Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial

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Summary

Background Bone metastases are a major cause of morbidity in metastatic castration-resistant prostate cancer. Abiraterone acetate potently disrupts intracrine androgen receptor signalling pathways implicated in the progression of the disease, including bone metastases. We assessed data for pain control and skeletal-related events prospectively collected as part of the randomised, phase 3 COU-AA-301 trial of abiraterone acetate plus prednisone versus placebo plus prednisone in patients with metastatic castration-resistant prostate cancer after docetaxel chemotherapy.

Methods The COU-AA-301 trial enrolled patients with metastatic castration-resistant prostate cancer in whom one or two lines of chemotherapy (one docetaxel based) had been unsuccessful and who had Eastern Cooperative Oncology Group performance statuses of 2 or less. Pain intensity and interference of pain with daily activities were assessed with the Brief Pain Inventory-Short Form questionnaire at baseline, day 15 of cycle 1, and day 1 of each treatment cycle thereafter until discontinuation. We assessed, with prospectively defined response criteria that incorporated analgesic use, clinically meaningful changes in pain intensity and interference with daily living. We measured time to first occurrence of skeletal-related events, which we defined as pathological fracture, spinal cord compression, palliative radiation to bone, or bone surgery, and regularly assessed them throughout the study. Pain palliation was assessed in patients who had clinically significant baseline pain, whereas all other analyses were done in the overall intention-to-treat population. COU-AA-301 is registered with ClinicalTrials.gov, number NCT00638690.

Findings Median follow-up was 20·2 months (IQR 18·4–22·1). In patients with clinically significant pain at baseline, abiraterone acetate and prednisone resulted in significantly more palliation (157 of 349 [45·0%] patients *vs* 47 of 163 [28·8%]; p=0·0005) and faster palliation (median time to palliation 5·6 months [95% CI 3·7–9·2] *vs* 13·7 months [5·4–not estimable]; p=0·0018) of pain intensity than did prednisone only. Palliation of pain interference (134 of 223 [60·1%] *vs* 38 of 100 [38·0%], p=0·0002; median time to palliation of pain interference 1·0 months [95% CI 0·9–1·9] *vs* 3·7 months [2·7–not estimable], p=0·0004) and median duration of palliation of pain intensity (4·2 months [95% CI 3·0–4·9] *vs* 2·1 months [1·4–3·7]; p=0·0056) were significantly better with abiraterone acetate and prednisone than with prednisone only. In the overall population, median time to occurrence of first skeletal-related event was significantly longer with abiraterone acetate and prednisone than with prednisone only (25·0 months [95% CI 25·0–not estimable] *vs* 20·3 months [16·9–not estimable]; p=0·0001).

Interpretation In patients with metastatic castration-resistant prostate cancer previously treated with docetaxel, abiraterone acetate and prednisone offer significant benefits compared with prednisone alone in terms of pain relief, delayed pain progression, and prevention of skeletal-related events.

Funding Janssen Research & Development and Janssen Global Services.

Introduction

Symptomatic bone metastases are a characteristic feature of progressing metastatic castration-resistant prostate cancer and account for much of the morbidity in patients with this illness.[1,2] The risk of mortality increases with the spread of cancer to bone, especially when accompanied by skeletal-related events; time to skeletal-related events is an important prognostic marker in metastatic castration-resistant prostate cancer.[3] The volume of bone metastases and associated pain correlate with poor survival.[4–6] These findings validate efforts to develop better methods for detection, monitoring, treatment, and prevention of bone metastases in prostate cancer.[7–12]

Several lines of experimental and clinical evidence support the hypothesis that molecular pathways central

to bone development and function are usurped by prostate cancer during disease progression and treatment resistance.[13,14] Androgen receptor signalling networks are key drivers of progression in prostate cancer,[15] and emerging data suggest that the shift from endocrine-driven to intracrine-driven (ie, paracrine and autocrine) prostate cancer under the selective pressure of castration is crucial.[1,14,16,17] The development of a dominant paracrine-signalling progression pathway within bone, part of a broader network of interacting progression pathways, might account for the unique phenotype of metastatic castration-resistant prostate cancer.[1]

Abiraterone acetate is a selective androgen biosynthesis inhibitor that blocks CYP17 (a key enzyme in testosterone and dihydrotestosterone production) and therefore shuts down androgen production in the adrenals and testes and prostate cancer cells. The results of a 2012 study[18] suggest that the expression of androgen receptors and CYP17 is predictive of abiraterone acetate's treatment benefit in patients with castration-resistant prostate cancer who have bone metastases.

We reasoned that a drug that has been previously shown to potently inhibit the signalling pathways implicated in the progression of bone metastases in prostate cancer might also positively affect bone-associated symptoms. To establish whether CYP17 inhibition with abiraterone acetate can improve pain and manifestations of bone metastases in metastatic castration-resistant prostate cancer after treatment with docetaxel, we prospectively measured and analysed patient-reported pain and the occurrence of skeletal-related events from the COU-AA-301 trial.[16]

Methods

Study design and patients

COU-AA-301 was a randomised, double-blind, placebo-controlled phase 3 study at 147 sites in 13 countries in patients with metastatic castration-resistant prostate cancer who had been treated unsuccessfully with one or two lines of chemotherapy (one of which was docetaxel based).[16] Patients were required to have a serum testosterone concentration of 50 ng/dL or less (≤2·0 nmol/L) and an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, and to meet predefined haematological and chemical laboratory values. Eligible patients were randomly assigned (2:1) to receive either abiraterone acetate and prednisone or placebo and prednisone. Randomisation was masked. Patients were stratified according to baseline ECOG performance status, number of previous chemotherapy regimens, type of disease progression, and baseline level of pain. The study sponsor, investigators, patients, and the independent data monitoring committee were masked to treatment assignment until study completion.

After randomisation, patients had 28-day cycles of treatment with either abiraterone acetate (1 g) or placebo orally once daily, in combination with 5 mg of oral prednisone twice daily. Concomitant bisphosphonates were permitted when patients were already taking them at study entry or after a new skeletal-related event was noted during the study.

Overall survival was the primary endpoint of the COU-AA-301 trial. Patients were encouraged to continue treatment until disease progression was noted on the basis of radiographic or clinical findings, or concen-

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***Panel 1:* Definitions for pain analyses**

- Pain intensity palliation: two consecutive follow-up visits (at least 4 weeks apart) at which the pain intensity score was at least 30% lower than that at baseline (previously reported as a clinically meaningful decrease[21]), without an increase in analgesic use (defined as a ≥1 point increase on the WHO analgesic scale). Duration of pain intensity palliation was also assessed in all patients meeting these criteria.
- Pain intensity progression: two consecutive follow-up visits at which the pain intensity score increased by 30% or more without a decreased analgesic usage score, or an increase in analgesic usage score of 30% or greater.
- Pain interference palliation: mean pain interference score (ie, the mean of the scores for the pain interference items) decreased by 1·25 points or more compared with baseline at two consecutive follow-up visits; we derived this threshold from the baseline standard deviation according to a generally accepted estimation process.[22]
- Pain interference progression: increase of 1·25 points or more in the mean pain interference score at two consecutive follow-up visits.

	Abiraterone acetate and prednisone (n=797)	Placebo and prednisone (n=398)
Age (years)	69 (42–95)	69 (39–90)
≥75 years	220/797 (27·6%)	111/397 (28·0%)
ECOG performance status		
0 or 1	715/797 (89·7%)	353/398 (88·7%)
2	82/797 (10·3%)	45/398 (11·3%)
Disease location		
Bone	710/797 (89·1%)	358/398 (89·9%)
Node	361/797 (45·3%)	164/398 (41·2%)
Liver	89/797 (11·2%)	29/398 (7·3%)
Number of previous cytotoxic chemotherapy regimens		
One	558/797 (70·0%)	275/398 (69·1%)
Two	239/797 (30·0%)	123/398 (30·9%)
BPI-SF worst pain intensity score	3 (0–10)	3 (0–10)
Previous bisphosphonate treatment	328/791 (41·5%)	174/394 (44·2%)
Prostate-specific antigen (μg/mL)	128·8 (0·4–9253·0)	137·7 (0·6–10 114·0)
Haemoglobin (g/L)	118 (73–161)	118 (72–165)
Lactase dehydrogenase (IU/L)	223 (84–3373)	238 (123–5125)
Alkaline phosphatase (IU/L)	134 (33–4896)	134 (20–4617)

Data are n/N (%) or median (range). ECOG=Eastern Cooperative Oncology Group. BPI-SF=Brief Pain Inventory-Short Form.

***Table 1:* Baseline characteristics in each group**

	Abiraterone acetate and prednisone		Placebo and prednisone	
	Pain absent (n=444)	Pain present (n=353)	Pain absent (n=223)	Pain present (n=175)
Gleason score				
<7	120/444 (27·0%)	83/353 (23·5%)	52/223 (23·3%)	33/175 (18·9%)
7	134/444 (30·2%)	104/353 (29·5%)	69/223 (30·9%)	55/175 (31·4%)
≥7	190/444 (42·8%)	166/353 (47·0%)	102/223 (45·7%)	87/175 (49·7%)
Metastatic distribution				
Bone metastases	389/444 (87·6%)	321/353 (90·9%)	194/223 (87·0%)	164/175 (93·7%)
Soft tissue metastases	273/444 (61·5%)	217/353 (61·5%)	125/223 (56·1%)	94/175 (53·7%)
Metastasis stage				
M0	205/404 (50·7%)	142/326 (43·6%)	94/200 (47·0%)	77/167 (46·1%)
M1	110/404 (27·2%)	118/326 (36·2%)	60/200 (30·0%)	61/167 (36·5%)
MX	89/404 (22·0%)	66/326 (20·2%)	46/200 (23·0%)	29/167 (17·4%)
Regional lymph node stage				
N0	195/385 (50·6%)	147/316 (46·5%)	80/191 (41·9%)	73/159 (45·9%)
N1	41/385 (10·6%)	45/316 (14·2%)	28/191 (14·7%)	18/159 (11·3%)
N2	15/385 (3·9%)	11/316 (3·5%)	10/191 (5·2%)	2/159 (1·3%)
N3	2/385 (0·5%)	3/316 (0·9%)	3/191 (1·6%)	4/159 (2·5%)
NX	132/385 (34·3%)	110/316 (34·8%)	70/191 (36·6%)	62/159 (39·0%)
Primary tumour stage				
T0	1/402 (0·2%)	0/330 (0%)	0/199 (0%)	0/162 (0%)
T1	56/402 (13·9%)	34/330 (10·3%)	25/199 (12·6%)	15/162 (9·3%)
T2	106/402 (26·4%)	95/330 (28·8%)	47/199 (23·6%)	52/162 (32·1%)
T3	154/402 (38·3%)	128/330 (38·8%)	79/199 (39·7%)	57/162 (35·2%)
T4	25/402 (6·2%)	31/330 (9·4%)	16/199 (8·0%)	15/162 (9·3%)
TX	60/402 (14·9%)	42/330 (12·7%)	32/199 (16·1%)	23/162 (14·2%)
Prostate-specific antigen (μg/L)	117 (0·4–9253)	162 (0·9–8100)	158 (3·2–5438)	129 (0·6–10 114)
Haemoglobin (g/L)	120 (73–161)	112 (81–145)	120 (80–165)	116 (72–164)
Lactase dehydrogenase (IU/L)	210 (84–1750)	250 (97–3373)	225 (131–2104)	257 (123–5125)
Alkaline phosphatase (IU/L)	108 (33–4896)	168 (33–4431)	110 (20–1920)	160 (40–4617)

Data are n/N (%) or median (range). Pain present was defined as a score of 4 of greater on item 3 of the Brief Pain Inventory-Short Form questionnaire.

Table 2: **Baseline factors according to presence or absence of pain**

trations of prostate-specific antigen. The review boards at all participating institutions approved COU-AA-301; all patients provided written informed consent.

Procedures

Patient-reported pain data were gathered with the Brief Pain Inventory-Short Form (BPI-SF) questionnaire during outpatient visits. This validated instrument, which assesses pain intensity and the interference of pain with daily life,[19,20] was given to patients during scheduled clinic visits at screening (baseline), day 15 of cycle 1, and day 1 of every subsequent treatment cycle until the end of study treatment or treatment discontinuation. The analgesic usage score was reported on a paper form by local investigators and coded by WHO's analgesic ladder (ie, 0=no analgesic; 1=non-opioid analgesics, including non-steroidal anti-inflammatory drugs, paracetamol, anti-depressants, and drugs for neuropathic pain; 2=opioids for moderate pain; 3=opioids for severe pain). We defined compliance as the number of available assessments divided by the number of alive, actively enrolled patients in the study at each timepoint (so-called planned assessments, which included all assessments from patients who did not attend a specific visit or did not fill out the paper form while at the visit); the proportion of patients with missing data was thought of as the proportion of non-compliant patients. We deemed an assessment for pain interference available only if 50% or more of the relevant questionnaire items were completed; otherwise the data were judged missing.

Consistent with the medical literature, we defined skeletal-related events as pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone.[11] Pathological fractures and spinal cord compression were assessed radiologically as needed throughout the study; bone scans were scheduled at baseline, day 1 of every third cycle, and treatment discontinuation.

Pain intensity was defined a priori in the analysis plan as worst pain intensity in the past 24 h (ie, item 3 of the BPI-SF), and pain interference as the mean score of all seven BPI-SF items assessing interference of pain with activities of daily living. We defined all pain palliation analyses and associated thresholds before data assessment (panel 1).

For all analyses, we judged non-consecutive visits to be consecutive when scores for intervening visits were missing. All patients were assessed for pain intensity and pain interference progression, but only patients with clinically significant pain at baseline and at least one postbaseline pain score were assessed for palliation. For the purpose of the pain intensity analyses, we defined clinically significant baseline pain as a score of 4 or more on BPI-SF item 3,[23] and, for the pain interference analyses, as a mean score of 4 or more on the BPI-SF pain interference scale. Time to palliation or progression was measured from the date of randomisation to the first date on which the criteria for palliation or progression were met. We measured duration of pain palliation from the first day palliation was noted to the first day of pain progression; patients without any progression were censored at the last known date of non-progression. For the purposes of these analyses, we assigned baseline pain intensity or interference or baseline analgesic usage scores of 0 a value of 0·1 to allow calculation of a percentage increase. We measured time to skeletal-related events from randomisation to the first date of documentation of an event. Proportions of patients with pain intensity palliation, time to pain intensity progression, and time to skeletal-related events were analysed prospectively as per the analysis plan.

Statistical analysis

We did all analyses with data obtained at a median follow-up of 20·2 months (IQR 18·4–22·1 months), the timepoint before unmasking and crossover from the

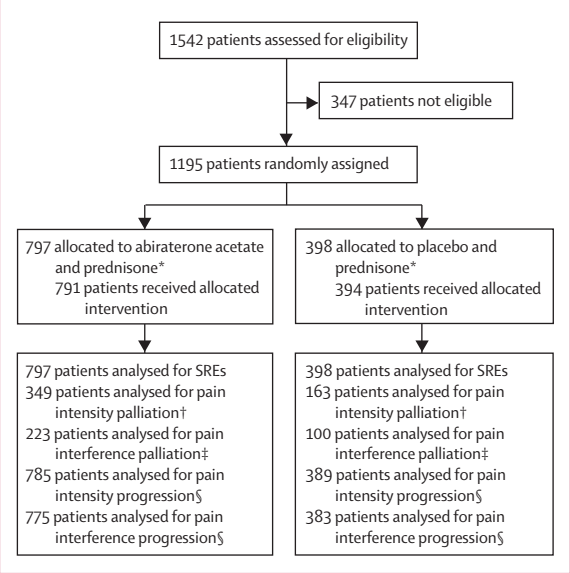

Figure 1: **COU-AA-301 trial profile**
SREs=skeletal-related events. *Intention-to-treat population. †Patients without clinically significant pain intensity at baseline and at least one postbaseline pain score were excluded from this analysis. ‡Patients without clinically significant pain interference at baseline and at least one postbaseline pain score were excluded from this analysis. §Patients without a baseline score were excluded from this analysis.

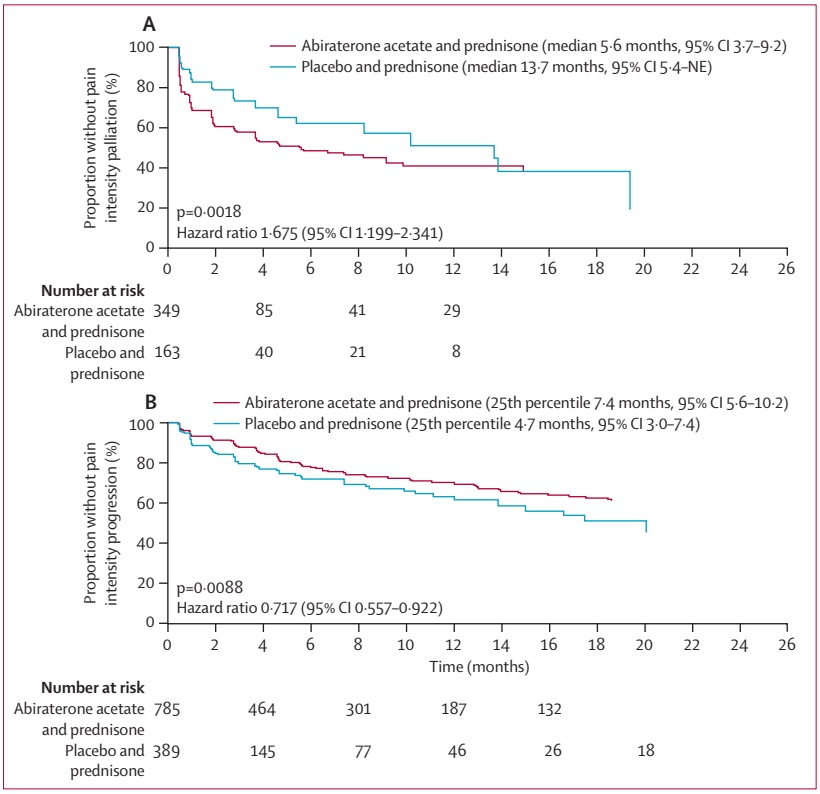

Figure 2: **Kaplan-Meier curves for pain palliation (A) and progression (B)**
p values were obtained from log-rank tests and stratified by Eastern Cooperative Oncology Group performance status score (0–1 *vs* 2), pain score (absent *vs* present), number of previous chemotherapy regimens (1 *vs* 2), and type of progression (prostate-specific antigen only *vs* radiographic plus prostate-specific antigen). Lines for each curve end at the last available observation. NE=not estimable.

prednisone only to the abiraterone acetate and prednisone group. We used χ^2 tests to assess differences between treatment groups in pain intensity and interference palliation. We used the Kaplan-Meier method to estimate median times to palliation or progression and duration of pain intensity palliation; log-rank tests stratified by baseline ECOG performance status score (0–1 *vs* 2), pain score (absent *vs* present), number of previous chemotherapy regimens (1 *vs* 2), and type of progression (prostate-specific antigen only *vs* radiographic plus prostate-specific antigen) were used to compare the distributions. Hazard ratios (HRs) were estimated from a stratified Cox proportional hazards model. We did all statistical analyses with SAS software (version 9.2). COU-AA-301 is registered with ClinicalTrials.gov, number NCT00638690.

Role of the funding source

Employees of Janssen Research & Development participated in trial design, data collection, and data analysis, and had a supporting role in data interpretation and writing of this 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 the conduct of the trial. Editorial support was provided to the authors and funded by the study sponsor, but all decisions relating to manuscript writing and content were made jointly by the authors. 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

Results of the COU-AA-301 trial[24] have been reported previously. 797 patients were randomly assigned to abiraterone acetate plus prednisone and 398 to placebo plus prednisone; these patients comprised the intention-to-treat population. Demographics were similar across treatment groups,[16] and median age was 69 years in both groups (table 1).

Table 2 lists patients' baseline factors on the basis of the presence or absence of baseline pain. 1068 of 1195 (89·4%) patients had bone metastases.[16] Mean baseline pain scores did not differ significantly between groups; mean pain intensity (expressed as mean of BPI-SF items 3 to 6) was 2·42 (SD 2·02) with abiraterone acetate and prednisone versus 2·39 (2·08) with predisone only (p=0·819), and mean pain interference was 2·52 (SD 2·43) versus 2·48 (2·32) (p=0·774). Mean baseline analgesic usage scores on the WHO scale were 1·2 (SD 1·08) in the abiraterone acetate and prednisone group and 1·3 (1·06) in the prednisone group. Similar proportions of patients had clinically significant baseline pain and were assessable for pain palliation; 349 of 797 (43·8%) patients in the abiraterone acetate and prednisone group and 163 of 398 (41·0%) in the

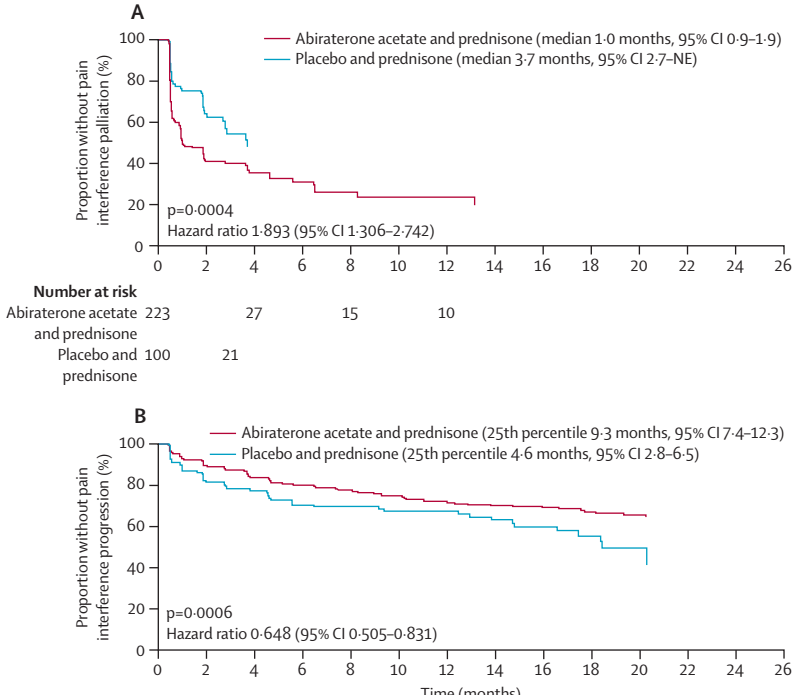

Figure 3: **Kaplan-Meier curves for pain interference palliation (A) and progression (B)**
p values were obtained from log-rank tests stratified by Eastern Cooperative Oncology Group performance status score (0–1 *vs* 2), pain score (absent *vs* present), number of previous chemotherapy regimens (1 *vs* 2), and type of progression (prostate-specific antigen only *vs* radiographic plus prostate-specific antigen). Lines for each curve end at the last available observation. NE=not estimable.

	Abiraterone acetate and prednisone (n=797)	Placebo and prednisone (n=398)
Total patients with SREs	180 (22·6%)	98 (24·6%)
One	137 (17·2%)	74 (18·6%)
Two	35 (4·4%)	20 (5·0%)
Three or more	8 (1·0%)	4 (1·0%)
Total number of SREs (n)	235	130
Radiation to bone	145 (61·7%)	92 (70·8%)
Pathological fracture	36 (15·3%)	8 (6·2%)
Surgery to bone	10 (4·3%)	2 (1·5%)
Spinal cord compression	45 (19·1%)	28 (21·5%)
SRE rate per 100 patients-years of exposure (%)*	38·9%	65·1%
Radiation to bone (%)	24·0%	46·1%
Pathological fracture (%)	6·0%	4·0%
Surgery to bone (%)	1·7%	1·0%
Spinal cord compression (%)	7·3%	14·0%

Data are n (%) unless otherwise specified. SRE=skeletal-related event. *Rates derived by dividing the total number of the respective SRE by the total patient-years of exposure (ie, 603·8 for abiraterone acetate and 199·6 for placebo).

Table 3: **Skeletal-related events in the intention-to-treat population**

prednisone only group were assessable for pain intensity palliation, and 223 (28·0%) and 100 (25·1%), respectively, for pain interference palliation. Figure 1 shows the trial profile.

Compliance with the BPI-SF questionnaire was high (appendix), with 12 126 of 13 013 (93·2%) planned assessments completed during the study. Compliance was similar between groups (8951 of 9554 [93·7%] for the abiraterone acetate and prednisone group *vs* 3175 of 3459 [91·8%] for the prednisone only group). Median time to pain palliation, but not time to pain progression, was reached.

The patient-reported rate of symptomatic improvement of both pain intensity and pain interference was better in the abiraterone acetate and prednisone group than in the prednisone only group, with significantly more patients in the abiraterone acetate and prednisone group experiencing palliation of pain and palliation of pain interference than those in the prednisone and placebo group (157 of 349 [45·0%] patients *vs* 47 of 163 [28·8%] for pain intensity palliation, p=0·0005; 134 of 223 [60·1%] patients *vs* 38 of 100 [38·0%] for palliation of pain interference, p=0·0002). Median time to palliation of both pain and pain interference favoured the abiraterone group, as did median time to progression of both pain and pain interference (figures 2 and 3). The median duration of pain intensity palliation was significantly longer with abiraterone acetate and prednisone (4·2 months, 95% CI 3·0–4·9) than with prednisone only (2·1 months, 1·4–3·7; p=0·0056). Continuous responder curves at 4, 8, 12, and 24 weeks suggest that, at any percent change level, substantial benefits were noted in patients in the abiraterone acetate and prednisone group compared with those in the placebo and prednisone group (appendix). Two separate sensitivity analyses (based on different approaches) to account for missing data further confirmed the noted results (appendix).

The results for pain palliation analyses, which were calculated only from patients with clinically significant baseline pain in the preplanned analyses, were similar in the overall ITT population in a post-hoc analysis (appendix).

The proportion of patients with skeletal-related events was similar in both treatment groups (table 3), but patients in the abiraterone acetate and prednisone group had significantly longer median time to first skeletal-related event than did those in the placebo group (figure 4). A lower proportion of patients had skeletal-related events at 6, 12, and 18 months in the abiraterone acetate and prednisone group than in the prednisone only group (table 4), and the overall rate of skeletal-related events, adjusted for duration of treatment exposure, was lower for patients in the abiraterone and prednisone group (table 3). 355 of 791 (44·9%) patients in the abiraterone acetate and prednisone group received concomitant bisphosphonates compared with 197 of 394 (50·0%) patients in the prednisone only group (p=0·0816).

Discussion

In this study we showed that abiraterone acetate plus prednisone favourably affects measures of bone-related symptoms (patient-reported pain palliation, delay in pain progression, and delayed time to skeletal-related events) in metastatic castration-resistant prostate cancer compared with prednisone alone (panel 2). Pain palliation also occurred faster with abiraterone acetate and prednisone than with placebo and prednisone. We interpret these findings to be supportive of the hypothesis that persistent androgen receptor signalling is centrally implicated in castration-resistant prostate cancer in bone. Notably, the improved palliation and delayed progression of both pain intensity and pain interference were sustained across treatment cycles. Kaplan-Meier curves suggest that the pain palliation with abiraterone acetate occurred early after treatment initiation and that the differences were maintained throughout the duration of treatment.

Bone pain is a predictive factor for the development of skeletal-related events.[5] Mortality risk is increased 6·6-fold in prostate cancer with bone metastases compared with that without bone involvement, and bone metastases in combination with skeletal-related events increase mortality risk 10·2-fold.[3] Retrospective analysis of clinical trials showed a significant association between pain interference scores and risk of death.[25]

As is generally the case for clinical trials done in populations with advanced prostate cancer, the main endpoint of interest was time to skeletal-related events, rather than incidence;[9–11] the incidences of events were provided only for descriptive purposes and are not meant to be inferential. The median duration of treatment with abiraterone acetate and prednisone was roughly twice as long as that with prednisone only, which might result from the survival benefit with abiraterone;[16] patients who lived longer had a longer period during which they might experience a skeletal-related event. When event rates were adjusted for treatment duration, the rate of skeletal-related events per 100 patient-years of treatment exposure was roughly 40% with abiraterone acetate and prednisone and 65% with prednisone only. Because of the small overall numbers in this trial, further investigation is needed to assess whether treatment with abiraterone acetate might be associated with an increased risk of pathological fractures. 50% of patients in the prednisone only group and roughly 45% in the abiraterone acetate and prednisone group received bisphosphonate treatment during the course of the study. These drugs protect against skeletal-related events and are thus a potential confounding factor that might have contributed to the treatment effect.

The effect of purely bone-targeting treatments on pain has been largely disappointing.[26] The results of a phase 3 clinical trial[9] published in 2011 showed that denosumab significantly prolonged time to first skeletal-related event compared with zoledronate but did not affect the reported incidence of back, bone, and extremity pain. By contrast, phase 2 results with the antiangiogenesis drug cabozantinib showed decreased pain and a high rate of bone lesion response on bone scans.[27] That the bone-homing radiopharmaceutical radium-223 chloride showed improved survival and delay in skeletal-related events should also be noted.[10] The benefits of drugs that concurrently reduce bone pain, delay time to skeletal-related events, and improve overall survival are probably the result of a decrease in tumour burden or activity within the bone microenvironment.

To further the development of treatments for bone metastases associated with prostate cancer, investigators will need to establish the magnitude of improvement in bone-related symptoms needed to yield clinically meaningful improvements in how patients feel and function, and how to integrate these treatments into an overall strategy for advanced prostate cancer. Although abiraterone acetate provided clinical benefits for patients with metastatic castration-resistant prostate cancer who had pain and bone disease, androgen depletion alone might not overcome all mechanisms driving progression in bone. Based on our improved understanding of the signalling networks implicated in prostate cancer progression, perhaps future studies should investigate the combined inhibition of androgen-receptor and

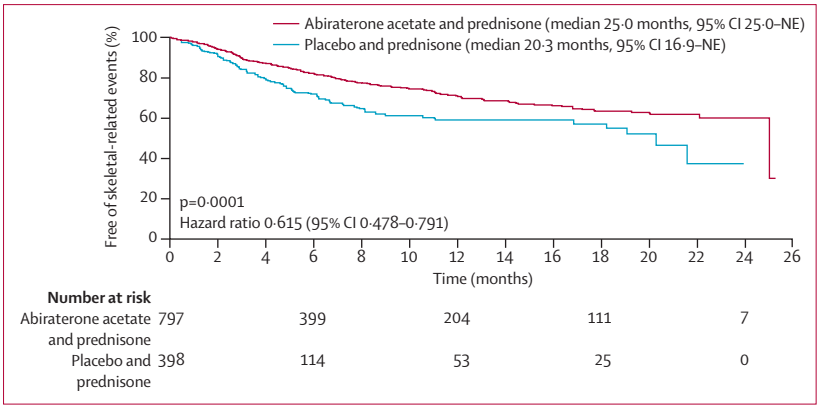

Figure 4: **Kaplan-Meier curves for occurrence of first skeletal-related event**
p values were obtained from log-rank tests stratified by Eastern Cooperative Oncology Group performance status score (0–1 *vs* 2), pain score (absent *vs* present), number of previous chemotherapy regimens (1 *vs* 2), and type of progression (prostate-specific antigen only *vs* radiographic plus prostate-specific antigen). Lines for each curve end at the last available observation. NE=not estimable.

	Abiraterone acetate and prednisone (n=797)	Placebo and prednisone (n=398)
6 month event-free	82·2% (79·0–85·0)	72·1% (65·9–77·3)
12 month event-free	71·1% (66·8–74·9)	59·1% (51·4–66·1)
18 month event-free	63·6% (58·4–68·3)	57·2% (48·7–64·8)

Data are rate (95% CI).

Table 4: **Skeletal-related events-free survival in the intention-to-treat population**

See **Online** for appendix

Panel 2: Research in context

Systematic review

We did not do a formal systematic review. However, a search of papers published on PubMed (a full list of search terms is in the appendix) suggested that bone metastases are a major cause of morbidity in this population and that few effective treatment options that both prolong survival and reduce bone-related symptoms are available.

Interpretation

Our results showed that abiraterone acetate and prednisone favourably affect measures of disease-related symptoms (ie, clinically meaningful pain palliation, delay in pain progression, and delayed time to skeletal-related events) compared with prednisone only in patients with metastatic castration-resistant prostate cancer after previous treatment with docetaxel. These findings indirectly support the previously reported hypothesis that persistent signalling of androgen receptors is centrally implicated in castration-resistant prostate cancer in bone.

non-androgen-receptor signalling as microenvironment-targeted treatments.[1] Ideally, drugs with entirely different mechanisms of action and toxic effects should be given. For instance, the combination of abiraterone acetate and radium-223 chloride might merit clinical assessment for the treatment of advanced prostate cancer that has spread to bone.

Investigators planning future clinical trials in metastatic castration-resistant prostate cancer should consider the inclusion of well designed pain endpoints (if applicable to their study hypothesis). The pain intensity endpoints in our study, for example, were predefined before data collection, and all analyses incorporated contemporary assessment standards, including assessment of fluctuations in patients' analgesic use. The chosen threshold for pain palliation is fairly well established as the amount of pain at which patients experience changes to their daily life and need narcotic analgesics.[23,28,29]

Pain palliation in the control group was noteworthy, suggesting a potential treatment benefit with prednisone; symptomatic relief with low dose prednisone in advanced prostate cancer has been shown previously.[30,31] The analgesic properties of prednisone might have contributed to the pain improvement that we noted in the abiraterone acetate and prednisone group. Differences in pain response between treatment groups were unlikely to be due to transient changes in opioids because analgesic use was incorporated into the pain intensity endpoint. Despite this precaution, our method of data collection might still have affected results. We obtained pain scores only once during each cycle, and WHO's analgesic ladder is not sensitive to dose fluctuations within the same analgesic class. More sensitive methods to measure analgesic use are difficult to implement in large clinical trials with several endpoints, and detailed analgesic use is hard to quantify at the patient level. Although the WHO ladder is a pragmatic and useful instrument that yields important information, changes in analgesic management undetectable by the WHO approach could have contributed to some of the pain improvement observed in both groups, especially because patients enrolled in clinical trials might receive increased attention to symptom management.

Other potential limitations include the unavailability of data for previous skeletal-related events before study entry, that bone scans were not done at each cycle, and that the potential correlation between pain palliation and overall survival or serum alkaline phosphatase was not analysed. Future studies should assess these and alternative approaches, such as the incremental benefit of inclusion of several days of consecutive reporting at each timepoint or more comprehensive approaches to analgesic tabulation. The effects of abiraterone acetate on pain control and skeletal-related events outside the restrictions of a clinical trial and a broader population of patients with metastatic castration-resistant prostate cancer should also be assessed further.

Contributors

CJL, EB, AM, and TSK had roles in study conception and design; collection, assembly, analysis, and interpretation of data; and writing of the paper. KF, SAN, KNC, RJJ, OBG, PNM, CNS, and EE collected and assembled data. DDG, MR, and CSL analysed and interpreted data. YH helped to conceive and design the study, analysed and interpreted data, and had a role in the writing of the paper. CMH had roles in study design and conception and data analysis and interpretation. HIS and JSdB helped to design and conceive the study and collected and assembled data. All authors critically reviewed the Article for important intellectual content, provided comments accordingly, and gave final approval.

Conflicts of interest

CJL has received consultancy fees and travel support from Ortho Biotech Research & Development (now Janssen Research & Development). EB is the study chair (uncompensated) of a clinical trial funded by Exelixis. AM and TSK are fulltime employees of Janssen Research & Development. KF has received research support from Cougar Biotechnology (now Janssen Research & Development). SAN has received consultancy fees from Amgen, AstraZeneca, GlaxoSmithKline, Novartis, Ortho Biotech Research & Development, Pfizer, and Sanofi-Aventis. KNC has received consultancy fees and speaker honoraria from Ortho Biotech Research & Development. RJJ has received grant support and travel support from Ortho Biotech Research & Development and research funding from Johnson & Johnson. CNS has received consultancy fees and speaker honoraria from Amgen, Astellas, Dendreon, Johnson & Johnson, Millennium, Novartis, and Sanofi-Aventis, and research funding from Cougar Biotechnology. EE has received consultancy fees from Ortho Biotech Research & Development and travel support from Janssen Biotech. DDG is a fulltime employee of Truven Health Analytics and served as a paid consultant to Janssen Global Services in connection with these analyses. MR and YH are fulltime employees of Janssen Global Services. CSL and CMH were fulltime employees of Cougar Biotechnology when this study was done. HIS has received consultancy fees from Amgen, Dendreon, Millennium, Novartis, Ortho Biotech Research & Development (donated to charity), and Sanofi-Aventis; grant support from Medivation, Ortho Research and Development, and Veridex; has served as an unpaid consultant for Exelixis, Medivation, and Veridex; and has owned stock in Johnson & Johnson (sold). JSdB has served as a consultant for Amgen, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Dendreon, Enzon, Exelixis, Genentech, GSK, Medivation, Merck, Novartis, Ortho Biotech

Research & Development, Pfizer, Roche, Sanofi-Aventis, Supergen, and Takeda, and has received grant support from AstraZeneca, speaker fees from Johnson & Johnson, and travel support from Amgen, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Dendreon, Enzon, Exelixis, Genentech, GSK, Medivation, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, Supergen, and Takeda. OBG and PNM declare that they have no conflicts of interest.

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