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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Final overall survival analysis of LATITUDE, a phase 3 study of abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer

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Summary

Background: In the interim analyses of LATITUDE study, abiraterone acetate plus prednisone added to androgen deprivation therapy (ADT) demonstrated significant improvement in overall survival (OS) and radiographic progression-free survival in men with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (mCSPC). The long-term survival benefits and safety of abiraterone acetate plus prednisone and ADT from the final analysis of the LATITUDE study are presented.

Methods: LATITUDE was a multicenter, phase 3, randomized study conducted at 235 sites in 34 countries. Eligible patients (men aged 18 years or older) had newly diagnosed, histologically or cytologically confirmed prostate cancer with metastases (as documented by a positive bone scan or metastatic lesions on CT or MRI), Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, and at least two of the three high-risk prognostic factors (Gleason score of ≥8, presence of ≥3 lesions on bone scan, or presence of measurable visceral metastasis, excluding lymph node disease). 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. Randomization was by a country-by-country scheme using permuted block randomization, stratified by presence of visceral disease and ECOG performance status. Following the results of first interim analysis (cutoff date, Oct 31, 2016), the study was unblinded 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 protocol amendment (issued on Feb 15, 2017) in an open-label extension phase of the study (lasted up to 18 months from the protocol amendment issued by the sponsor). One of the coprimary endpoints

was OS and was assessed in the intent-to-treat population in this final analysis. This study is registered at ClinicalTrials.gov, NCT01715285 and is closed to follow-up. This report presents the final analysis performed at the end of the open-label extension phase and at the clinical cutoff date August 15, 2018.

Findings: Between February 12, 2013, and December 11, 2014, 1199 patients were randomized to abiraterone acetate plus prednisone group (n=597) or placebo group (n=602). The final analysis was conducted after a median follow-up of 51·8 (IQR: 47·15–57·03) months and 618 deaths were observed (275 [46%] of 597 in the abiraterone acetate plus prednisone group and 343 [57%] of 602 in the placebo group). Treatment was ongoing for 157 (26%) of 597 patients in the abiraterone acetate plus prednisone group; 72 (12%) of 602 patients crossed-over from placebo to abiraterone acetate plus prednisone, of which 59 (82%) of 72 remained on treatment. OS was significantly longer in the abiraterone acetate plus prednisone group vs the placebo group (median [95% CI]: 53·3 [48·2 – not reached] months vs 36·5 [33·5-40.0] months, respectively; HR: 0·66; 95% CI: 0·56–0·78; p<0·0001). Median (IQR) treatment duration in the abiraterone acetate plus prednisone group vs placebo group was 25·8 (12·25–49·0) months vs 14·4 (7·33–25·79), respectively. The most common Grade 3-4 adverse events (AEs) were hypertension (125 [21%] in the abiraterone acetate plus prednisone group vs 60 [10%] in the placebo group) and hypokalemia (70 [12%] in the abiraterone acetate plus prednisone group vs 10 [2%] in the placebo group). Serious AEs of any grade occurred in 192 (32%) of 597 patients in the abiraterone acetate plus prednisone group, 151 (25%) of 602 patients in the placebo group and 4 (6%) of 72 in the crossover group. Treatment-related deaths occurred in three patients each in the abiraterone acetate plus prednisone group (one case each of gastric ulcer perforation,

sudden death, and cerebrovascular accident) and the placebo group (one case each of sudden death, cerebrovascular accident, and pneumonia).

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

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Introduction

Newly-diagnosed metastatic castration-sensitive prostate cancer (mCSPC) is recognized 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 is able to achieve long-term disease control in some mCSPC patients with low-risk features and fewer metastases. However, treatment with ADT alone in de novo mCSPC with high-risk features has been associated with poor survival outcomes due to 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 therapies to ADT has emerged as a desirable approach to delay disease progression and improve overall survival (OS). Combination of docetaxel with ADT in men with mCSPC has shown statistically significantly improved survival outcomes compared with ADT alone in two randomized controlled phase 3 studies, CHAARTED and STAMPEDE.[7,8] However, the combination did not show statistically significant OS improvement in GETUG-AFU 15 study where docetaxel was tested alone and the magnitude of benefit was also less convincing in one of the STAMPEDE arms where docetaxel was combined with zoledronic acid, although progression-free survival was significantly improved in these studies.[6,8] Whether the benefit of docetaxel in men with mCSPC is restricted to men with a high burden of metastases is currently debated.[9-11] However, patient-specific comorbidities, including patients at high-risk of myelosuppression, patient preferences, patient age, and toxicity profile may limit the use of docetaxel in mCSPC.[12,13]

Abiraterone acetate (AA), a prodrug of abiraterone, which is a selective irreversible inhibitor of the key enzyme cytochrome P17A1 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 OS in patients in both chemotherapy-naive and chemotherapy-treated patients with mCRPC.[14,15] Further, the addition of abiraterone acetate plus prednisone to neoadjuvant luteinizing hormone-releasing hormone (LHRH) agonists was associated with marked lowering of prostate tissue androgens compared with LHRH agonists alone in hormone-sensitive patients.[16] This finding suggests that abiraterone acetate plus prednisone may also inhibit extragonadal androgen biosynthesis and thereby help delay the emergence of resistance in mCSPC patients.

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 OS compared with the placebo group (median not reached vs. 34·7 months; 3-year event-free rate: 66% [95% CI: 61% to 70%] vs 49% [95% CI: 44% to 55%).[17] Treatment with abiraterone acetate plus prednisone versus placebos was associated with a hazard ratio (HR) of 0·62 (95% confidence interval [CI], 0·51 to 0·76; p<0·001) for OS and median radiographic progression-free survival (rPFS) was 33 months (abiraterone acetate plus prednisone group) versus 14·8 months (placebo group), with a HR of 0·47 (95% CI, 0.39 to 0.55; P<0·001) for radiographic progression or death.[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, OS improvement was also seen with abiraterone acetate plus prednisone and

ADT in the STAMPEDE phase 3 study in a subgroup of patients with metastases (HR: 0·61; 95% CI: 0·49 to 0·75) and was confirmed in a meta-analysis of the two studies.[19,20] Based on 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 LATITUDE study, the secondary endpoints, including time to initiation of chemotherapy, pain progression, symptomatic skeletal event, and subsequent prostate cancer therapy are mature, and the median OS has now been reached for the abiraterone acetate and prednisone plus ADT arm. Here, the long-term results from the final analysis of the LATITUDE study of abiraterone acetate and prednisone plus ADT versus placebos plus ADT in patients with newly diagnosed high-risk mCSPC are presented.

Methods

Study design and participants

LATITUDE was a multicenter, randomized, phase 3, double-blind, active control study conducted in patients with newly diagnosed high-risk mCSPC at 235 sites in 34 countries, including 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 study are available in the protocol (appendix pp 10-109). Briefly, men aged ≥18 years with newly diagnosed (within three months before randomization), 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) 1·1 criteria, and with Eastern Cooperative Oncology Group (ECOG) performance

status score of 0 to 2 were included. Additionally, patients were required to have at least two out of three high- risk prognostic factors (Gleason score ≥8, three or more lesions on bone scan, and measurable visceral metastases, excluding lymph node). Patients were also required to have adequate hematologic, hepatic, and renal function: hemoglobin ≥9.0 g/dL independent of transfusions, neutrophils ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, total bilirubin ≤1.5 × upper limit of normal (ULN) (except for patients with documented Gilbert's disease in which case total bilirubin not to exceed 10 × ULN), alanine (ALT) and aspartate (AST) aminotransferase ≤2.5 × ULN, serum creatinine <1.5 × ULN or calculated creatinine clearance ≥50 mL/min, and serum potassium ≥3.5 mM. Patients who had received prior chemotherapy, radiation therapy, or surgery for metastatic prostate cancer were excluded; however, up to three months of ADT with LHRH analogs or orchiectomy with or without concurrent anti-androgens prior to baseline or single course of prior palliative radiation or surgical therapy for the symptoms of the metastatic disease was permitted. Patients with small cell carcinoma of the prostate, brain metastasis, or with clinically significant cardiac, adrenal, or liver disease, or malignancy other than prostate or non-melanoma skin cancer within five years, were excluded.

The study protocol was approved by the local Institutional Review Board and was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The study 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 to participate in the study.

Randomization and masking

Eligible patients were enrolled by the investigators at each site, stratified by presence of measurable visceral disease and ECOG performance status, and randomly assigned (1:1) to receive ADT along with abiraterone acetate plus prednisone or ADT with matching placebos based on a computer-generated randomization schedule. A country-by-country scheme was performed using permuted block randomization. A unique identification number and treatment number to each patient were generated by a centralized interactive web response system (IWRS). The randomization codes were maintained within IWRS and treatment allocations were masked to investigators, patients, study personnel until the study completion, except during medical emergencies wherein appropriate patient management would be required by knowing the treatment allocation status. In addition, treatment allocations were unmasked based on the Independent Data Monitoring Committee (IDMC) recommendations for the purpose of safety analysis at regular intervals. The IDMC also reviewed all efficacy and safety data at the planned interim analyses. Following the positive results of the first interim analysis (cutoff date: October 31, 2016) and the IDMC recommendation, the sponsor made a decision to unblind the treatment allocation to the investigators and the patients. After unblinding, scientific advice was sought on a regular basis from the publication steering committee members that comprised of selected study investigators (appendix, p 6)

Procedures

After a screening phase of up to 28 days, patients in the abiraterone acetate plus prednisone group were planned to receive abiraterone acetate 1000 mg (4 × 250-mg tablets) once daily and prednisone 5 mg once daily in addition to ADT, while patients in the placebo group were planned to receive matching placebos of abiraterone acetate and prednisone once daily plus ADT

during a double-blind treatment phase (28 days treatment cycles).[17,18] All patients received ADT (LHRH agonists) if they had not undergone surgical castration. Patients received study medications at least 1 hour before or 2 hours after a meal. Two dose reductions were allowed in the study for the management of adverse events (AEs). At each dose reduction, one tablet of abiraterone acetate or matching placebo were reduced. Treatment continued until disease progression, withdrawal of consent, the occurrence of unacceptable toxicity, or death. The treatment was withheld and appropriate medical management was instituted in patients who developed drug-related Grade 3 or higher toxicities, including hypertension, hypokalemia, edema, and other non-mineralocorticoid toxicities. Treatment with abiraterone acetate was not reinitiated until symptoms of the toxicity were resolved to Grade 1 or baseline. 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, lost to follow up, withdrawal of consent or study termination). Patients were withdrawn from the study if they withdrew the consent for subsequent data collection or were lost to follow-up.

Patients in the placebo group were allowed to cross over to abiraterone acetate plus prednisone treatment as per protocol amendment (on February 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 arm who had not experienced cancer progression and who consented to receive active treatment after unblinding. Moreover, the cross over to abiraterone acetate plus prednisone from placebo was not considered as an event and the rPFS was not re-analyzed. Patients who were in the

follow-up phase were not eligible to enroll in the open-label extension phase. The purpose of open-label extensions 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 elect 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. There were regulatory requirements in certain EU countries for the protocol to specify a definite time to when the study should end as clinical trials are not to be used as a provision to allow access to study drug.

Outcomes

The co-primary endpoints of the study were OS (defined as the time from randomization to date of death from any cause) and rPFS (time from randomization to occurrence of radiographic progression, based on modified Prostate Cancer Working Group 2 [PCWG2] criteria or Response Evaluation Criteria in Solid Tumors version 1.1 criteria) and were not centrally reviewed. In this report, the long-term, updated OS from the final analysis, secondary endpoints, including time to initiation of chemotherapy (defined as time from randomization to the date of initiation of chemotherapy for prostate cancer), time to pain progression (defined as the time from randomization to first increase of 30% or more from baseline in Brief Pain Inventory-Short Form [Item 3]), time to symptomatic skeletal event (defined as time from randomization to any one of the following skeletal-related event: clinical or pathological fracture, spinal cord compression, palliative radiation to bone or surgery to bone), time to subsequent prostate cancer therapy (defined as time from randomization to the date of initiation of all subsequent therapy for prostate cancer, including hormonal therapy, chemotherapy, surgery, and radiation therapy), and time to secondary progression-free survival (PFS2; defined as time from randomization to

progression on subsequent treatment or to death), and safety are presented. The rPFS was not re-analyzed in this final OS analysis. AEs, vital signs, serum hematologic and biochemistry parameters, serum testosterone levels, and liver-function were monitored up to the 30 days post-treatment discontinuation. Hematological parameters (hemoglobin, white blood cells including neutrophil count, platelet count), serum chemistry (potassium, creatinine, fasting glucose, lactate dehydrogenase), liver function test (ALT, AST, total bilirubin) were monitored at each clinic visit which was monthly for the first year and subsequently, every alternate month. AEs were graded using the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 4·0.

Statistical analysis

A sample size of 1200 patients was planned for this study. For coprimary endpoint of OS, a total of 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 OS, and 0.001 allocated in the testing of rPFS. Two interim analyses for OS were planned after 50% (~426) of expected deaths (first interim) and 65% (~554) of expected deaths (second interim) were observed and final analysis was planned when approximately 852 death events were observed. A single final analysis of rPFS was planned after observing 426 expected events. Accordingly, the first interim analysis of OS (clinical cutoff: October 31, 2016) was performed after 406 deaths (169 in the abiraterone acetate plus prednisone group and 237 in the placebo group) were observed at a median follow up of 30·4 months. The results of the first interim analysis of OS along with final analysis of rPFS have been reported elsewhere.[17] The second interim analysis (clinical cutoff: October 2, 2017) was

conducted after observing 535 deaths (230 in the abiraterone acetate plus prednisone group and 305 in the placebo group) at a median follow-up of 41·4 months.[21]

Of note, the preplanned death events at the final analysis were intended per the study protocol to achieve the desired statistical power. Since the criterion for superiority was met and the study was unblinded, the preplanned total event size (852 events) was no longer relevant, and the study sponsor, therefore, made the decision to analyze the data before the pre-planned events at a cutoff date of August 15, 2018. The final analysis was performed 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 may be higher at the final analysis due to more events. However, the analysis was confounded by patients in the control group crossing over to receive the active treatment after unblinding and therefore the power could have been negatively impacted.

The OS endpoint incorporated the group sequential design with an alpha spending function calculated as Wang-Tsiatis power boundaries of shape parameter 0·2 (East® software). Secondary endpoints were assessed using Hochberg test procedure at overall two-sided 0.05 significance level to control the familywise type I error rate. Kaplan-Meier estimates were used to analyze OS distribution, and median OS. Estimation of HR and its associated 95% CI was done using the Cox proportional-hazards model. The OS in prespecified subgroups based on age (<65 years, ≥65 years, ≥75 years), ECOG score at randomization (0/1 vs. 2), Gleason score (<8 vs ≥8), number of baseline bone lesions (≤10 vs >10), presence of visceral disease at randomization (yes vs no), other potential baseline prognostic factors (baseline prostate specific antigen and lactate dehydrogenase), and region (Asia, Eastern Europe, Western Europe, rest of

world) was analyzed using nonstratified univariate model to investigate the consistency of treatment effects. The primary and secondary efficacy endpoints were analyzed in the intention-to-treat (ITT) population that included all randomized patients who received at least one dose of study medication. No formal imputation for missing data was performed. A post hoc analysis was performed to analyze OS and rPFS based on disease "volume" (high vs low). The "high volume" disease was defined as presence of visceral metastases and/or four or more bone metastases, with at least one outside the vertebral column or pelvis. Disease pattern not meeting that criteria was defined as "low volume" disease. The safety parameters were also analyzed in all randomized patients who received at least one dose of study medication. Patients were deemed assessable if results for a given study assessment were evaluable. All key analyses were done with SAS software, version 9·4. This study is registered with Clinicaltrials.gov, number NCT01715285.

Role of the funding sources

The employees of the sponsor and academic authors participated in the design of this study, data collection, data analysis, data interpretation and preparation of the manuscript. Writing assistance was provided by medical writer and funded by the sponsor. The corresponding author had final responsibility for the decision to submit the article for publication.

Results

Between February 12, 2013, and December 11, 2014, a total of 1209 patients were assessed for eligibility, of whom 1199 patients were randomized to abiraterone acetate plus prednisone group (n=597) or placebo group (n=602) and were included in the analysis (Figure 1). Ten patients were ineligible due to study site violation. The baseline demographic characteristics were well-

balanced between two groups as described previously.[17] When this final analysis was conducted at the cutoff date of August 15, 2018, 618 deaths (275 [46%] in the abiraterone acetate plus prednisone group and 343 [57%] in the placebo group) were observed, with a median follow-up of 51·8 (IQR: 47·15–57·03) months, which is nearly 22 months of additional follow-up and 212 additional events from the first interim analysis. 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 crossed over to abiraterone acetate plus prednisone from the placebo group (Figure 1). Life-extending subsequent therapy was most frequently reported in the placebo group (345 [57%] of 602) than abiraterone acetate plus prednisone group (176 [30%] of 597), with docetaxel being the most commonly used subsequent therapy in both the groups. At the final analysis, 84 (14%) patients in the placebo group received abiraterone acetate plus prednisone as life-extending subsequent therapy (Table 1). The most common reason for treatment discontinuation across treatment groups was disease progression (254 [43%] in the abiraterone acetate plus prednisone group and 388 [65%] in the placebo group) (Figure 1). The median (IQR) treatment duration was 25·8 (12·25–49·0) months with abiraterone acetate plus prednisone, 14·4 (7·33–25·79) months with placebo, and 11·9 (9·23–12·91) months with placebo to abiraterone acetate plus prednisone cross-over group.

The median OS continued to be longer in the abiraterone acetate plus prednisone group than the placebo group (53·3 [95% CI: 48·2–not reached] vs 36·5 [95% CI: 33·5–40·0] months), with a significant decrease in the risk of death with abiraterone acetate plus prednisone treatment as compared to the placebo group (HR: 0·66; 95% CI: 0·56–0·78; p<0·0001) (Table 2 and Figure

2). Analysis of OS by patient subgroups is shown in Figure 3. Consistent with the findings of the interim analyses, abiraterone acetate plus prednisone treatment showed significant improvement in the secondary endpoints of time to pain progression, skeletal-related event, chemotherapy initiation, subsequent therapy for prostate cancer, and time to PFS2 (all p <0·02) (Table 2 and Figure 4).

The overall incidence of AEs was comparable between abiraterone acetate plus prednisone group (569 [95%] of 597) and placebo group (561 [93%] of 602) (Table 3). The AEs were reported in 44 (61%) of 72 patients in the placebo crossover group. All Grade 1–2 AEs that occurred in at least 10% of patients in either group are shown in Table 3. Of note, the crossover group had a much shorter exposure period (median treatment duration: 11·9 months; IQR: 9·23–12·91) when compared with abiraterone acetate plus prednisone group (25·8 months; IQR: 12·25–49·0). Grade 3 or 4 AEs 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 or 4 AEs were hypertension (125 [21%] in the abiraterone acetate plus prednisone group, 60 [10%] in the placebo group, and 3 [4%] in the placebo crossover group) and hypokalemia (70 [12%] in the abiraterone acetate plus prednisone group, 10 [2%] in the placebo group, and 2 [3%] in the placebo crossover group) (Table 3). Serious AEs were observed in 192 (32%) patients in the abiraterone acetate plus prednisone group, 151 (25%) in the placebo group, and 4 (6%) in the placebo crossover group. Grade 3 or 4 serious AEs occurred in 160 (27%) patients in the abiraterone acetate plus prednisone group, 120 (20%) in the placebo group and 3 (4%) in the placebo cross-over group. The most common Grade 3 or 4 serious AE was spinal cord compression (11 [2%] patients in the abiraterone acetate plus prednisone group, 10

[2%] in the placebo group and none in the placebo cross-over group). Treatment-related serious AEs were reported in 30 (5%) patients in the abiraterone acetate plus prednisone group, 13 (2%) in the placebo group and 1 (1%) in the placebo cross-over group. The most common treatment-related serious AE was hypokalemia (4 [1%] patients in the abiraterone acetate plus prednisone group, and none in the placebo and placebo crossover groups). AEs leading to treatment discontinuation were reported in 93 (16%) patients in the abiraterone acetate plus prednisone group, 63 (11%) in the placebo group and 3 (4%) in the placebo cross-over group. Treatment-related AEs leading to treatment discontinuation were reported in 24 (4%) patients in the abiraterone acetate plus prednisone group, 11 (2%) in the placebo group and 1 (1%) in the placebo cross-over group (appendix p 7). AEs 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 7 (10%) in the placebo cross-over group. Grade 3 or 4 mineralocorticoid AEs such as hypertension, hypokalemia, fluid retention/edema, and other AEs of special interest were commonly reported in the abiraterone acetate plus prednisone group than the placebo group and the incidence was consistent to that reported in the interim analysis (Table 4). One patient in the placebo crossover group reported Grade 5 acute cardiac failure. Overall, AEs led to 38 (6%) deaths in the abiraterone acetate plus prednisone group, 27 (5%) deaths in the placebo group, and 2 (3%) deaths in the placebo crossover group (Table 3). 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 in one patient each) and the placebo group (sudden death, cerebrovascular accident, and pneumonia in one patient each) and none in the crossover group.

In the post hoc analysis, the median OS observed with abiraterone acetate plus prednisone versus placebos in the high-volume disease subgroup (n=955) was 49·7 versus 33·3 months, respectively and HR for death was 0·62; 95% CI: 0·52–0·74; p<0·0001. The number of patients with the low-volume disease was limited in this study (n=243) and the median OS in this subgroup was not reached in either study arms nor did the HR for death reach statistical significance at this time (HR: 0·72, 95% CI: 0·47–1·10; p=0·1242). (Appendix p 7). In the high-volume disease subgroup, a significantly longer median rPFS was observed with abiraterone acetate plus prednisone versus placebos (33·1 vs 14·7 months), with 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, abiraterone acetate plus prednisone treatment showed significantly longer median rPFS compared with placebos (49·8 vs 22·4 months; HR: 0·59; 95% CI: 0·40–0·85; p= 0·0048) (Appendix p 8).

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 OS versus placebos and ADT. These findings further substantiated the significant treatment benefits with abiraterone acetate plus prednisone shown earlier by interim analysis of coprimary endpoints of OS and rPFS.[17] Furthermore, significant improvements in all secondary endpoints were observed with abiraterone acetate plus prednisone and ADT, by delaying the time to initiation of chemotherapy, subsequent prostate cancer therapy, pain progression, and symptomatic skeletal event. Also, the significantly improved PFS2 seen in the final analysis also may indicate that early treatment with abiraterone acetate plus prednisone

may retain the therapeutic advantage even post study treatment. There were no new safety signals or apparent change in the safety profile of abiraterone acetate plus prednisone observed during this follow-up period.

Consistent with interim analyses, the addition of abiraterone acetate plus prednisone to ADT versus placebo resulted in an HR of 0.66 (95% CI: 0·56–0·78; p<0·0001) for OS, with a median follow-up time of 51·8 months. It is noteworthy that treatment with abiraterone acetate plus prednisone and ADT demonstrated a survival advantage versus placebo and ADT, despite a higher proportion of patients in the placebo group receiving life-prolonging subsequent therapy, including docetaxel and next-generation androgen receptor axis targeted agents such as enzalutamide or abiraterone acetate plus prednisone. The proportion of patients receiving subsequent therapy in the control group of this study (57%, including cross-over to abiraterone acetate plus prednisone) was numerically higher than that of the STAMPEDE study (50%) and CHAARTED study (48%).[7,8,22] The proportion of patients in control arms of these studies receiving subsequent treatment for mCRPC likely reflects the real world situation. A significant delay in the initiation of chemotherapy, subsequent therapy, and longer PFS2 support the early use of abiraterone acetate plus prednisone. The overall survival remained consistently in favor of abiraterone acetate plus prednisone arm despite the placebo arm including patients who had not progressed but elected to cross over to receive open-label abiraterone acetate plus prednisone. Early treatment with abiraterone acetate and prednisone thus may be beneficial in high risk mCSPC patients. The subsequent therapy in this study was allowed after radiographic progression assessed by the investigators. Similar to real-world setting, treatment was initiated only after multiparametric verification of CRPC progression especially when disease progressed

from castration sensitive to castration-resistant state. The survival benefit was observed across all other subgroups of patients, including patients of different age categories, those with presence or absence of visceral disease, and those with bone lesions ≤10 or >10 at study entry. The subgroup of patients with an ECOG score of ≥2 did not reach statistical significance for survival benefit, however, represented less than 3% of enrolled patients. Thus, the findings of this study reflect and confirm the effective blockade of androgen receptor signaling with abiraterone acetate plus prednisone and ADT in patients with mCSPC with high-risk features and major benefits of delaying the disease progression. Recently, a post hoc analysis of the STAMPEDE study not only confirmed that OS is improved with abiraterone acetate plus prednisone and ADT over ADT alone in men with high-risk *de novo* M1 disease by the LATITUDE definition (HR for OS: 0·54 [95% CI: 0·41–0·70]; p<0·001), but also that this OS benefit applies to men with low-risk disease (HR for OS: 0·66 [95% CI: 0·44–0·98); p=0·041).[23] It is worth noting that 48% of mCSPC patients 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. However, only 20% of the patients in this study had low-volume disease and this study was not powered to investigate these associations in low-volume disease subgroup. Treatment with abiraterone acetate plus prednisone and ADT significantly improved rPFS in patients with low-volume disease in both the LATITUDE and the STAMPEDE studies.

Post hoc analysis from STAMPEDE suggests that PFS, but not OS, may be better with abiraterone acetate plus prednisone than docetaxel. Indirect comparisons of randomized studies

using the Bayesian method favor abiraterone acetate plus prednisone for PFS and other secondary outcomes. [24-27] In view of the survival benefits observed with both abiraterone acetate plus prednisone and docetaxel, addition of abiraterone acetate plus prednisone and docetaxel is currently being evaluated to understand whether 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 conducted in mCRPC patients, thus confirming the long-term benefits of abiraterone acetate plus prednisone in mCSPC.[14,15,17] Incidence of expected mineralocorticoid-related AEs such as hypertension, hypokalemia, and fluid retention was common with abiraterone acetate plus prednisone treatment. Close monitoring for hypokalemia 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 or 4 mineralocorticoid-related AE and other AEs of special interest such as hepatotoxicity and cardiac disorders was observed, consistent with data reported in men with mCRPC.[28] Most AEs were medically manageable and rarely led to treatment discontinuation. There were no unexpected safety signals identified with abiraterone acetate plus prednisone treatment, 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 M1 disease and although STAMPEDE provides some evidence,

additional prospective evidence will underscore the clinical benefit of early androgen signaling axis inhibition in broader mCSPC patients. Also, all patients had *de novo* metastatic disease and it is unknown whether 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. 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 outcome would benefit from cross over 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 this data is currently not available in LATITUDE study. Currently available evidence support the maintained activity of taxanes in the majority of mCRPC men who have progressed on abiraterone acetate plus prednisone.[30,31]

In summary, the final updated data underscores significant survival benefits of adding abiraterone acetate plus prednisone to ADT in newly diagnosed patients with high-risk mCSPC, by further prolonging the OS along with a delay in initiation of chemotherapy and 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 high-risk mCSPC patients.

Research in context

Evidence before the study: A PubMed search was performed to retrieve studies of prostate cancer published in English language from January 01, 2008 to November 28, 2018. The search strategy encompassed wide range of key terms, including but not limited to "prostate cancer", "overall survival", and "androgen deprivation" to identify randomized controlled studies, post hoc analysis, systematic reviews, and meta-analysis evaluating efficacy and safety of treatments in men with newly diagnosed metastatic castration sensitive prostate cancer (mCSPC). A total of 35 relevant articles were identified. 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 may be restricted owing to its toxicity profile and patient-specific comorbidities. Addition of abiraterone acetate plus prednisone to ADT in a preplanned interim analysis of 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 along with ADT continued to show survival benefits compared with ADT alone, by further prolonging the overall survival and delaying the initiation of chemotherapy and subsequent therapy in newly diagnosed patients with high-risk mCSPC. Combination of abiraterone acetate plus prednisone with ADT showed a manageable safety profile, which is consistent with that of the 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.

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Contributors

KF, NT, SL, YL, and KNC were involved in the conception and design of the study. KF, LF, NM, ARA, BYA, MO, DY, SF, AP, and KNC were investigators who participated in the conduct of the study and were involved in the data collection. KF, NT, GS, SL, KNC, SM, and YL were involved in data analysis. 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, MSD, Orion and Sanofi. KNC's institution received funding from Janssen for the conduct of the study. AP has received personal fees for consulting/advisory

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Data sharing statement: The data sharing policy of the study sponsor, Janssen Pharmaceutical Companies of Johnson & Johnson, is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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Figure Legends

Figure 1. Patient disposition

ADT=androgen deprivation therapy; ITT=intent-to-treat

Figure 2. Kaplan-Meier curve of overall survival (Intent-to-treat population)

ADT=androgen deprivation therapy

Figure 3. Subgroup analysis of overall survival (Intent-to-treat population)

ADT=androgen deprivation therapy. LDH=lactate dehydrogenase. PSA, prostate specific antigen.

Figure 4. Kaplan-Meier curves of secondary endpoints (Intent-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 secondary progression-free survival (PFS2) (E).

ADT=androgen deprivation therapy. PFS2=second disease progression, which is defined as time from randomization to progression on subsequent treatment or to death

Table 1. Life-extending subsequent therapy for prostate cancer (Intent-to-treat population)

	Abiraterone acetate and prednisone plus ADT (n=597)	Placebos plus ADT (n=602)
Patients with life prolonging subsequent therapy	176 (30)	345 (57)
Docetaxel	144 (24)	212 (35)
Enzalutamide	57 (10)	99 (16)
Radium Ra 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 (%). Note that one patient may have multiple life-extending subsequent therapies.
ADT=androgen deprivation therapy.

Table 2. Efficacy endpoints (Intent-to-treat population)

Median, months	Abiraterone acetate and prednisone plus ADT (n = 597)		Placebos plus ADT (n = 602)		HR (95% CI)	p value
	Events, n (%)	Median, months (95%CI)	Events, n (%)	Median, months (95%CI)		
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, time to						
Pain progression	245 (41)	47·4 (33·2, NR)	292 (49)	16·6 (11·1, 24·0)	0·72 (0·61–0·86)	0·0002
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 PC therapy	248 (42)	54·9 (45·4, NE)	355 (59)	21·2 (18·6, 23·5)	0·45 (0·38–0·53)	<0·0001
PFS2 (randomization to progression on subsequent therapy/death)	267 (45)	53·3 (44·7, 58·1)	336 (56)	30·1 (26·2, 33·4)	0·58 (0·49–0·68)	<0·0001

ADT=androgen deprivation therapy. NR=not reached. PC=prostate cancer. PFS2=second disease progression, which is defined as time from randomization to progression on subsequent treatment or to death.*3-year event free rate for skeletal-related events: 78% (95% CI: 74%–82%) for abiraterone acetate plus prednisone + ADT vs 73% (95% CI: 69%–77%) for placebo+ADT; †3-year event free rate for initiation of chemotherapy: 76% (95% CI: 71%–79%) for abiraterone acetate plus prednisone +ADT vs 56% (95% CI: 51%–61%) for placebos+ADT.

Table 3. Summary of adverse events (Safety population)

	Abiraterone acetate and prednisone plus ADT (n = 597)			Placebos plus ADT (n=602)			Placebo cross over to abiraterone acetate and prednisone (n=72)		
AEs by grade*	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Back pain	108 (18)	15 (3)	0	107 (18)	21 (4)	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 (13)	1 (<1)	0	1 (1)	0	0
Arthralgia	87 (15)	9 (2)	0	71 (12)	15 (3)	0	4 (6)	0	0
Hypokalaemia	73 (12)	65 (11)	5 (1)	13 (2)	9 (2)	1 (<1)	7 (10)	2 (3)	0
Fatigue	73 (12)	11 (2)	0	76 (13)	14 (2)	0	1 (1)	0	0
ALT increased	67 (11)	32 (5)	2 (<1)	69 (12)	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 (2)	0	57 (10)	13 (2)	0	2 (3)	0	0
AST increased	65 (11)	26 (4)	1 (<1)	59 (10)	9 (2)	0	4 (6)	1 (1)	0
Oedema peripheral	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 (9)	22 (4)	0	3 (4)	2 (3)	0
Anaemia	45 (8)	14 (2)	3 (1)	63 (11)	26 (4)	1 (<1)	2 (3)	1 (1)	0
Blood lactate dehydrogenase increased	27 (5)	12 (2)	1 (<1)	21 (4)	9 (2)	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 (4)	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 (3)	10 (2)	0	1 (1)	0	0
Dyspnoea	24 (4)	5 (1)	0	15 (3)	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 (3)	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 (4)	7 (1)	0	0	0	0
Dysuria	22 (4)	4 (1)	0	27 (5)	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 mellitus	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
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

AEs by grade*	Abiraterone acetate and prednisone plus ADT (n = 597)			Placebos plus ADT (n=602)			Placebo cross over to abiraterone acetate and prednisone (n=72)		
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 (%). AE=adverse event; ADT, androgen deprivation therapy; ALT=alanine aminotransferase; AST=aspartate aminotransferase. *Any Grade 1–2 adverse events occurring in ≥10% of patients in any treatment group, and all Grade 3 and 4 adverse events occurring in ≥1% of patients in any treatment group are listed. There were total 38 Grade 5 AEs in the abiraterone acetate plus prednisone group (3 cases each of cardiac arrest, pneumonia, sudden death; 2 each of cardio-respiratory arrest, cardiopulmonary failure, myocardial infarction, cerebrovascular accident, spinal cord compression, respiratory failure, subdural haematoma, acute kidney injury; 1 each of acute coronary syndrome, acute myocardial infarction, cardiac failure, cardiac failure congestive, cerebral haemorrhage, depressed level of consciousness, lower respiratory tract infection, lung infection, acute pulmonary oedema, aspiration, pulmonary embolism, multi-organ failure, gastric ulcer perforation, intestinal ischaemia, intestinal obstruction, and nasal sinus cancer). In the placebo group, 27 Grade 5 AEs were recorded (4 cases of sudden death, 3 cases of cerebrovascular accident, two each of cardio-respiratory arrest, multi-organ failure, sepsis, and completed suicide, 1 each of pneumonia, cardiac arrest, spinal cord compression, acute coronary syndrome, pulmonary embolism, arthralgia, urinary retention, bronchopneumonia, cardiac failure acute, atrioventricular block complete, urosepsis, coma, optic nerve compression, traumatic intracranial haemorrhage, and pleural effusion). Two Grade 5 AEs were reported in placebo cross-over group (1 each of cardiac failure acute and circulatory collapse).

Table 4. Adverse events of special interest (Safety population)

	Abiraterone acetate and prednisone plus ADT (n = 597)			Placebos plus ADT (n=602)			Placebo cross over to abiraterone acetate plus prednisone (n=72)		
Graded adverse events*	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Hypertension	243 (41)	130 (22)	1 (<1)	144 (24)	62 (10)	1 (<1)	4 (6)	3 (4)	0
Hepatotoxicity	146 (25)	49 (8)	4 (1)	109 (18)	21 (4)	0	7 (10)	3 (4)	0
ALT increased	101 (17)	32 (5)	2 (<1)	77 (13)	8 (1)	0	5 (7)	2 (3)	0
AST increased	92 (15)	26 (4)	1 (<1)	68 (11)	9 (2)	0	5 (7)	1 (1)	0
Hypokalemia	143 (24)	65 (11)	5 (1)	23 (4)	9 (2)	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/edema	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 (5)	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 (%). ADT=androgen deprivation therapy. ALT=alanine aminotransferase. AST=aspartate aminotransferase. *Listed are the AEs of special interest reported in at least 2% of patients in either group.