroup analyses to examine known adverse prognostic factors for men with metastatic castration-resistant prostate cancer. The treatment effect of abiraterone acetate plus prednisone—relative to placebo plus prednisone—on overall survival was consistent across all the protocol-specified subgroups, although some differences were not statistically significant, perhaps due to small sample size in some groups (table 3, figure 3, appendix). The test for heterogeneity of treatment effect between subgroups showed no significant finding (all p values >0·1).

All other efficacy endpoints examined (ie, time to PSA progression, radiographic progression-free survival, the proportion of patients with a PSA response, and objective response assessed by RECIST) were improved with abiraterone acetate plus prednisone compared with placebo plus prednisone (table 4).

In a post-hoc analysis of the effect of abiraterone acetate by previous docetaxel use, treatment groups were balanced with respect to previous docetaxel use and reasons for docetaxel discontinuation, as reported by investigators at the time of randomisation (appendix). In both groups, almost half discontinued docetaxel because of progressive disease; the remainder discontinued docetaxel because they received the planned number of cycles of treatment, because of toxic effects, or for other reasons not further specified.

	Abiraterone acetate plus prednisone		Placebo plus prednisone		Hazard ratio (95% CI)
	Events/N	Median overall survival (months; 95% CI)	Events/N	Median overall survival (months; 95% CI)	
Baseline ECOG status*					
0–1	432/715	17·0 (15·6–17·7)	237/353	12·3 (10·8–14·5)	0·74 (0·63–0·87)
2	69/82	7·3 (6·4–8·6)	37/45	7·0 (4·0–8·1)	0·77 (0·50–1·17)
Pain at study entry*					
Pain absent (0–3)	244/440	18·4 (17·2–19·9)	137/219	13·9 (11·7–15·9)	0·69 (0·56–0·85)
Pain present (4–10)	257/357	13·3 (11·1–14·7)	137/179	9·3 (7·9–10·7)	0·78 (0·63–0·96)
Previous lines of chemotherapy*					
1	329/557	17·1 (15·6–18·2)	185/275	11·7 (10·4–13·9)	0·71 (0·59–0·85)
2	172/240	14·2 (11·8–15·3)	89/123	10·4 (8·8–13·5)	0·80 (0·61–1·02)
Type of progression*†					
PSA progression	126/238	18·3 (16·7–20·8)	79/125	13·6 (10·8–16·8)	0·63 (0·47–0·84)
Radiographic progression with or without PSA progression	375/559	14·8 (14·0–16·1)	195/273	10·5 (8·9–12·5)	0·78 (0·65–0·93)
Previous docetaxel usage					
From first dose of docetaxel	494/787	32·6 (30·7–35·0)	274/397	27·6 (25·9–30·3)	0·75 (0·65–0·88)
From last dose of docetaxel	494/787	23·2 (22·4–24·5)	274/397	19·4 (17·5–20·8)	0·74 (0·64–0·86)
Reason for discontinuation of docetaxel					
Progressive disease	241/362	14·2 (12·0–15·8)	129/182	10·5 (9·3–11·8)	0·77 (0·62–0·97)
All other reasons	258/431	17·0 (15·6–18·2)	145/215	12·6 (10·4–14·9)	0·73 (0·59–0·89)
Treatment of abiraterone acetate plus prednisone started					
≤3 months after last dose of docetaxel	144/227	15·0 (13·7–17·4)	82/112	10·7 (8·9–13·0)	0·62 (0·47–0·83)
>3 months after last dose of docetaxel	346/554	16·1 (14·9–17·3)	190/282	11·8 (10·3–14·6)	0·77 (0·64–0·92)
Docetaxel exposure time					
≤3 months	98/140	14·6 (11·9–16·7)	51/69	10·8 (8·4–14·9)	0·76 (0·53–1·08)
>3 months	252/401	16·2 (14·9–17·3)	223/328	11·2 (10·3–13·6)	0·74 (0·63–0·87)

ECOG=Eastern Cooperative Oncology Group. PSA=prostate-specific antigen. Overall survival is presented in months. Patients who were not deceased at the time of analysis were censored on the last date the patient was known to be alive or lost to follow-up. All subgroup analyses were adjusted for baseline stratification factors. Every test was done at significance level of 0·05. Patient numbers are not consistent across subgroups because of missing data. *Stratification factors at baseline. †Progression occurred before study entry.

Table 3: **Overall survival by subgroup (univariate analysis)**

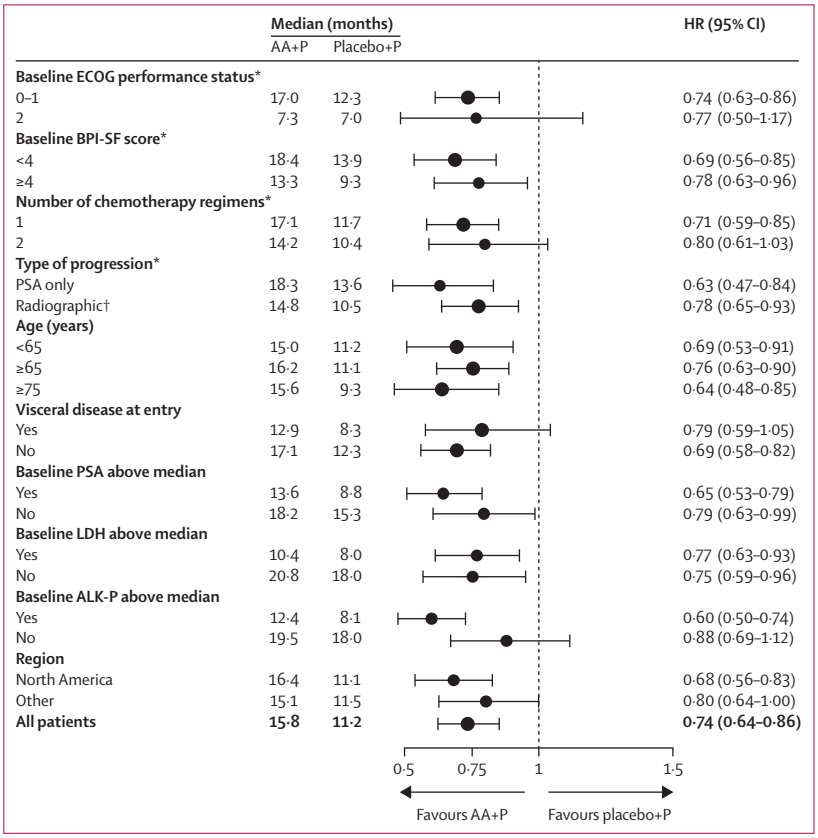

Figure 3: **Overall survival by subgroup analyses**
AA=abiraterone acetate. P=prednisone. HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group. BPI-SF=Brief Pain Inventory-Short Form. PSA=prostate-specific antigen. LDH=lactate dehydrogenase. ALK-P=alkaline phosphatase. HR is based on a non-stratified proportional hazards model. This figure includes all protocol-specified subgroups. *Stratification variables for the study. †With or without PSA progression.

	Abiraterone acetate plus prednisone (95% CI; n=797)	Placebo plus prednisone (95% CI; n=398)	Hazard ratio (95% CI)	p value
Time to PSA progression (months)*	8·5 (8·3–11·1)	6·6 (5·6–8·3)	0·63 (0·52–0·78)	<0·0001
Radiographic progression-free survival (months)*	5·6 (5·6–6·5)	3·6 (2·9–5·5)	0·66 (0·58–0·76)	<0·0001
PSA response (%)†	235 (29·5%)	22 (5·5%)	..	<0·0001
Objective response by RECIST (%)‡	118 (14·8%)	13 (3·3%)	..	<0·0001

Data are median (95% CI) or number (%). PSA=prostate-specific antigen. RECIST=Response Evaluation Criteria in Solid Tumors. PSAWG=Prostate-Specific Antigen Working Group. *Calculated from date of randomisation to date of PSA progression (per PSAWG criteria) or date of radiographically documented disease progression or death. †Proportion of patients with a PSA decline of 50% or higher according to PSAWG criteria; unstratified analysis. ‡Additional (not secondary) endpoint.

Table 4: **Other efficacy endpoints**

Duration from last dose of docetaxel to first dose of study treatment (≤3 months *vs* >3 months) and duration of docetaxel exposure (≤3 months *vs* >3 months) were similar between groups (appendix). The 3-month cutoff was considered appropriate as it is also the recommended timeframe for assessing efficacy in patients with castration-resistant prostate cancer;[22] this specifically applies to chemotherapy agents because of the PSA surge effect.[23] The median duration of exposure to docetaxel was 5·3 months (range 1–105, or about eight cycles) in the abiraterone group and 5·0 months (range 1–55, or about seven cycles) in the placebo group.

Median overall survival was significantly longer in the abiraterone group than in the placebo group irrespective of whether measured from first or last dose of docetaxel (table 3, appendix). Patients in the abiraterone group had longer median overall survival than did those in the placebo group irrespective of reason for discontinuation of docetaxel (table 3, appendix). Median overall survival was also longer in the abiraterone group than in the placebo group irrespective of time between discontinuation of docetaxel and initiation of abiraterone acetate (table 3, appendix). There was no significant difference in median overall survival between the abiraterone group and the placebo group for patients who received docetaxel for 3 months or less (table 3, appendix). For patients who received docetaxel for longer than 3 months, median overall survival was significantly longer in the abiraterone group than in the placebo group (table 3, appendix).

In both treatment groups, the proportion of patients who had grade 3–4 adverse events and laboratory abnormalities remained similar after longer term follow-up compared to those reported in the interim analysis (table 5). As expected, mineralocorticoid-related adverse events associated with abiraterone acetate were reported in a higher proportion of patients in the abiraterone group than in the placebo group. The incidence of events of fluid retention or oedema was higher in patients taking abiraterone acetate than in those taking placebo; grade 1 or 2 peripheral oedema accounted for most of these events (table 5). Hypokalaemia also occurred in a higher proportion of patients in the abiraterone group than in the placebo group, as did cardiac disorders (table 5). The most frequently observed cardiac events were grade 1 and 2 tachycardia events; and grade 3 or lower atrial fibrillation events. The incidence of treatment-related adverse events was similar in both groups (610 [77%] of 791 in the abiraterone group *vs* 305 [77%] of 394 in the placebo group; appendix). Deaths due to adverse events occurred in similar proportions of patients in the two groups (105 [13%] in the abiraterone group *vs* 61 [16%] in the placebo group), as did deaths due to cardiac adverse events (nine [1%] in the abiraterone group *vs* five [1%] in the placebo group; appendix).

105 (13%) of 791 patients in the abiraterone group and 71 (18%) 394 in the placebo group had to discontinue treatment due to adverse events. 73 (9%) patients in the abiraterone group and 28 (7%) patients in the placebo group had to interrupt treatment due to serious adverse events or admission to hospital.

Discussion

This final analysis of the COU-AA-301 study in patients with metastatic castration-resistant prostate cancer who had progressed after docetaxel confirms that abiraterone acetate plus prednisone improves overall survival relative to placebo plus prednisone. In general, the survival benefit for patients assigned to the abiraterone group compared with the placebo group favoured abiraterone acetate across most of the subgroups analysed, providing proof of principle that metastatic castration-resistant prostate cancer remains androgen driven.[10–13,24] Our data also suggest that the survival benefit of abiraterone acetate versus placebo was independent of previous docetaxel use when analysed on the basis of timing of docetaxel administration and reason for docetaxel discontinuation.

Although the present analysis includes 3% fewer death events than what was prespecified in the protocol (775 of 797 death events), the effect on the overall results is probably negligible. Notably, these analyses are based on data collected before unblinding and patient crossover from placebo to abiraterone acetate treatment.

Although successive endocrine manipulations in patients with castration-resistant prostate cancer have been used empirically for decades,[25] none have shown a significant survival benefit in a randomised phase 3 study (panel). The COU-AA-301 study shows that this strategy can lead to survival improvement. Bone-targeting drugs such as zoledronic acid[26] and denosumab[27] improved time to skeletal-related events and are now part of standard treatment in patients with bone metastases from castration-resistant prostate cancer. A first-in-class α-emitting radiopharmaceutical, radium-223, has also shown improvement in overall survival and time to skeletal-related events compared with placebo.[28] Until recently, taxane-based chemotherapy was the only proven treatment to show increased survival in patients with castration-resistant prostate cancer.[10,11,13] Based on phase 3 data, 3-weekly docetaxel prescribed (75 mg/m²) has been used as standard treatment in castration-resistant prostate cancer within the past decade, with a reasonable safety profile even in fit elderly patients,[29] while cabazitaxel improved survival compared with mitoxantrone (HR 0·70; p<0·0001) in docetaxel-pretreated patients.[13] More recently, enzalutamide (MDV3100) has showed a survival benefit compared with placebo, confirming the relevance of targeting the signalling pathway of the androgen receptor in metastatic castration-resistant prostate cancer after docetaxel treatment.[30,31]

The effect of abiraterone acetate plus prednisone on overall survival noted in the whole patient population was substantiated by a multivariate analysis in which overall survival was analysed by adjusting for baseline stratification factors. This analysis showed that the stratification factors are all prognostic for survival and that treatment with abiraterone acetate plus prednisone independently improved overall survival. Importantly, most subgroups favoured abiraterone acetate plus prednisone in overall survival, suggesting that, from an efficacy standpoint, it could be considered a treatment option for patients with docetaxel-pretreated castration-resistant prostate cancer who fulfil the inclusion and exclusion criteria of the COU-AA-301 population.

One limitation of our study is that the activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer and neuroendocrine differentiation or in those who previously progressed on ketoconazole cannot be assessed from the results of this trial since those patients were excluded.

Whether cabazitaxel and abiraterone acetate will provide incremental benefit when used sequentially or in combination will need to be addressed in future

	Abiraterone acetate plus prednisone (n=791)			Placebo plus prednisone (n=394)		
	All grades* N (%)	Grade 3 N (%)	Grade 4 N (%)	All grades* N (%)	Grade 3 N (%)	Grade 4 N (%)
Haematological						
Anaemia	198 (25%)	53 (7%)	9 (1%)	110 (28%)	26 (7%)	6 (2%)
Thrombocytopenia	30 (4%)	8 (1%)	3 (<1%)	15 (4%)	1 (<1%)	1 (<1%)
Neutropenia	8 (1%)	1 (<1%)	0	2 (<1%)	1 (<1%)	0
Febrile neutropenia	3 (<1%)	0	3 (<1%)	0	0	0
Non-haematological						
Diarrhoea	156 (20%)	8 (1%)	1 (<1%)	58 (15%)	5 (1%)	0
Fatigue	372 (47%)	70 (9%)	2 (<1%)	174 (44%)	38 (10%)	3 (<1%)
Asthenia	122 (15%)	26 (3%)	0	54 (14%)	7 (2%)	1 (<1%)
Back pain	262 (33%)	53 (7%)	3 (<1%)	141 (36%)	39 (10%)	1 (<1%)
Nausea	258 (33%)	16 (2%)	1 (<1%)	130 (33%)	11 (3%)	0
Vomiting	191 (24%)	20 (3%)	1 (<1%)	101 (26%)	12 (3%)	0
Haematuria	73 (9%)	12 (2%)	0	34 (9%)	9 (2%)	0
Abdominal pain	102 (13%)	18 (2%)	0	47 (12%)	8 (2%)	0
Pain in extremity	156 (20%)	23 (3%)	1 (<1%)	82 (21%)	20 (5%)	0
Dyspnoea	116 (15%)	12 (2%)	2 (<1%)	49 (12%)	7 (2%)	2 (<1%)
Constipation	223 (28%)	10 (1%)	0	126 (32%)	4 (1%)	0
Pyrexia	80 (10%)	3 (<1%)	0	36 (9%)	5 (1%)	0
Arthralgia	239 (30%)	40 (5%)	0	95 (24%)	17 (4%)	0
Urinary tract infection	105 (13%)	12 (2%)	0	29 (7%)	3 (<1%)	0
Pain	38 (5%)	7 (<1%)	0	21 (5%)	7 (2%)	1 (<1%)
Bone pain	216 (27%)	49 (6%)	2 (<1%)	117 (30%)	27 (7%)	4 (1%)
Adverse events of special interest						
Fluid retention or oedema	261 (33%)	18 (2%)	2 (<1%)	94 (24%)	4 (1%)	0
Hypokalaemia	143 (18%)	31 (4%)	4 (<1%)	36 (9%)	3 (<1%)	0
Cardiac disorders†	126 (16%)	32 (4%)	9 (1%)	46 (12%)	7 (2%)	2 (<1%)
Abnormalities in liver function tests	89 (11%)	28 (4%)	2 (<1%)	35 (9%)	11 (3%)	3 (<1%)
Hypertension	88 (11%)	10 (1%)	0	32 (8%)	1 (<1%)	0

Data are n (%).*Includes adverse events of grades 1–4. †Cardiac disorders associated with abiraterone acetate treatment as defined with the standardised Medical Dictionary for Regulatory Activities Queries included ischaemic heart disease, myocardial infarction, supraventricular tachyarrhythmias, ventricular tachyarrhythmias, cardiac failure, and possible arrhythmia-related investigations, signs, and symptoms.

Table 5: **Adverse events reported during treatment**

Panel: Research in context

Systematic review

At the time the trial was designed, only docetaxel had been shown to improve survival in metastatic castration-resistant prostate cancer. Before beginning the trial, we searched the medical literature for evidence of phase 3 clinical trials with agents for the treatment of metastatic castration-resistant prostate cancer (PubMed search, phase 3 clinical trial, "("secondary"[Subheading] OR metastatic[Text Word]) AND ("orchiectomy"[MeSH Terms] OR "castration"[MeSH Terms] OR castration[Text Word]) AND resistant[All Fields] AND ("prostatic neoplasms"[MeSH Terms] OR prostate cancer[Text Word]") and found no evidence of novel agents providing significant clinical benefit in patients progressing post-docetaxel. At that time, once the disease progressed after failing docetaxel-based therapy, no standard of care or treatment proven to improve survival existed, and this was also indicated in the relevant treatment guidelines (eg, NCCN) for prostate cancer. The study sponsor furthermore conducted advisory boards with international clinical experts in the treatment of metastatic castration-resistant prostate cancer in designing the trial.

In preparing this manuscript, we comprehensively reviewed the scientific literature to identify phase 2 and 3 trials with agents to treat metastatic castration-resistant prostate cancer (docetaxel, cabazitaxel, MDV3100, zoledronic acid, denosumab, and Ra-223) and cite key primary publications for these agents. We discuss our results in the context of these publications and highlight differences between the endpoints of the studies.

Interpretation

This final analysis of the COU-AA-301 trial confirms that abiraterone acetate significantly prolongs overall survival in patients with metastatic castration-resistant prostate cancer who have progressed after docetaxel treatment. No new safety signals were identified with increased follow-up.

clinical trials. Other ongoing research might also identify biomarkers that aid and refine treatment selection.[32,33] Further analyses of other assessments in this study, including measures of pain, fatigue, and quality of life will be published elsewhere.[34–36] Results from a second abiraterone acetate study, COU-AA-302,[37] have also been reported, and showed clinical benefits with abiraterone acetate in chemotherapy-naive patients with metastatic castration-resistant prostate cancer;[37] these results might further affect treatment selection.

Even with longer follow-up, the safety profile of abiraterone acetate plus prednisone remained similar to the profile reported at the interim analysis. Mineralocorticoid-related adverse events, hypokalaemia, hypertension, and fluid retention were reported in a higher proportion in the abiraterone group than in the placebo group. Hypokalaemia was generally managed with oral potassium supplementation, and hypertension was generally amenable to increased dosage of an anti-hypertensive drug present at the outset of treatment, or addition of an anti-hypertensive agent. These adverse events are easily managed medically with appropriate patient monitoring and are generally less severe than the adverse events associated with cytotoxic therapies. Adverse events known to affect the quality of life of patients with metastatic castration-resistant prostate cancer—eg, myelosuppression (including febrile neutropenia)—were uncommon. Adverse events were generally reversible and, generally, allowed for continuation of treatment without interruption or dose modification. Treatment-related adverse events that led to death were noted in much the same proportion of patients in both groups. Future analyses of safety data, including correlating the toxic effects with efficacy, might provide additional detail.

Lastly, unlike current alternatives for this patient population, abiraterone plus prednisone therapy can be given orally in an outpatient setting, providing an additional benefit for both patients and clinicians. In conclusion, these final updated results confirm the efficacy and safety of abiraterone in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received previous chemotherapy containing docetaxel, with consistent benefit observed across baseline clinical subgroups.

Contributors

KF, HIS, AM, CJL, CNS, TK, CMH, and JSdB contributed to the conception and design of the study. KF, HIS, CJL, KNC, RJJ, JNS, SN, NJV, FS, PM, SH, OBG Jr, CNS, and JSdB contributed to the provision of study materials, patient recruitment, or acquisition of data. AM, JHL, TK, and CMH participated in the collection and assembly of data. KF, HIS, AM, CJL, JHL, TK, CMH, JSdB participated in the data analysis and interpretation. All authors participated in the draft of the manuscript, revised it critically, and gave final approval to submit for publication.

Conflicts of interest

KF served as consultant to Janssen Research & Development (formerly Ortho Biotech Research & Development, a unit of Cougar Biotechnology) and received payment for lectures from Janssen-Cilag. HIS has served as a consultant to Janssen Research & Development (formerly Ortho Biotech Research & Development, a unit of Cougar Biotechnology), Janssen Global Services, Sanofi-Aventis, Medivation, Enzon, Aragon, Bristol-Myers Squibb, Millennium, Novartis, and AstraZeneca, and previously owned stock in Johnson and Johnson. AM is an employee of Janssen Research & Development and holds stock options of Johnson & Johnson. CJL reports having served as a consultant and received travel support from Janssen Research & Development. KNC has served as a consultant to Janssen Research & Development. RJJ received grant and travel support from Janssen Research & Development. JNS has served as a consultant to Janssen Research & Development and Pierre-Fabre, received travel support from Sanofi-Aventis, and is a stock holder of Johnson & Johnson. SN reports having served as a consultant to AstraZeneca, Pfizer, Sanofi-Aventis, Novartis, Abraxis, Ortho-Biotech, Amgen, and GlaxoSmithKline; and received payment for lectures from Novartis and Ortho-Biotech. NJV has served as a consultant to Janssen Research & Development, Pfizer, Astellas, Dendreon, Veridex LLC, a division of Johnson & Johnson, Progenix, Tokai, Takeda/Millennium, Novartis, Exelixis, and Bayer; and has received payment for lectures from Sanofi-Aventis, Veridex, Novartis, Dendreon and Astellas. FS has

served as a consultant to Amgen, Novartis, Sanofi-Aventis, and AstraZeneca; and received payment for development of educational presentations from Amgen and Novartis. PM has served as a consultant to Janssen Research & Development. SH has received travel support from Janssen Research & Development and served as a consultant to Sanofi-Aventis. OBG Jr has served as a consultant and received payment for lectures from Veridex LLC, a division of Johnson & Johnson. CNS has served as a consultant and has received payment for lectures for Amgen, Astellas, Dendreon, Johnson & Johnson, Millennium, Novartis, and Sanofi-Aventis, and has received research funding from Cougar Biotechnology (now Janssen Research & Development), and received travel support from Janssen Research & Development. JHL and TK are employees of Janssen Research & Development and hold stock options of Johnson & Johnson. CMH was an employee of Janssen Research & Development and owns stock of Johnson & Johnson. JSdB has served as a consultant to Janssen Research & Development, Sanofi-Aventis, Medivation, Astellas, and Dendreon.

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