Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial

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See Comment page 609

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Summary

Background In the interim analyses of the LATITUDE study, the addition of abiraterone acetate plus prednisone to androgen deprivation therapy (ADT) led to a significant improvement in overall survival and radiographic progression-free survival compared with placebos plus ADT in men with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (mCSPC). Here, we present long-term survival outcomes and safety of abiraterone acetate plus prednisone and ADT from the final analysis of the LATITUDE study.

Methods This is a multicentre, randomised, double-blind, phase 3 trial done at 235 sites in 34 countries. Eligible patients (men aged ≥18 years) had newly diagnosed, histologically or cytologically confirmed prostate cancer with metastases, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and at least two of the three high-risk prognostic factors (Gleason score of ≥8, presence of three or more lesions on bone scan, or presence of measurable visceral metastasis except lymph node metastasis). Patients were randomly assigned (1:1) to receive abiraterone acetate (1000 mg) once daily orally plus prednisone (5 mg) once daily orally and ADT (abiraterone acetate plus prednisone group) or matching placebos plus ADT (placebo group); each treatment cycle was 28 days. Randomisation was done by a centralised interactive web response system in a country-by-country scheme using permuted block randomisation, stratified by presence of visceral disease and ECOG performance status. The coprimary endpoint of overall survival was assessed in the intention-to-treat population. This study is registered at ClinicalTrials.gov, number NCT01715285 and is complete.

Findings Between Feb 12, 2013, and Dec 11, 2014, 1209 patients were screened, of whom ten were ineligible because of study site violations. 1199 patients were randomly assigned to either the abiraterone acetate plus prednisone group (n=597) or placebo group (n=602). After the results of the first interim analysis (cutoff date Oct 31, 2016), the study was unmasked to patients and investigators, and patients in the placebo group were allowed to cross over to receive abiraterone acetate and prednisone plus ADT treatment as per a protocol amendment (Feb 15, 2017) in an open-label extension phase of the study (up to 18 months from the protocol amendment). This final analysis (data cutoff Aug 15, 2018) was done after a median follow-up of 51·8 months (IQR 47·2–57·0) and 618 deaths (275 [46%] of 597 in the abiraterone acetate plus prednisone group and 343 [57%] of 602 in the placebo group). Overall survival was significantly longer in the abiraterone acetate plus prednisone group (median 53·3 months [95% CI 48·2–not reached]) than in the placebo group (36·5 months [33·5–40·0]), with a hazard ratio of 0·66 (95% CI 0·56–0·78; p<0·0001). The most common grade 3–4 adverse events were hypertension (125 [21%] in the abiraterone acetate plus prednisone group *vs* 60 [10%] in the placebo group *vs* three [4%] in the 72 patients who crossed over from placebo to abiraterone acetate plus prednisone) and hypokalaemia (70 [12%] *vs* ten [2%] *vs* two [3%]). Serious adverse events of any grade occurred in 192 (32%) of 597 patients in the abiraterone acetate plus prednisone group, 151 (25%) of 602 in the placebo group, and four (6%) of 72 in the crossover group. The most common treatment-related serious adverse event was hypokalaemia (four [1%] patients in the abiraterone acetate plus prednisone group and none in the other groups). Treatment-related deaths occurred in three (<1%) patients each in the abiraterone acetate plus prednisone group (gastric ulcer perforation, sudden death, and cerebrovascular accident) and the placebo group (sudden death, cerebrovascular accident, and pneumonia), with none in the crossover group.

Interpretation The combination of abiraterone acetate plus prednisone with ADT was associated with significantly longer overall survival than placebos plus ADT in men with newly diagnosed high-risk mCSPC and had a manageable safety profile. These findings support the use of abiraterone acetate plus prednisone as a standard of care in patients with high-risk mCSPC.

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Research in context

Evidence before this study

We searched PubMed to retrieve studies of prostate cancer published in English from Jan 1, 2008, to Nov 28, 2018. The search strategy encompassed a wide range of key terms, including "prostate cancer", "overall survival", and "androgen deprivation", to identify randomised controlled studies, post-hoc analyses, systematic reviews, and meta-analyses assessing efficacy and safety of treatments in men with newly diagnosed metastatic castration-sensitive prostate cancer (mCSPC). We identified 35 relevant articles. The published studies suggest that treatment with androgen deprivation therapy (ADT) alone has been associated with poor survival outcomes because of rapid disease progression, and the addition of docetaxel to ADT has become a standard approach to delay disease progression and improve survival outcomes in men with mCSPC. However, the use of docetaxel might be restricted because of its toxicity profile and patient-specific comorbidities. The addition of abiraterone acetate plus prednisone to ADT in a preplanned interim analysis of the phase 3 LATITUDE study showed significant survival benefits and clinical benefits in patient-reported outcomes in patients with newly diagnosed high-risk mCSPC.

Added value of this study

In this final analysis of LATITUDE, abiraterone acetate plus prednisone with ADT continued to show survival benefits compared with ADT alone, by further prolonging overall survival and delaying initiation of chemotherapy and subsequent therapy in newly diagnosed patients with high-risk mCSPC. The combination of abiraterone acetate plus prednisone with ADT showed a manageable safety profile, which is consistent with that of the interim analysis and other previously published studies.

Implications of all the available evidence

The addition of abiraterone acetate plus prednisone to ADT could be a new standard-of-care treatment in patients with newly diagnosed high-risk mCSPC. The findings also show that early initiation of these drugs might be beneficial in patients with high-risk mCSPC. Thus far, abiraterone acetate plus prednisone has been recommended for the treatment of mCSPC by National Comprehensive Cancer Network clinical practice guidelines and European Society for Medical Oncology and European Association of Urology guidelines.

Introduction

Newly diagnosed metastatic castration-sensitive prostate cancer (mCSPC) is recognised as an aggressive form of the disease with rapid progression to castration-resistant state and poor survival.[1,2] Androgen deprivation therapy (ADT) is the frontline treatment for mCSPC and can lead to long-term disease control in some patients who have low-risk features and few metastases. However, treatment with ADT alone in de-novo mCSPC with high-risk features has been associated with poor survival outcomes because of rapid progression to metastatic castration-resistant prostate cancer (mCRPC),[3,4] which is often associated with debilitating symptoms such as bone pain and skeletal-related events, fatigue, and urinary symptoms.[5,6] Therefore, the addition of other treatments to ADT has emerged as a desirable approach to delay disease progression and improve overall survival. The combination of docetaxel with ADT in men with mCSPC has shown statistically significantly improved survival outcomes compared with ADT alone in two randomised controlled phase 3 trials, CHAARTED[7] and STAMPEDE.[8] However, the combination did not lead to a statistically significant overall survival improvement in the GETUG-AFU 15 study,[6] in which docetaxel was tested alone, and the magnitude of benefit was also less convincing in one of the STAMPEDE[8] groups in which docetaxel was combined with zoledronic acid, although progression-free survival was significantly improved in these studies. Whether or not the benefit of docetaxel in men with mCSPC is restricted to men with a high burden of metastases is debated.[9–11] However, patient-specific comorbidities, including patients at high risk of myelosuppression, patient preferences, patient age, and toxicity profile might limit the use of docetaxel in patients with mCSPC.[12,13]

Abiraterone acetate, a prodrug of abiraterone, which is a selective irreversible inhibitor of the key enzyme cytochrome P17A1 that is required in androgen biosynthesis, has been approved in combination with prednisone for the treatment of mCRPC. Treatment with abiraterone acetate plus low-dose prednisone has been associated with significant improvement in overall survival in patients in both chemotherapy-naive and chemotherapy-treated patients with mCRPC.[14,15] Furthermore, the addition of abiraterone acetate plus prednisone to neoadjuvant luteinising hormone-releasing hormone (LHRH) agonists such as leuprolide acetate was associated with notable lowering of prostate tissue androgens compared with LHRH agonists alone in hormone-sensitive patients.[16] This finding suggests that abiraterone acetate plus prednisone might also inhibit extragonadal androgen biosynthesis and thereby help delay the emergence of resistance in patients with mCSPC.

In a preplanned interim analysis of the phase 3 LATITUDE study in newly diagnosed patients with high-risk features of mCSPC, the addition of abiraterone acetate plus prednisone to ADT was associated with significantly longer overall survival compared with that of the placebo group (median not reached with the addition of abiraterone acetate *vs* 34·7 months [95% CI 33·1–not reached] with placebo; 3-year event-free survival 66% [95% CI 61–70] *vs* 49% [44–55]).[17] Treatment with abiraterone acetate plus prednisone versus placebos was

associated with a hazard ratio (HR) of 0·62 (95% CI 0·51–0·76; p<0·001) for overall survival, and median radiographic progression-free survival was 33·0 months (95% CI 29·6–not reached) in the abiraterone acetate plus prednisone group versus 14·8 months (14·7–18·3) in the placebo group (HR for radiographic progression or death 0·47 [95% CI 0·39–0·55]; p<0·001).[17] In addition to the survival benefits, abiraterone acetate plus prednisone treatment showed clinical benefits in patient-reported outcomes, including pain and fatigue symptoms, and overall health-related quality of life.[18] Furthermore, an improvement in overall survival was also seen with abiraterone acetate plus prednisone and ADT compared with ADT alone in the STAMPEDE phase 3 study[19] in a subgroup of patients with metastases (HR 0·61; 0·49–0·75) and was confirmed in a meta-analysis of the two studies.[20] On the basis of these findings, the addition of abiraterone acetate plus prednisone to ADT has been regarded as a new treatment standard in patients with newly diagnosed mCSPC.[12] In the final analysis of the LATITUDE study, the secondary endpoints, including time to initiation of chemotherapy, time to pain progression, time to symptomatic skeletal event, time to prostate-specific antigen progression, and time to subsequent prostate cancer therapy are reported, and median overall survival has now been reached for the abiraterone acetate and prednisone plus ADT group. The results of this final analysis are presented in this Article.

Methods

Study design and participants

LATITUDE was a multicentre, randomised, double-blind, active control, phase 3 trial done in patients with newly diagnosed high-risk mCSPC at 235 clinical sites in 34 countries in Europe, Africa, South America, Canada, Mexico, and the Asia-Pacific region (appendix pp 2–5).[17,18] Full details of the study design and inclusion and exclusion criteria of this phase 3 trial are available in the protocol (appendix pp 34–173) and have been published previously.[18] Briefly, men aged 18 years and older with newly diagnosed (in the 3 months before randomisation) and histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology, with distant metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI as per the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 criteria, and with Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2 were included. Additionally, patients were required to have at least two of three high-risk prognostic factors (Gleason score ≥8, three or more lesions on bone scan, and measurable visceral metastases, excluding lymph node metastasis). Patients were also required to have adequate haematological, hepatic, and renal function (haemoglobin 9·0 g/dL independent of transfusions, neutrophils ≥1·5×10⁹ cells per L, platelets ≥100×10⁹ per L, total bilirubin ≤1·5 times the upper limit of normal [ULN; except for patients with documented Gilbert's disease, in which case, total bilirubin should not exceed ten times the ULN], alanine and aspartate aminotransferase ≤2·5 times the ULN, serum creatinine <1·5 times the ULN or calculated creatinine clearance ≥50 mL/min, serum potassium ≥3·5 mM, and serum albumin ≥3·0 g/dL). Patients who had received previous chemotherapy, radiotherapy, or surgery for metastatic prostate cancer were excluded; however, up to 3 months of ADT with LHRH analogues or orchiectomy with or without concurrent antiandrogens before baseline or a single course of previous palliative radiotherapy or surgical therapy for the symptoms of the metastatic disease (as long as this was administered at least 28 days before the start of study treatment) were permitted. Patients with small-cell carcinoma of the prostate, brain metastasis, uncontrolled hypertension, or with clinically significant cardiac, adrenal, or liver disease, or malignancy other than prostate or non-melanoma skin cancer within the previous 5 years were excluded.

The trial protocol was approved by the local Institutional Review Boards for each site and was done in accordance with the ethical principles outlined in the Declaration of Helsinki. The trial was consistent with International Conference on Harmonization and Good Clinical Practice guidelines, applicable regulatory requirements, and was compliant with the protocol. Written informed consent was obtained from all patients before participation in the study.

See Online for appendix

Randomisation and masking

Eligible patients were enrolled by the investigators at each site, stratified by presence of measurable visceral disease (yes *vs* no) and ECOG performance status (0–1 *vs* 2), and randomly assigned (1:1) to receive ADT with abiraterone acetate plus prednisone or ADT with matching placebos, using a computer-generated randomisation schedule. A country-by-country scheme was done using permuted block randomisation. A unique identification number and treatment number for each patient were generated by a centralised interactive web response system. The randomisation codes were maintained within the interactive web response system and treatment allocations were masked to investigators, patients, and study personnel until study completion, except during medical emergencies wherein appropriate patient management would be required by knowing the treatment allocation status. Additionally, treatment allocations were unmasked if recommended by the Independent Data Monitoring Committee for the purpose of safety analysis at regular intervals.

Procedures

After a screening phase of up to 28 days, patients in the abiraterone acetate plus prednisone group were to receive abiraterone acetate 1000 mg (four 250 mg tablets orally)

once daily and prednisone 5 mg orally once daily and ADT (LHRH agonists, unless surgically castrated, per investigator decision), whereas patients in the placebo group were planned to receive placebos given as five matching tablets of abiraterone acetate and prednisone once daily plus the same ADT as in the experimental group (per investigator decision) during a double-blind treatment phase (28-day treatment cycles).[17,18] Patients received study medications at least 1 h before or 2 h after a meal. Up to two dose reductions were allowed in the study for the management of adverse events. At each dose reduction, one tablet of abiraterone acetate or matching placebo were reduced. Dose reductions for prednisone were permitted if clinically indicated for adverse events. Treatment continued until disease progression, withdrawal of consent, the occurrence of unacceptable toxicity, or death. Treatment was withheld and appropriate medical management was instituted in patients who developed drug-related grade 3 or worse toxicities, including hypertension, hypokalaemia, oedema, and other non-mineralocorticoid toxicities. Treatment with abiraterone acetate was not reinitiated until symptoms of the toxicity were resolved to grade 1 or baseline and treatment was stopped altogether if the symptoms did not resolve. Patients who discontinued from the double-blind treatment phase were monitored for survival status, subsequent prostate cancer therapies, and disease status on subsequent therapies during a follow-up phase (up to 60 months or until death, loss to follow-up, withdrawal of consent, or study termination, whichever occurred first). Patients were withdrawn from the study if they withdrew consent for subsequent data collection or were lost to follow-up. Adverse events, vital signs, serum haematological and biochemistry parameters, serum testosterone concentrations, and liver function were monitored up to 30 days after treatment discontinuation. Haematological parameters (haemoglobin, white blood cells, including neutrophil count, and platelet count), serum chemistry (potassium, creatinine, fasting glucose, and lactate dehydrogenase), liver function test (alanine aminotransferase, aspartate aminotransferase, and total bilirubin) were monitored at each clinic visit, which was monthly for the first year and every alternate month thereafter. Adverse events were graded using the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 4.0.

Patients in the placebo group were allowed to cross over to abiraterone acetate plus prednisone treatment as per a protocol amendment (on Feb 15, 2017) in an open-label extension phase of the study (up to 18 months since protocol amendment issued by the sponsor). Patients who crossed over to abiraterone acetate plus prednisone from placebo were patients from the control group who had not had cancer progression and who consented to receive active treatment after unmasking. Moreover, the crossover to abiraterone acetate plus prednisone from placebo was not considered as an event and therefore the radiographic progression-free survival was not re-analysed after crossover. Patients who were in the follow-up phase were not eligible to enrol in the open-label extension phase. The purpose of the open-label extension phase was to collect additional safety data for patients who crossed over to receive abiraterone acetate plus prednisone treatment for at least 6 months. Patients who elected to remain on active treatment entered the long-term extension phase to continue receiving the treatment for an additional period of up to 3 years. Regulation in some EU countries required the protocol to specify a definite time to when the study should end so that clinical trials are not used as a provision to allow access to the study drug.

Outcomes

The coprimary endpoints of the study were overall survival (time from randomisation to death from any cause) and radiographic progression-free survival (time from randomisation to occurrence of radiographic progression, based on the modified Prostate Cancer Working Group 2 criteria or RECIST, version 1.1) and were not centrally reviewed. In this Article, we report the long-term, updated overall survival from the final analysis. We also report the secondary endpoints, namely time to initiation of chemotherapy (time from randomisation to initiation of chemotherapy for prostate cancer), time to pain progression (time from randomisation to first increase of ≥30% from baseline in Brief Pain Inventory–Short Form [item 3]), time to next symptomatic skeletal event (time from randomisation to any one of the following skeletal-related events: clinical or pathological fracture, spinal cord compression, palliative radiotherapy to bone, or surgery to bone), time to subsequent prostate cancer therapy (time from randomisation to initiation of any subsequent therapy for prostate cancer, including hormonal therapy, chemotherapy, surgery, or radiotherapy), time to prostate-specific antigen progression (time to progression by Prostate Cancer Working Group 3 criteria), and safety results. Secondary progression-free survival (time from randomisation to progression on subsequent treatment or death) was assessed in an exploratory analysis. Radiographic progression-free survival was not re-analysed in this final analysis. Other prespecified exploratory endpoints were prostate-specific antigen response; time to symptomatic local progression, defined as occurrence of urethral obstruction or bladder outlet obstruction; prostate cancer-specific survival; and patient-reported outcome measures, such as EuroQol five-dimensions, five-levels questionnaire, Brief Pain Inventory—Short Form, Brief Fatigue Inventory, and Functional Assessment of Cancer Therapy Prostate scale, version 4, and were not analysed in this final analysis.

Statistical analysis

A sample size of 1200 patients was planned for this study. For the coprimary endpoint of overall survival,

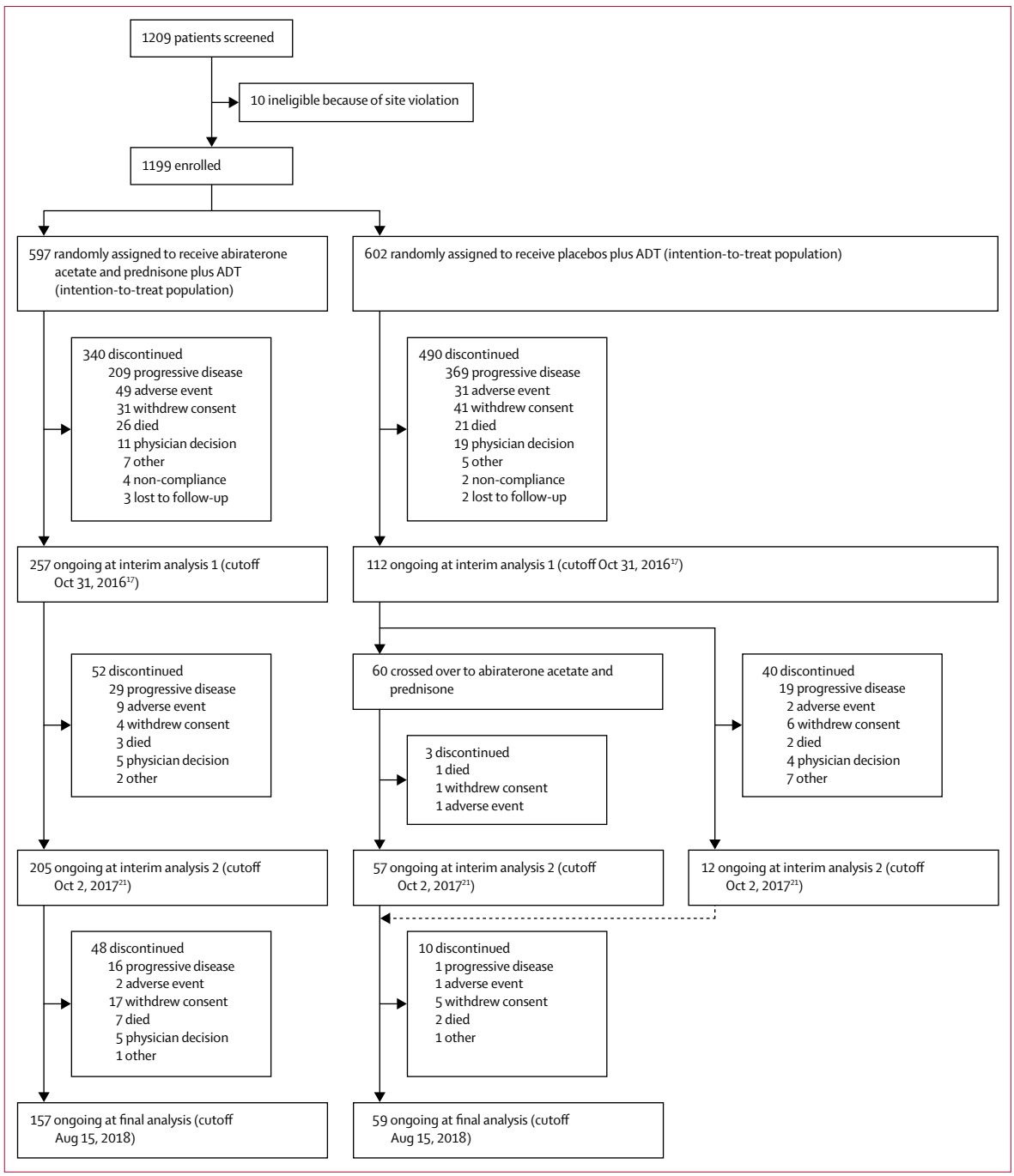


Figure 1: **Trial profile**
Dotted line shows 12 patients who crossed over to abiraterone acetate and prednisone after second interim analysis. ADT=androgen deprivation therapy.

852 deaths was calculated to provide 85% statistical power with a two-sided significance level of 0·049 to detect an HR of 0·81. The overall level of significance for the study was 0·05, with 0·049 allocated in the testing of overall survival, and 0·001 allocated in the testing of radiographic progression-free survival. Two interim analyses for overall survival were planned after 50% (about 426) of expected deaths (first interim analysis) and 65% (about 554) of the total 852 expected deaths (second interim analysis) and the final analysis was planned when about 852 death events had occurred. A single final analysis of radiographic progression-free survival was planned after observing 565 radiographic progression-free survival events (which was expected to

be at the first interim analysis for overall survival, when 426 deaths had occurred).

The overall survival endpoint incorporated the group sequential design with an α spending function calculated as Wang-Tsiatis power boundaries of shape parameter 0·2 (using East software). Secondary endpoints were assessed using the Hochberg test procedure at an overall two-sided 0·05 significance level to control the familywise type I error rate. Kaplan-Meier estimates were used to analyse the overall survival distribution and median overall survival. Estimations of HR and its associated 95% CI were done using the Cox proportional hazards model. The overall survival in prespecified subgroups based on age (<65 years *vs* ≥65 years *vs* ≥75 years), ECOG score at randomisation (0–1 *vs* 2), Gleason score (<8 *vs* ≥8), number of baseline bone lesions (≤10 *vs* >10), presence of visceral disease at randomisation (yes *vs* no), other potential baseline prognostic factors (baseline prostate-specific antigen and lactate dehydrogenase concentrations), and region (Asia *vs* eastern Europe *vs* western Europe *vs* the rest of the world) was analysed using a non-stratified univariate model to investigate the consistency of treatment effects. The primary and secondary efficacy endpoints were analysed in the intention-to-treat population of all randomly assigned patients. No formal imputation for missing data was done. A post-hoc analysis was done to analyse overall survival and radiographic progression-free survival on the basis of disease volume (high *vs* low). High-volume disease was defined as presence of visceral metastases or four or more bone metastases, with at least one outside the vertebral column or pelvis. Disease patterns not meeting that criteria were defined as low-volume disease. Safety parameters were analysed in all randomly assigned patients who received at least one dose of study medication. Patients were deemed assessable if results for a given study assessment were evaluable. The Independent Data Monitoring Committee also reviewed all efficacy and safety data at the planned interim analyses. Following the positive results of the first interim analysis (cutoff date Oct 31, 2016) and the Independent Data Monitoring Committee recommendation, the sponsor made a decision to unmask the treatment allocation to investigators and patients. After unmasking, scientific advice was sought regularly from members of the publication steering committee, which comprised of selected study investigators (appendix p 6). All key analyses were done with SAS software, version 9.4. This study is registered with ClinicalTrials.gov, number NCT01715285.

Role of the funding source

The employees of the funder had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all data in the study and final responsibility for the decision to submit for publication.

	Abiraterone acetate and prednisone plus ADT (n=597)	Placebos plus ADT (n=602)
Age, years	67·3 (8·5)	66·8 (8·7)
Gleason score at initial diagnosis		
<7	4 (1%)	1 (<1%)
7	9 (2%)	15 (2%)
≥8	584 (98%)	586 (97%)
Bone metastases at screening		
≥3	586 (98%)	585 (97%)
<3	11 (2%)	17 (3%)
Extent of disease*		
Bone	580 (97%)	585 (98%)
Liver	32 (5%)	30 (5%)
Lungs	73 (12%)	72 (12%)
Lymph nodes	283 (47%)	287 (48%)
Prostate mass	151 (25%)	154 (26%)
Viscera	18 (3%)	13 (2%)
Soft tissue	9 (2%)	15 (3%)
Other	2 (<1%)	0
Baseline pain score per Brief Pain Inventory—short form item 3†		
0–1	284 (50%)	288 (50%)
2–3	123 (22%)	137 (24%)
≥4	163 (29%)	154 (27%)
Previous prostate cancer therapy‡		
Radiotherapy	19 (3%)	26 (5%)
Hormonal	559 (>99%)	558 (>99%)
Gonadotropin-releasing hormone agonists or antagonists	449 (80%)	450 (80%)
Orchiectomy	73 (13%)	71 (13%)
First-generation androgen receptor agonists	373 (67%)	371 (66%)
Other	7 (1%)	10 (2%)

Data are mean (SD) or n (%). ADT=androgen deprivation therapy. *Denominators are 596 for abiraterone acetate and prednisone plus ADT and 600 for placebos plus ADT. †Denominators are 570 for abiraterone acetate and prednisone plus ADT and 579 for placebos plus ADT. ‡Denominators are 560 for abiraterone acetate and prednisone plus ADT and 560 for placebos plus ADT.

Table 1: **Baseline characteristics**

	Abiraterone acetate and prednisone plus ADT (n=597)	Placebos plus ADT (n=602)
Patients with life-extending subsequent therapy	176 (30%)	345 (57%)
Docetaxel	144 (24%)	212 (35%)
Enzalutamide	57 (10%)	99 (16%)
Radium 223 dichloride	27 (5%)	44 (7%)
Cabazitaxel	25 (4%)	50 (8%)
Abiraterone acetate plus prednisone	18 (3%)	84 (14%)
Placebo crossover to abiraterone acetate plus prednisone	..	72 (12%)

Data are n (%). A patient might have more than one life-extending subsequent therapy. ADT=androgen deprivation therapy.

Table 2: **Life-extending subsequent therapy for prostate cancer in the intention-to-treat population**

	Abiraterone acetate and prednisone plus ADT (n=597)		Placebos plus ADT (n=602)		Hazard ratio (95% CI)	p value
	Events	Median, months	Events	Median, months		
Primary endpoint						
Overall survival	275 (46%)	53·3 (48·2–NR)	343 (57%)	36·5 (33·5–40·0)	0·66 (0·56–0·78)	<0·0001
Secondary endpoints						
Pain progression	245 (41%)	47·4 (33·2–NR)	292 (49%)	16·6 (11·1–24·0)	0·72 (0·61–0·86)	0·00024
Skeletal-related event*	132 (22%)	NR (NR–NR)	150 (25%)	NR (NR–NR)	0·75 (0·60–0·95)	0·0181
Chemotherapy initiation†	150 (25%)	NR (62·6–NR)	218 (36%)	57·6 (38·2–NR)	0·51 (0·41–0·63)	<0·0001
Subsequent prostate cancer therapy	248 (42%)	54·9 (45·4–NR)	355 (59%)	21·2 (18·6–23·5)	0·45 (0·38–0·53)	<0·0001
Prostate-specific antigen progression	273 (46%)	33·3 (29·4–46·1)	448 (74%)	7·4 (7·2–9·2)	0·31 (0·27–0·36)	<0·0001
Exploratory endpoint						
Secondary progression-free survival‡	267 (45%)	53·3 (44·7–58·1)	336 (56%)	30·1 (26·2–33·4)	0·58 (0·49–0·68)	<0·0001

Data are n (%) or median (95% CI). ADT=androgen deprivation therapy. NR=not reached. *3-year event-free survival for skeletal-related events was 78% (95% CI 74–82) for abiraterone acetate plus prednisone plus ADT *vs* 73% (69–77) for placebos plus ADT. †3-year event-free survival for initiation of chemotherapy was 76% (95% CI 71–79) for abiraterone acetate and prednisone plus ADT *vs* 56% (51–61) for placebos plus ADT. ‡Randomisation to progression on subsequent therapy or death.

Table 3: **Efficacy endpoints in the intention-to-treat population**

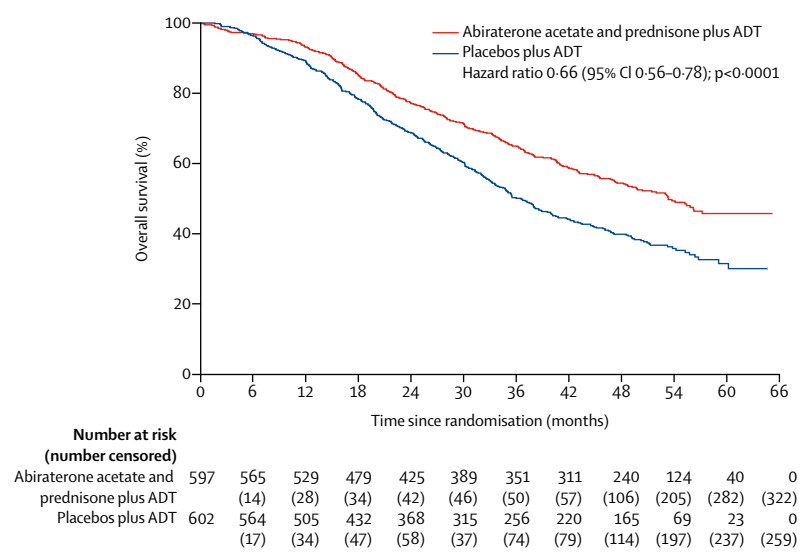


Figure 2: **Kaplan-Meier curve of overall survival in the intention-to-treat population**
ADT=androgen deprivation therapy.

Results

Between Feb 12, 2013, and Dec 11, 2014, 1209 patients were assessed for eligibility, of whom ten were ineligible because of study site violations. 1199 patients were randomly assigned to either the abiraterone acetate plus prednisone group (n=597) or placebo group (n=602) and were included in analyses (figure 1). The baseline demographic characteristics were well balanced between the two groups (table 1), as described previously.[17]

The first interim analysis of overall survival (clinical cutoff Oct 31, 2016) was done after 406 deaths had occurred (169 in the abiraterone acetate plus prednisone group and 237 in the placebo group) with a median follow-up of 30·4 months (IQR 18·4–32·2). The results of the first interim analysis of overall survival and the final analysis of radiographic progression-free survival have been reported previously.[17] The second interim analysis (clinical cutoff Oct 2, 2017) was done after 535 deaths (230 in the abiraterone acetate plus prednisone group and 305 in the placebo group) with a median follow-up of 41·4 months (IQR 18·4–41·7) and the results have also been reported previously.[21]

Notably, the preplanned number of death events at the final analysis were intended per the study protocol to achieve the desired statistical power. Because the criterion for superiority was met at the first interim analysis and the study was unmasked, the preplanned total event size (852 events) was no longer relevant, and the study sponsor, therefore, made the decision to analyse the data before the preplanned number of events at a cutoff date of Aug 15, 2018. The final analysis was done at the end of the open-label extension phase to obtain updated estimates of treatment effect after longer follow-up. The power of the study might be higher at this final analysis because of more events. However, the analysis was confounded by patients in the control group crossing over to receive the active treatment after unmasking and therefore the power could have been negatively affected.

When this final analysis was done at the cutoff date of Aug 15, 2018, 618 patients had died (275 [46%] of 597 in the abiraterone acetate plus prednisone group and 343 [57%] of 602 in the placebo group), with a median follow-up of 51·8 months (IQR 47·2–57·0), which is nearly 22 months of additional follow-up and 212 additional events since the first interim analysis.[17] At the time of final analysis, 72 patients had crossed over to abiraterone acetate plus prednisone treatment from the placebo group. Treatment was ongoing in 157 (26%) of 597 patients in the abiraterone acetate plus prednisone group, and in 59 (82%) of 72 patients who

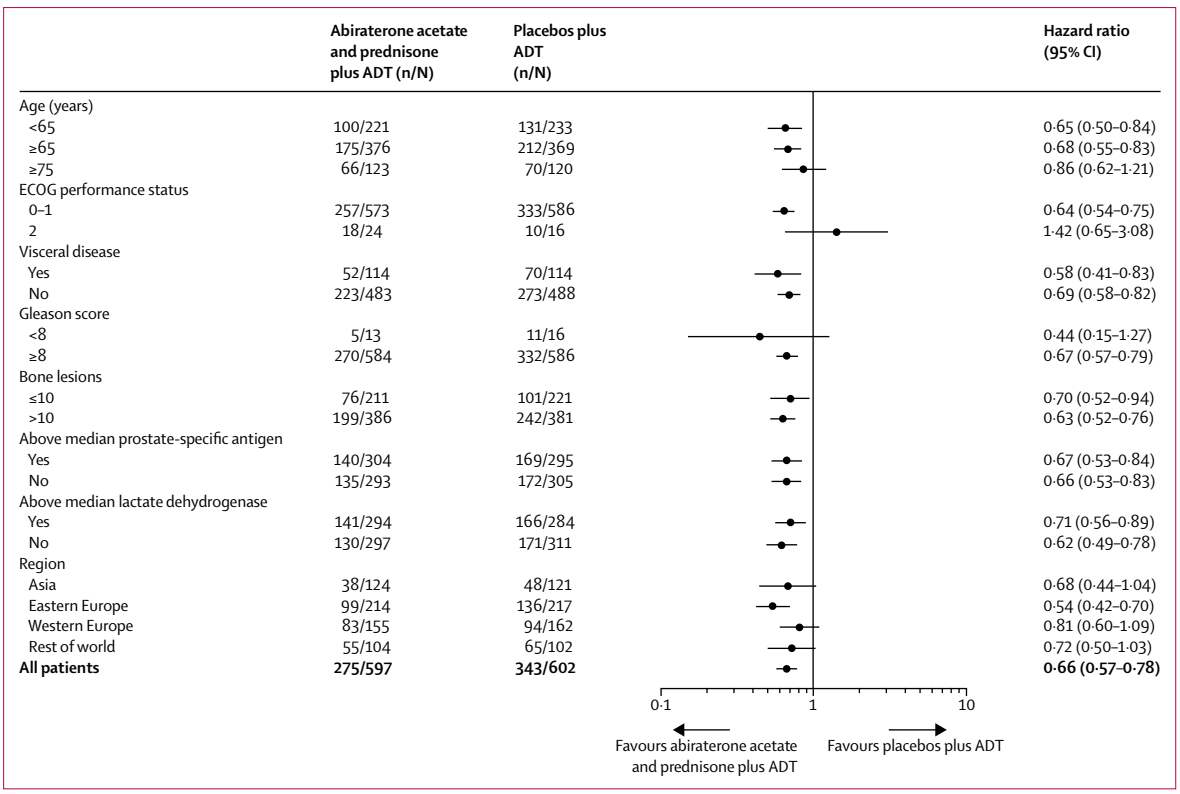


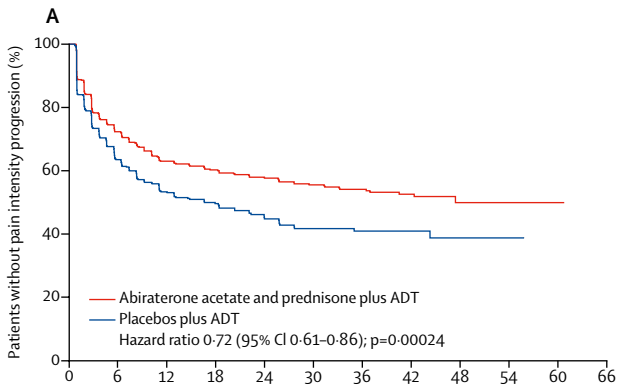
Figure 3: **Subgroup analysis of overall survival in the intention-to-treat population**
ADT=androgen deprivation therapy. ECOG=Eastern Cooperative Oncology Group.

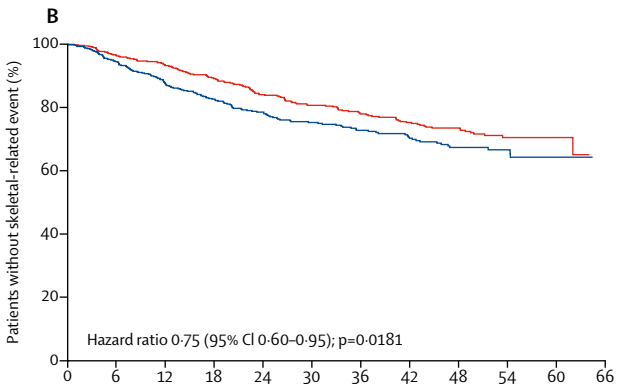
crossed over to abiraterone acetate plus prednisone from the placebo group (figure 1). Use of life-extending subsequent therapy was reported more frequently in the placebo group (345 [57%] of 602) than the abiraterone acetate plus prednisone group (176 [30%] of 597), with docetaxel being the most commonly used therapy in both groups (table 2). At the final analysis, 84 (14%) patients in the placebo group had received abiraterone acetate plus prednisone as life-extending subsequent therapy (table 2). The most common reason for treatment discontinuation across treatment groups was disease progression (254 [43%] of 597 patients in the abiraterone acetate plus prednisone group and 388 [64%] of 602 patients in the placebo group; figure 1). Median treatment duration was 25·8 months (IQR 12·3–49·0) with abiraterone acetate plus prednisone, 14·4 months (7·3–25·8) with placebo, and 11·9 months (9·2–12·9) with abiraterone acetate plus prednisone in the crossover group.

Median overall survival continued to be longer in the abiraterone acetate plus prednisone group (53·3 months [95% CI 48·2–not reached]) than the placebo group (36·5 months [33·5–40·0]), with an HR of 0·66 (95% CI 0·56–0·78; p<0·0001; table 3, figure 2). Analysis of overall survival by patient subgroups (figure 3) showed that improvement in overall survival was in favour of abiraterone acetate plus prednisone over placebos in most subgroups of patients, except for those with an ECOG performance status of 2 and those with a Gleason score less than 8.

Consistent with the findings of the interim analyses, abiraterone acetate plus prednisone treatment significantly improved the secondary endpoints of time to pain progression, symptomatic skeletal-related events, chemotherapy initiation, subsequent therapy for prostate cancer, and prostate-specific antigen progression and the exploratory endpoint of secondary progression-free survival (table 3, figure 4).

The overall incidence of adverse events was similar between the abiraterone acetate plus prednisone group (569 [95%] of 597) and the placebo group (561 [93%] of 602; table 4). Adverse events were reported in 44 (61%) of 72 patients in the placebo crossover group. Notably, the crossover group had a much shorter exposure period (median treatment duration 11·9 months [IQR 9·2–12·9]) than the abiraterone acetate plus prednisone group (25·8 months [12·3–49·0]). Grade 3–4 adverse events were reported in 403 (68%) patients in the abiraterone acetate plus prednisone group, 299 (50%) in the placebo group, and 14 (19%) in the placebo crossover group. The most common grade 3–4 adverse events were hypertension (125 [21%] in the abiraterone acetate plus prednisone group, 60 [10%] in the placebo group, and three [4%] in the placebo crossover group) and hypokalaemia (70 [12%] in the abiraterone acetate plus

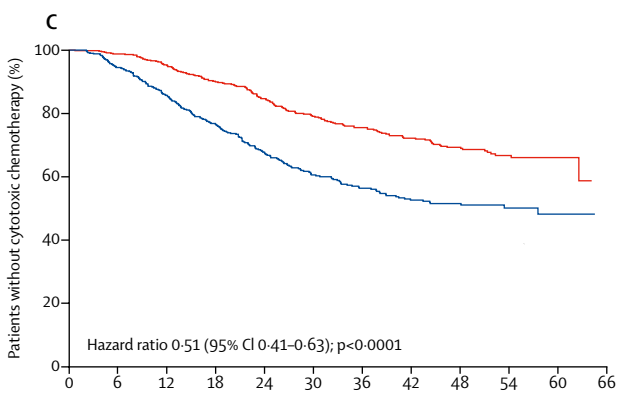


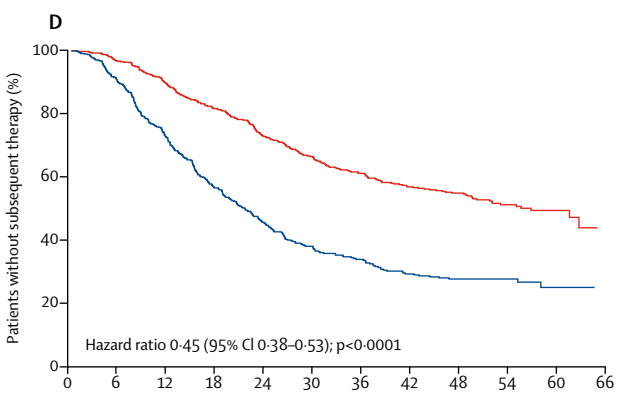


Number at risk (number censored)

Abiraterone acetate and prednisone plus ADT	597	394 (44)	297 (93)	248 (130)	200 (168)	167 (194)	121 (236)	74 (280)	19 (333)	5 (347)	1 (351)	0 (352)
Placebos plus ADT	602	332 (59)	215 (128)	141 (189)	95 (223)	70 (242)	46 (265)	27 (284)	7 (303)	1 (310)	0 (310)	0 (310)

Abiraterone acetate and prednisone plus ADT	597	547 (30)	501 (59)	443 (95)	386 (128)	346 (153)	303 (186)	268 (210)	208 (264)	103 (362)	32 (433)	0 (464)
Placebos plus ADT	602	538 (32)	459 (74)	382 (126)	323 (167)	272 (205)	219 (250)	192 (271)	138 (317)	62 (392)	19 (433)	0 (452)

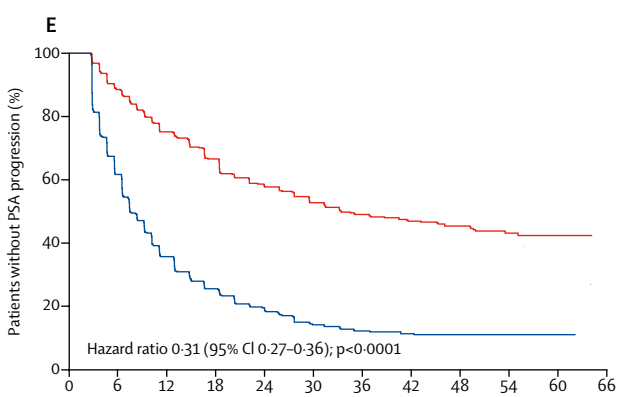


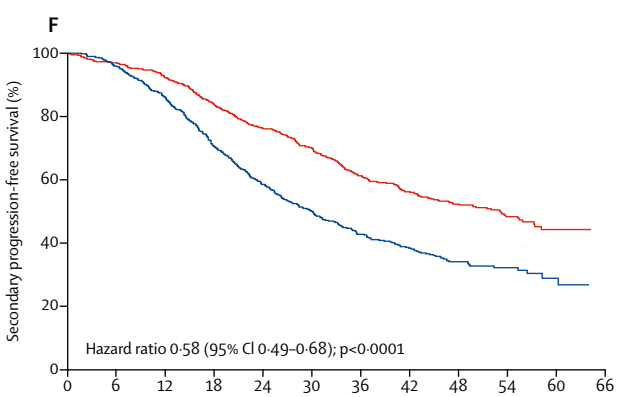


Number at risk (number censored)

Abiraterone acetate and prednisone plus ADT	597	561 (29)	508 (62)	448 (95)	388 (130)	340 (153)	305 (173)	267 (198)	203 (252)	105 (344)	33 (415)	0 (447)
Placebos plus ADT	602	534 (36)	438 (85)	343 (136)	266 (175)	213 (202)	175 (226)	148 (242)	114 (272)	47 (338)	16 (368)	0 (384)

Abiraterone acetate and prednisone plus ADT	597	551 (27)	483 (50)	422 (71)	355 (93)	306 (107)	268 (122)	235 (139)	182 (184)	96 (260)	28 (325)	0 (351)
Placebos plus ADT	602	510 (31)	378 (63)	267 (99)	192 (122)	146 (134)	117 (149)	95 (158)	71 (178)	31 (218)	8 (239)	0 (247)





Number at risk (number censored)

Abiraterone acetate and prednisone plus ADT	597	482 (51)	379 (83)	316 (104)	249 (130)	215 (143)	191 (152)	171 (164)	128 (202)	62 (263)	20 (304)	0 (324)
Placebos plus ADT	602	320 (72)	172 (88)	116 (96)	74 (108)	51 (114)	41 (117)	38 (117)	20 (134)	7 (147)	1 (153)	0 (154)

Abiraterone acetate and prednisone plus ADT	597	565 (14)	516 (36)	459 (47)	406 (58)	365 (66)	310 (77)	271 (91)	207 (137)	109 (224)	32 (295)	0 (327)
Placebos plus ADT	602	558 (20)	473 (49)	366 (74)	287 (92)	227 (112)	180 (127)	155 (134)	110 (163)	45 (223)	14 (251)	0 (264)

prednisone group, ten [2%] in the placebo group, and two [3%] in the placebo crossover group; table 4). Serious adverse events occurred in 192 (32%) patients in the abiraterone acetate plus prednisone group, 151 (25%) in the placebo group, and four (6%) in the placebo crossover group (appendix pp 17–23). Grade 3–4 serious adverse events occurred in 160 (27%) patients in the abiraterone acetate plus prednisone group, 120 (20%) in the placebo group and three (4%) in the placebo crossover group. The most common grade 3–4 serious adverse event was spinal cord compression (11 [2%] patients in the abiraterone acetate plus prednisone group, ten [2%] in the placebo group, and none in the placebo crossover group). Treatment-related serious adverse events were reported in 30 (5%) patients in the abiraterone acetate plus prednisone group, 13 (2%) in the placebo group, and one (1%) in the placebo crossover group (appendix pp 24–25). The most common treatment-related serious adverse event was hypokalaemia (four [1%] patients in the abiraterone acetate plus prednisone group and none in the other groups). Adverse events leading to treatment discontinuation were reported in 93 (16%) of 597 patients in the abiraterone acetate plus prednisone group, 63 (10%) of 602 in the placebo group and three (4%) of 72 in the placebo crossover group. Treatment-related adverse events leading to treatment discontinuation were reported in 24 (4%) patients in the abiraterone acetate plus prednisone group, 11 (2%) in the placebo group and one (1%) in the placebo crossover group (appendix p 26). Adverse events leading to dose reduction or interruption were reported in 209 (35%) patients in the abiraterone acetate plus prednisone group, 108 (18%) in the placebo group and seven (10%) in the placebo crossover group (appendix p 27–31). Grade 3–4 mineralocorticoid adverse events such as hypertension, hypokalaemia, fluid retention or oedema, and other adverse events of special interest were more frequently reported in the abiraterone acetate plus prednisone group than the placebo group and the incidence was consistent with that reported in the interim analyses (table 5). One patient in the placebo crossover group died from acute cardiac failure. Overall, adverse events led to 38 (6%) deaths in the abiraterone acetate plus prednisone group, 25 (4%) deaths in the placebo group, and two (3%) deaths in the placebo crossover group (table 4). Treatment-related deaths were reported in three (<1%) patients each in the abiraterone acetate plus prednisone group (gastric ulcer perforation, sudden death, and cerebrovascular accident) and the placebo group (sudden death, cerebrovascular accident, and pneumonia) and none in the crossover group.

In our post-hoc exploratory analysis of the high-volume disease subgroup (n=487 in the abiraterone acetate plus prednisone and 468 in the placebo group), median overall survival was 49·7 months (95% CI 43·2–55·4) with abiraterone acetate plus prednisone compared with 33·3 months (30·2–36·7) with placebos, with an HR for death of 0·62 (95% CI 0·52–0·74; p<0·0001). Few patients had low-volume disease in this study (n=110 in the abiraterone acetate and prednisone group and n=133 in the placebo group) and the median overall survival in this subgroup was not reached in either study group, nor was the HR for death significant (HR 0·72 [95% CI 0·47–1·10]; p=0·1242; appendix p 32). In the high-volume disease subgroup, the abiraterone acetate plus prednisone group had a significantly longer median radiographic progression-free survival (33·1 months [95% CI 29·0–36·8]) than the placebo group (14·7 months [14·5–16·1]), with an HR for radiographic progression or death of 0·46 (95% CI 0·39–0·54; p<0·0001). Similarly, in the low-volume disease subgroup, patients in the abiraterone acetate plus prednisone group had significantly longer median radiographic progression-free survival (49·8 months [IQR 29·6–55·2]) than those in the placebo group (22·4 months [18·2–29·8]) with an HR of 0·59 (95% CI 0·40–0·85; p=0·0048; appendix p 33).

Discussion

In this final analysis of the LATITUDE study, treatment with abiraterone acetate plus prednisone and ADT in men with newly diagnosed mCSPC with high-risk prognostic factors continued to show significant improvement in overall survival versus matching placebos and ADT. These findings further substantiate the significant treatment benefits with abiraterone acetate plus prednisone over placebos plus ADT shown previously in our interim analysis of coprimary endpoints of overall survival and radiographic progression-free survival.[17] Furthermore, significant improvements in all secondary endpoints were observed with abiraterone acetate plus prednisone and ADT compared with placebos plus ADT, delaying the time to initiation of chemotherapy, subsequent prostate cancer therapy, pain progression, and symptomatic skeletal events. Moreover, the significantly improved secondary progression-free survival seen in the final analysis might indicate that early treatment with abiraterone acetate plus prednisone might retain a therapeutic advantage even after study treatment has ended. No new safety events or apparent changes in the safety profile of abiraterone acetate plus prednisone occurred during this follow-up period.

Notably, treatment with abiraterone acetate plus prednisone and ADT showed a survival advantage over placebo and ADT, despite a higher proportion of patients in the placebo group receiving life-extending subsequent

Figure 4: **Kaplan–Meier curves of secondary and exploratory endpoints in the intention-to-treat population**

Time to pain progression (A), time to symptomatic skeletal event (B), time to initiation of chemotherapy (C), time to subsequent prostate cancer therapy (D), time to PSA progression (E), and time to secondary progression-free survival (F). Secondary disease progression is defined as time from randomisation to progression on subsequent treatment or to death. ADT=androgen deprivation therapy. PSA=prostate-specific antigen.

	Abiraterone acetate and prednisone plus ADT (n= 597)			Placebos plus ADT (n=602)			Placebo crossover to abiraterone acetate and prednisone (n=72)		
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4
Any	161 (27%)	344 (58%)	29 (5%)	257 (43%)	267 (44%)	17 (3%)	30 (42%)	13 (18%)	0
Back pain	108 (18%)	15 (3%)	0	107 (18%)	21 (3%)	0	5 (7%)	0	0
Hypertension	104 (17%)	125 (21%)	0	73 (12%)	59 (10%)	1 (<1%)	1 (1%)	3 (4%)	0
Hot flush	92 (15%)	0	0	75 (12%)	1 (<1%)	0	1 (1%)	0	0
Arthralgia	87 (15%)	9 (2%)	0	71 (12%)	15 (2%)	0	4 (6%)	0	0
Hypokalaemia	73 (12%)	65 (11%)	5 (1%)	13 (2%)	9 (1%)	1 (<1%)	7 (10%)	2 (3%)	0
Fatigue	73 (12%)	11 (2%)	0	76 (13%)	14 (2%)	0	1 (1%)	0	0
Alanine aminotransferase increased	67 (11%)	32 (5%)	2 (<1%)	69 (11%)	8 (1%)	0	3 (4%)	2 (3%)	0
Constipation	66 (11%)	2 (<1%)	0	65 (11%)	3 (<1%)	0	2 (3%)	0	0
Pain in extremity	65 (11%)	8 (1%)	0	57 (9%)	13 (2%)	0	2 (3%)	0	0
Aspartate aminotransferase increased	65 (11%)	26 (4%)	1 (<1%)	59 (10%)	9 (1%)	0	4 (6%)	1 (1%)	0
Peripheral oedema	59 (10%)	2 (<1%)	0	53 (9%)	3 (<1%)	0	2 (3%)	0	0
Bone pain	58 (10%)	24 (4%)	1 (<1%)	76 (13%)	17 (3%)	0	0	0	0
Hyperglycaemia	52 (9%)	30 (5%)	1 (<1%)	51 (8%)	22 (4%)	0	3 (4%)	2 (3%)	0
Anaemia	45 (8%)	14 (2%)	3 (1%)	63 (10%)	26 (4%)	1 (<1%)	2 (3%)	1 (1%)	0
Blood lactate dehydrogenase increased	27 (5%)	12 (2%)	1 (<1%)	21 (3%)	9 (1%)	0	1 (1%)	0	0
Spinal cord compression	2 (<1%)	12 (2%)	0	2 (<1%)	7 (1%)	3 (<1%)	0	0	0
Urinary retention	10 (2%)	11 (2%)	0	21 (3%)	7 (1%)	0	0	0	0
Pneumonia	5 (1%)	8 (1%)	1 (<1%)	7 (1%)	2 (<1%)	0	0	0	0
Haematuria	21 (4%)	9 (2%)	0	17 (3%)	3 (<1%)	0	0	0	0
Cataract	7 (1%)	8 (1%)	0	3 (<1%)	1 (<1%)	0	0	0	0
Urinary tract infection	38 (6%)	6 (1%)	0	18 (3%)	5 (1%)	0	3 (4%)	0	0
Weight increased	48 (8%)	6 (1%)	0	44 (7%)	7 (1%)	0	0	0	0
Hyperkalaemia	10 (2%)	5 (1%)	2 (<1%)	15 (2%)	10 (2%)	0	1 (1%)	0	0
Dyspnoea	24 (4%)	5 (1%)	0	15 (2%)	2 (<1%)	1 (<1%)	1 (1%)	0	0
Syncope	2 (<1%)	5 (1%)	0	3 (<1%)	1 (<1%)	0	0	0	0
General physical health deterioration	4 (1%)	5 (1%)	0	1 (<1%)	6 (1%)	0	0	0	0
Blood pressure increased	12 (2%)	4 (1%)	0	6 (1%)	3 (<1%)	0	0	0	0
Muscular weakness	10 (2%)	4 (1%)	0	15 (2%)	7 (1%)	0	1 (1%)	0	0
Musculoskeletal pain	28 (5%)	4 (1%)	0	36 (6%)	6 (1%)	0	2 (3%)	0	0
Osteonecrosis of jaw	4 (1%)	4 (1%)	0	0	1 (<1%)	0	0	0	0
Asthenia	27 (5%)	4 (1%)	0	21 (3%)	7 (1%)	0	0	0	0
Dysuria	22 (4%)	4 (1%)	0	27 (4%)	3 (<1%)	0	1 (1%)	0	0
Pathological fracture	3 (1%)	4 (1%)	0	5 (1%)	0	0	0	0	0
Nausea	40 (7%)	3 (1%)	0	38 (6%)	2 (<1%)	0	1 (1%)	0	0
Vomiting	37 (6%)	3 (1%)	0	34 (6%)	2 (<1%)	0	0	0	0
Spinal pain	9 (2%)	3 (1%)	0	14 (2%)	1 (<1%)	0	0	0	0
Diabetes	7 (1%)	3 (1%)	1 (<1%)	8 (1%)	2 (<1%)	1 (<1%)	2 (3%)	1 (1%)	0
Angina pectoris	6 (1%)	3 (1%)	1 (<1%)	5 (1%)	0	0	0	0	0
Neutropenia	5 (1%)	3 (1%)	1 (<1%)	5 (1%)	4 (1%)	1 (<1%)	0	0	0
Neutrophil count decreased	3 (1%)	3 (1%)	0	2 (<1%)	1 (<1%)	1 (<1%)	0	0	0
Leukocytosis	2 (<1%)	3 (1%)	0	0	0	0	0	0	0

(Table 4 continues on next page)

	Abiraterone acetate and prednisone plus ADT (n= 597)			Placebos plus ADT (n=602)			Placebo crossover to abiraterone acetate and prednisone (n=72)		
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4
(Continued from previous page)									
Deep vein thrombosis	1 (<1%)	3 (1%)	0	2 (<1%)	3 (<1%)	0	0	0	0
Pyrexia	29 (5%)	2 (<1%)	0	19 (3%)	3 (<1%)	0	0	0	0
Decreased appetite	21 (4%)	2 (<1%)	0	29 (5%)	4 (1%)	0	0	0	0
Urinary tract obstruction	4 (1%)	2 (<1%)	0	1 (<1%)	4 (1%)	0	0	0	0
Acute kidney injury	2 (<1%)	2 (<1%)	0	2 (<1%)	3 (<1%)	0	0	0	0
Pulmonary embolism	2 (<1%)	2 (<1%)	0	0	5 (1%)	0	0	0	0
Platelet count decreased	15 (3%)	1 (<1%)	1 (<1%)	7 (1%)	4 (1%)	0	0	1 (1%)	0
Neck pain	16 (3%)	1 (<1%)	0	14 (2%)	4 (1%)	0	2 (3%)	0	0
Blood alkaline phosphatase increased	1 (<1%)	1 (<1%)	0	3 (<1%)	4 (1%)	0	0	0	0
Blood creatinine increased	14 (2%)	1 (<1%)	2 (<1%)	12 (2%)	3 (<1%)	1 (<1%)	0	0	0
Abdominal pain	25 (4%)	1 (<1%)	0	30 (5%)	3 (<1%)	0	0	0	0
Paraparesis	0	1 (<1%)	0	0	3 (<1%)	0	0	0	0
Hepatic function abnormal	1 (<1%)	1 (<1%)	0	2 (<1%)	1 (<1%)	0	0	1 (1%)	0
Dental caries	6 (1%)	1 (<1%)	0	3 (<1%)	0	0	0	1 (1%)	0
Spinal compression fracture	6 (1%)	0	0	0	3 (<1%)	0	0	0	0
Thrombocytopenia	8 (1%)	0	1 (<1%)	8 (1%)	3 (<1%)	0	0	0	0
Pain	4 (1%)	0	0	10 (2%)	3 (<1%)	0	0	0	0
Tumour pain	1 (<1%)	0	0	0	1 (<1%)	0	1 (1%)	1 (1%)	0
Gastritis	9 (2%)	0	0	3 (<1%)	0	0	0	1 (1%)	0
Osteomyelitis acute	0	0	0	0	0	0	0	1 (1%)	0

Data are n (%). The table lists any grade 1–2 adverse events occurring in at least 10% of patients in any treatment group and all grade 3–4 adverse events occurring in at least 1% of patients in any treatment group. 38 (6%) deaths occurred in the abiraterone acetate plus prednisone group, 25 (4%) in the placebo group, and two (3%) in the placebo crossover group (appendix pp 7–16). ADT=androgen deprivation therapy.

Table 4: **Summary of all-cause adverse events in the safety population**

therapy, including docetaxel and next-generation androgen receptor axis-targeted drugs such as enzalutamide or abiraterone acetate plus prednisone. The proportion of patients receiving subsequent therapy in the control group of this study (345 [57%] of 602, including crossover to abiraterone acetate plus prednisone) was numerically higher than that of the STAMPEDE study (383 [32%] of 1184) and CHAARTED study (187 [48%] of 393).[7,8,22] The proportion of patients in the control groups of these studies receiving subsequent treatment for mCRPC probably reflects the real-world situation. A substantial delay in the initiation of chemotherapy and need for subsequent therapy, and longer secondary progression-free survival support the early use of abiraterone acetate plus prednisone in these patients.

Overall survival remained consistently in favour of the abiraterone acetate plus prednisone group despite the fact that the placebo group included patients who had not progressed but elected to cross over to receive open-label abiraterone acetate plus prednisone. Thus, early treatment with abiraterone acetate and prednisone might be beneficial in patients with high-risk mCSPC. The subsequent therapy in this study was allowed after radiographic progression assessed by the investigators. Similar to the real-world setting, treatment was initiated only after multiparametric verification of castration-resistant prostate cancer progression, especially when disease progressed from a castration-sensitive to castration-resistant state. Moreover, the overall survival benefit was observed across most subgroups of patients, including patients in most age categories, those with presence or absence of visceral disease, and those with ten or fewer or more than ten bone lesions at study entry. The subgroup of patients with an ECOG score of at least 2 did not have a significant survival benefit; however, these patients accounted for less than 3% of all enrolled patients (28 of 1199 patients). Therefore, the findings of this study reflect and confirm the effective blockade of

	Abiraterone acetate and prednisone plus ADT (n=597)			Placebos plus ADT (n=602)			Placebo crossover to abiraterone acetate plus prednisone (n=72)		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Hypertension	243 (41%)	130 (22%)	1 (<1%)	144 (24%)	62 (10%)	1 (<1%)	4 (6%)	3 (4%)	0
Hepatotoxicity	146 (24%)	49 (8%)	4 (1%)	109 (18%)	21 (3%)	0	7 (10%)	3 (4%)	0
Alanine aminotransferase increased	101 (17%)	32 (5%)	2 (<1%)	77 (13%)	8 (1%)	0	5 (7%)	2 (3%)	0
Aspartate aminotransferase increased	92 (15%)	26 (4%)	1 (<1%)	68 (11%)	9 (1%)	0	5 (7%)	1 (1%)	0
Hypokalaemia	143 (24%)	65 (11%)	5 (1%)	23 (4%)	9 (1%)	1 (<1%)	9 (13%)	2 (3%)	0
Cardiac disorders	95 (16%)	18 (3%)	5 (1%)	52 (9%)	6 (1%)	0	1 (1%)	0	0
Atrial fibrillation	10 (2%)	2 (<1%)	0	2 (<1%)	1 (<1%)	0	0	0	0
Fluid retention or oedema	81 (14%)	5 (1%)	0	71 (12%)	6 (1%)	0	3 (4%)	0	0
Osteoporosis, including osteoporosis-related fractures	43 (7%)	9 (2%)	0	27 (4%)	13 (2%)	1 (<1%)	1 (1%)	0	0
Cataract	22 (4%)	8 (1%)	0	8 (1%)	1 (<1%)	0	0	0	0

Data are n (%). The table lists all events that occurred in at least 2% of patients in any treatment group. ADT=androgen deprivation therapy.

Table 5: **All-cause adverse events of special interest in the safety population**

androgen receptor signalling by abiraterone acetate plus prednisone and ADT in patients with mCSPC with high-risk features and the major benefits of delaying the disease progression. A post-hoc analysis of the STAMPEDE study not only confirmed that overall survival is improved with abiraterone acetate plus prednisone and ADT over ADT alone in men with high-risk de-novo distant metastasis (HR for overall survival 0·54 [95% CI 0·41–0·70]; p<0·001), but also that this overall survival benefit applies to men with low-risk disease (HR for overall survival 0·66 [0·44–0·98]; p=0·041).[23] Notably, 48% of patients with mCSPC from the STAMPEDE abiraterone acetate plus prednisone comparison study had low-risk and low-volume disease. The post-hoc analysis of the present study did not show a significant survival advantage for abiraterone acetate plus prednisone in the subgroup of patients with low-volume disease, as defined by the CHAARTED definition.[7] However, only 20% of the patients in this study had low-volume disease and this study was not powered to investigate these associations in the low-volume disease subgroup. Treatment with abiraterone acetate plus prednisone and ADT significantly improved radiographic progression-free survival in patients with low-volume disease in both the LATITUDE and the STAMPEDE studies.[8,17]

A post-hoc analysis from STAMPEDE suggests that progression-free survival, but not overall survival, might be longer with abiraterone acetate plus prednisone than with docetaxel.[24] Indirect comparisons of randomised trials using the Bayesian method favour abiraterone acetate plus prednisone for progression-free survival and other secondary outcomes.[24–27] In view of the survival benefits with both abiraterone acetate plus prednisone and docetaxel, the addition of abiraterone acetate plus prednisone and docetaxel is being assessed to establish whether or not this combination can offer an additive benefit by prolonging survival in patients with mCSPC (PEACE-1; NCT01957436).

The overall safety findings of abiraterone acetate plus prednisone noted in this final analysis were consistent with those of the interim report as well as the previous studies done in patients with mCRPC, thus confirming the long-term benefits of abiraterone acetate plus prednisone in mCSPC.[14,15,17] Expected mineralocorticoid-related adverse events such as hypertension, hypokalaemia, and fluid retention were common with abiraterone acetate plus prednisone. Close monitoring for hypokalaemia and timely correction is necessary during the treatment to avoid undesirable sequelae, especially cardiovascular effects. Similarly, hypertension needs regular monitoring and treatment. In the final analysis with a longer follow-up, no further increase in the incidence of grade 3–4 mineralocorticoid-related adverse events and other adverse events of special interest such as hepatotoxicity and cardiac disorders was observed, consistent with data reported in men with mCRPC.[28] Most adverse events were medically manageable and rarely led to treatment discontinuation. No unexpected safety signals were identified with abiraterone acetate plus prednisone, including in patients who crossed over from placebo to abiraterone acetate plus prednisone.

The study had some limitations. Based on the inclusion criteria, the study population was restricted to men with high-risk distant metastatic disease and although STAMPEDE provides some evidence, additional prospective evidence will underscore the clinical benefit of early androgen signalling axis inhibition in broader categories of patients with mCSPC. Moreover, all patients had de novo metastatic disease, and whether or not men who developed a high-risk metastatic relapse after local

treatment of their primary prostate cancer also derive similar benefits from abiraterone acetate plus prednisone and ADT remains unknown. Next-generation imaging was not routinely used in LATITUDE and whether men with metastatic disease detected only by one of these techniques (PET scans or whole-body MRI) would benefit is unknown. It is also unclear whether a subgroup of patients with better prognoses would benefit from crossover to active treatment. Finally, not much is known about how best to treat men developing mCRPC who had received upfront intensified systemic treatment (abiraterone acetate plus prednisone and ADT or docetaxel plus ADT),[29] and these data are not available in the LATITUDE study. Available evidence supports the maintained activity of taxanes in most men with mCRPC who have progressed on abiraterone acetate plus prednisone.[30,31]

In summary, the final updated data underscore significant survival benefits of adding abiraterone acetate plus prednisone to ADT in newly diagnosed patients with high-risk mCSPC, by further prolonging the overall survival, along with a delay in initiation of chemotherapy and need for subsequent therapy. No new safety concerns were identified during this long-term period. These findings thus reinforce the use of abiraterone acetate plus prednisone as a standard of care for patients with high-risk mCSPC.

Contributors

KF, NT, SL, YL, and KNC conceived and designed the study. KF, LF, NM, AR-A, BYA, MÖ, DY, SF, AP, and KNC were investigators who conducted the study and collected data. KF, NT, GS, SL, KNC, SM, and YL analysed the data. All authors participated in data interpretation, manuscript writing, review, and approval of the final version of the manuscript for submission.

Declaration of interests

GS, SL, YL, SM and NT are employees of Janssen Research & Development and hold company stock. KF has received personal fees from Amgen, Astellas, AstraZeneca, Bayer, Clovis, Curevac, Essa, Genentech, Janssen, Merck Sharp and Dohme (MSD), Orion, and Sanofi. KNC's institution has received funding from Janssen for this study. AP has received personal fees for consulting or advisory roles, travel, accommodation, and expenses from Ipsen, Bayer, Roche, Bristol-Myers Squibb, and Merck; and has received research funding from Merck. AR-A has received funds for consulting services and expert testimony from Astellas, Bayer, and Janssen. LF has received grant support and personal fees from Novartis, Pfizer, Roche, Merck, and MSD, and grant support from Janssen and AbbVie. MÖ received personal fees from Janssen and Sanofi. BYA reports personal fees from Janssen, Pfizer, Merck, Roche, and Sanofi. SF has served on advisory boards for Janssen, Boehringer Ingelheim Pharma, and Aventis, and has received honorarium from Janssen, and travel and accommodation expenses from Aventis. All other authors declared no competing interests.

Data sharing

The data sharing policy of the study sponsor, Janssen Pharmaceutical Companies of Johnson & Johnson, is available online. Requests for access to the study data can be submitted through the Yale Open Data Access Project site.

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