Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial

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Summary

Background In the LATITUDE trial, addition of abiraterone acetate plus prednisone to androgen deprivation therapy (ADT) improved overall survival compared with placebos plus ADT in patients with newly diagnosed, high-risk, metastatic castration-naive prostate cancer. Understanding the effects of treatments on patient-reported outcomes (PROs) and health-related quality of life (HRQOL) is important for treatment decisions; therefore we aimed to analyse the effects of ADT plus abiraterone acetate and prednisone versus ADT plus placebos on PROs and HRQOL in patients in the LATITUDE study.

Methods In the multicentre, international, randomised, phase 3 LATITUDE trial, eligible patients were aged 18 years or older, had newly diagnosed, high-risk, metastatic castration-naive prostate cancer confirmed by bone scan (bone metastases) or by CT or MRI (visceral, soft tissue, or nodal metastases), and an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less. Patients from 235 clinical sites in 34 countries were randomly assigned (1:1) following a country-by-country scheme done by permuted block randomisation (with two blocks) and stratified by the presence of visceral metastasis and ECOG performance status to receive ADT plus 1000 mg oral abiraterone acetate and 5 mg oral prednisone once daily or ADT plus placebos. Selection of ADT, chemical or surgical, was at the investigator's discretion. The co-primary endpoints of the trial, overall survival and radiographic progression-free survival, have been published. PRO data were collected directly on electronic tablet devices at the clinical sites during screening and before any other visit procedure on day 1 of cycles 1–3, monthly during cycles 4–13, and then every 2 months until the end of treatment, by use of the Brief Pain Inventory—Short Form (BPI-SF), Brief Fatigue Inventory (BFI), Functional Assessment of Cancer Therapy Prostate scale (FACT-P), and the EuroQol (EQ-5D-5L) questionnaires. PRO analyses were an exploratory endpoint. Analyses were by intention-to-treat. Results from the first pre-planned interim analysis (Oct 31, 2016), are presented here. This ongoing study is registered with Clinicaltrials.gov, number NCT01715285.

Findings Between Feb 12, 2013, and Dec 11, 2014, 1199 patients were randomly assigned: 597 to ADT plus abiraterone acetate and prednisone and 602 to ADT plus placebos. Median follow-up was 30·9 months (IQR 21·2–33·2) in the ADT plus abiraterone acetate and prednisone group versus 29·7 months (1·4–43·5; 16·1–31·3) in the ADT plus placebos group. Median time to worst pain intensity progression assessed by the BPI-SF score was not reached in either group (ADT plus abiraterone acetate and prednisone, not reached [95% CI not reached to not reached]; 25th percentile 11·07 months [95% CI 9·23–18·43]; ADT plus placebos group, not reached [95% CI not reached to not reached]; 25th percentile 5·62 [95% CI 4·63–7·39]; hazard ratio [HR] 0·63 [95% CI 0·52–0·77]; p<0·0001). Median time to worst fatigue intensity was not reached in either the ADT plus abiraterone acetate and prednisone group (not reached [95% CI not reached to not reached]; 25th percentile 18·4 months [95% CI 12·9–27·7]) or the ADT plus placebos group (not reached [95% CI not reached to not reached]; 25th percentile 6·5 months [95% CI 5·6–9·2]; HR 0·65 [95% CI 0·53–0·81], p=0·0001). Median time to deterioration of functional status assessed by the FACT-P total score scale was 12·9 months (95% CI 9·0–16·6) in the ADT plus abiraterone acetate and prednisone group versus 8·3 months (7·4–11·1) in the ADT plus placebos group (HR 0·85 [95% CI 0·74–0·99]; p=0·032).

Interpretation The addition of abiraterone acetate plus prednisone to ADT in patients with newly diagnosed, high-risk metastatic castration-naive prostate cancer improved overall PROs by consistently showing a clinical benefit in the progression of pain, prostate cancer symptoms, fatigue, functional decline, and overall HRQOL.

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Research in context

Evidence before this study

We did a systematic review of literature published between Jan 1, 2005, and Sept 24, 2015, to identify studies evaluating efficacy and health-related quality-of-life (HRQOL) outcomes in patients with metastatic castration-naive prostate cancer. Databases searched were EMBASE, Medline, and the Cochrane Library. Search term categories included but were not limited to "prostate cancer", "androgen dependent", HRQOL and related patient-reported outcomes, "quality-adjusted life years", and utilities, brand names, and generic drug names of prostate cancer treatments. The review included randomised controlled trials and prospective and retrospective observational studies, and was limited to publications in English. Results of 18 publications describing eight studies that met the eligibility criteria suggested that patients with metastatic, castration-naive prostate cancer have poor HRQOL and that investigation of new treatments that maintain or improve quality of life for these patients is warranted. Androgen deprivation therapy (ADT) plus docetaxel has become a standard treatment approach for patients with advanced prostate cancer, particularly for patients with high metastatic burden. However, ADT can have negative effects on quality of life, and the addition of docetaxel increases the frequency of adverse events. Abiraterone acetate plus prednisone was found to improve overall survival in patients with metastatic castration-resistant prostate cancer who had previously received docetaxel (COU-AA-301 trial) and in patients with chemotherapy-naive metastatic castration-resistant prostate

cancer (COU-AA-302 trial); importantly, in these trials patients also showed improvements in HRQOL and pain. Based on these results and the unmet need for alternative treatment options that can improve quality of life in patients with newly diagnosed, high-risk metastatic castration-naive prostate cancer, the phase 3 LATITUDE study was done to evaluate the addition of abiraterone acetate and prednisone to ADT in this setting. Patient-reported outcome data were prospectively collected and analysed as exploratory endpoints.

Added value of this study

In this analysis of patient-reported outcomes, the combination of ADT plus abiraterone acetate and prednisone provided clinically and statistically significant improvements compared with ADT plus placebos by delaying time to worst pain intensity and pain interference, as well as worst fatigue intensity and fatigue interference, and by prolonging time to HRQOL deterioration as per the Functional Assessment of Cancer Therapy-Prostate total score in patients with newly diagnosed, high-risk metastatic castration-naive prostate cancer.

Implications of all available evidence

The improvements in both survival and HRQOL shown in the LATITUDE trial suggest that treatment with ADT plus abiraterone acetate and prednisone could be considered as a new standard-of-care option for patients with metastatic castration-naive prostate cancer.

Introduction

Androgen deprivation therapy (ADT) has been the standard treatment for patients with newly diagnosed, metastatic castration-naive prostate cancer.[1,2] Most patients with metastatic castration-naive prostate cancer who receive ADT alone will progress to castration-resistant disease within approximately 1 year.[2] Addition of docetaxel to ADT in men with metastatic castration-naive prostate cancer showed improved survival outcomes compared with ADT alone in three randomised, phase 3 trials (CHAARTED,[3] STAMPEDE,[4] and GETUG-AFU15[5]) . This treatment has become a standard approach for patients with advanced prostate cancer, particularly for those with a high metastatic burden.

Patients with metastatic prostate cancer frequently have bone pain, fatigue, and reduced physical functioning, as well as age-related comorbidities.[6,7] ADT alone can have negative effects on quality of life in patients with prostate cancer, including loss of libido and erectile dysfunction, and impaired memory, attention, and executive functions.[8] Addition of docetaxel to ADT is associated with an increase in adverse events, such as grade 3–5 fatigue, neutropenia, and febrile neutropenia,[3,4] that restrict its use; many patients are considered unfit for chemotherapy because of their age and comorbidities. The goal of all treatment

for patients with incurable cancer is to both delay disease progression and extend survival without increasing the symptom burden.

In the randomised, phase 3 LATITUDE trial, addition of abiraterone acetate and prednisone to ADT, when compared with placebos plus ADT, significantly lengthened overall survival and radiographic progression-free survival, as well as time to pain progression, time to next subsequent therapy for prostate cancer, time to initiation of chemotherapy, and time to prostate-specific antigen progression in men with newly diagnosed, high-risk, metastatic castration-naive prostate cancer.[9] Although overall survival and disease progression outcomes are used to evaluate new treatment approaches, to be truly valuable to patients new treatment approaches should not only improve symptoms but also improve or maintain quality of life. The present report describes patient-reported outcomes (PROs) and health-related quality of life (HRQOL) results from the LATITUDE trial.

Methods

Study design and participants

In this multicentre, international, randomised, phase 3, double-blind, active control trial, patients with newly diagnosed, high-risk metastatic castration-naive prostate

cancer were recruited at 235 clinical sites in 34 countries in Europe, Africa, South America, Canada, Mexico, and the Asia-Pacific region (appendix pp 3–7). Eligible men were 18 years or older and had histologically or cytologically confirmed prostate cancer with metastases (confirmed by bone scan or by CT or MRI [visceral, soft tissue, or nodal metastases]) diagnosed up to 3 months before randomisation; an Eastern Cooperative Oncology (ECOG) performance status of 2 or less; and at least two of three high-risk prognostic factors (Gleason score ≥8, three or more lesions identified by bone scan, or measurable visceral metastases other than lymph nodes). All patients were required to have adequate haemato-logical, hepatic, and renal function. Patients who showed neuroendocrine differentiation or small cell histology, or who had previously received pharmacotherapy, radiation therapy, or surgery for metastatic prostate cancer, other than orchiectomy, were excluded; however, a single course of previous palliative radiation or surgical therapy to treat symptoms of metastatic disease, if administered 28 or more days before the first treatment, was allowed. Patients with active infections, known brain metastases, uncontrolled hypertension, atrial fibrillation, clinically significant heart disease, active or symptomatic hepatitis or chronic liver disease, or another malignancy within the past 5 years were excluded. The estimated median survival of eligible patients was 33 months. Details of study design, ethical considerations, and eligibility criteria have been previously reported.[9] All patients provided written informed consent.

Randomisation and masking

After eligibility criteria were met, patients were randomly assigned (1:1) to receive ADT plus abiraterone acetate and prednisone or ADT plus placebos. Detailed randomisation procedures have been previously reported.[9] Briefly, a country-by-country randomisation scheme was implemented by permuted block randomisation (with two blocks). Randomisation was stratified by presence or absence of measurable visceral disease and ECOG performance status score (0 or 1 vs 2). The randomisation schedule was prepared by an independent statistician who was otherwise not involved with the study. Patients were assigned unique identifiers by use of a centralised interactive web response system. Blinding of both investigators and patients to the randomisation codes was maintained until study completion, independent data monitoring committee recommendation, or specific medical need for an individual patient.

Procedures

A screening phase of up to 28 days before randomisation established eligibility and baseline measurements. Patients received either ADT plus 1000 mg abiraterone acetate (4×250 mg oral tablets) and 5 mg prednisone (oral tablet) once daily or ADT plus placebos once daily (oral tablets were matched in size, colour, and shape to abiraterone acetate and prednisone). No food was consumed for at least 2 h before and 1 h after each dose of abiraterone acetate and prednisone or the corresponding placebo treatments. Each treatment cycle lasted 28 days. Treatment continued until disease progression, withdrawal of consent, or unacceptable toxicity. Selection of ADT was at the investigator's discretion; patients had either surgical castration within 3 months before randomisation or were on a stable chemical castration regimen. After the treatment phase, survival and subsequent prostate cancer therapy were monitored during a follow-up phase of up to 60 months.

PRO data describing pain, fatigue, prostate cancer symptoms, and HRQOL were collected by use of the Brief Pain Inventory-Short Form (BPI-SF),[10,11] Brief Fatigue Inventory (BFI)[12], Functional Assessment of Cancer Therapy Prostate scale (FACT-P, version 4),[13–15] and the EuroQol five-dimensions, five-levels questionnaire (EQ-5D-5L).[16,17] The questionnaires were administered and data were collected directly on electronic tablet devices at the clinical sites during screening (within 2 days of starting the study) and before any other visit procedure on day 1 of cycles 1–3, monthly during cycles 4–13, and then every 2 months until the end of treatment (appendix p 18). The last analyses before the first dose of study drug provided the baseline values. Patients who discontinued treatment also discontinued completion of all PRO assessments except for the EQ-5D-5L questionnaire, which was collected during the follow-up phase every 4 months for a total of 12 months after the end of treatment. During this follow-up phase, the protocol allowed for the EQ-5D-5L questionnaire to be administered to patients by telephone.

Using the BPI-SF, patients evaluated their least and worst pain in the past 24 h, their average pain, and their pain at the time of the survey on a scale of 0 (no pain) to 10 (worst imaginable pain). Because patients were evaluating their worst pain in the past 24 h for the time to worst pain progression parameter, the results assessed a delay in pain progression rather than a reduction in existing pain. Patients also answered seven questions to assess the degree to which pain interfered with daily activities (ie, general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life on a scale of 0 for no interference to 10 for complete interference) at the time of the survey. By use of the BFI, patients evaluated their average and worst fatigue in the past 24 h and their fatigue at the time of the survey on a scale of 0 (no fatigue) to 10 (worst imaginable fatigue); patients also evaluated the extent to which fatigue interfered with daily activities (ie, general activity, mood, walking, work, relationships, and enjoyment of life). Similar to the BPI-SF, the BFI assessed whether there was a delay in fatigue progression and fatigue interference rather than an alleviation of existing symptoms. The FACT-P scales include the general FACT-G subscale, a 27-item questionnaire that measures

general HRQOL in patients with cancer; the prostate-cancer-specific subscale that contains 12 items to measure prostate-cancer-specific quality of life; and a trial outcome index. We assessed the total FACT-P score, including physical wellbeing, social and family wellbeing, emotional wellbeing, and additional concerns items, which indicates overall HRQOL; the FACT-G subscale score, including physical, social and family, emotional, and functional wellbeing items; the prostate-cancer-specific subscale score, including items from the additional concerns section of the questionnaire; and the trial outcome index, including items from the physical and functional wellbeing, and prostate cancer-specific subscales. We also calculated a pain-related score (items GP4 and P1–P3 specific to pain); an emotional wellbeing score (items GE1–GE6); a functional wellbeing score (items GF1–GF7); a physical wellbeing score (items GP1–GP7); and a social and family wellbeing score (items GS1–GS7). Questions on sexual function and symptoms are part of the FACT-P questionnaire, and the results are reflected in summary scores of the prostate cancer-specific subscale. EQ-5D-5L evaluates aspects of health and consists of a visual analogue scale (EQ-VAS) of 0–100, with 0 being the worst health imaginable and 100 being the best health imaginable, and five additional questions assessing the patient's mobility, self-care, usual activities, pain and discomfort, and anxiety and depression, at five different levels of severity.[16,17] Responses are converted into summary measures describing overall health status and an index score reflecting health utility (0 [death] to 1 [best possible health]).

The study was unblinded after the first interim analysis (cutoff date Oct 31, 2016), as per recommendation of the independent data monitoring committee. Because of the improved efficacy observed in the ADT plus abiraterone acetate and prednisone group, patients in the ADT plus placebos group were allowed as per protocol amendment to cross over to active treatment in an open-label extension phase of the trial. FACT-P and EQ-5D-5L assessments are being collected in the ongoing open-label extension phase with a schedule similar to that used in the treatment phase.

Outcomes

The overall survival co-primary endpoint was defined as the time from randomisation to date of death from any cause, and the radiographic progression-free survival (based on Prostate Cancer Working Group 2 and Response Evaluation Criteria In Solid Tumors version 1.1) co-primary endpoint as the time from randomisation to radiographic progression or death from any cause.[9] Exploratory PRO endpoints were time to average pain progression (defined as the time from randomisation to first increase of 30% or more in average pain compared with baseline, as determined by the average of BPI-SF items 3–6), time to worst pain intensity progression (defined as the time from

randomisation to the first increase of 30% or more in worst pain intensity as evaluated by item 3 in the BPI-SF reported at two consecutive evaluations 4 or more weeks apart), time to pain interference progression (defined as the time from randomisation to the first increase by one half the standard deviation of baseline scores from baseline in the combined scale of items 9A–G from the BPI-SF), time to worst fatigue intensity progression (defined as the time from randomisation to the first date a patient had an increase of 2 or more points from baseline at two consecutive evaluations 4 or more weeks apart, based on item 3 of the BFI), time to fatigue interference progression (defined as an increase of 1·25 points or more from baseline at two consecutive evaluations 4 or more weeks apart, based on items 4A–F of the BFI), time to deterioration of FACT-P total score and subscales, EQ-VAS, and EQ-5D-5L health utility scores over time.

Statistical analysis

The statistical analysis plan for the evaluation of PROs is in the appendix (pp 22–35). The trial was powered for the co-primary endpoint of overall survival, reported previously, and was not specifically powered for the secondary and exploratory PRO analyses. Two interim analyses were pre-planned for this trial; PRO results from the first interim analysis for overall survival and a co-incident final analysis for radiographic progression-free survival (cutoff date Oct 31, 2016) are presented here. Analyses were done by intention-to-treat; only scheduled assessments were included in the by-visit analysis whereas all assessments were included in time-to-event analysis.

Time-to-event and time to PRO deterioration analyses were estimated by use of the Kaplan-Meier product limit method. Inferences for time-to-event endpoints were assessed by a log-rank test stratified by the stratification factors at randomisation. Hazard ratios (HR) and associated 95% CIs were ascertained with a Cox proportional hazards model. Patients with no progression or deterioration at the time of analysis were censored on the last date they were known to have not progressed or deteriorated. Changes in threshold values used for ascertaining progression or deterioration, which were used to assess time to deterioration in the subscales of FACT-P, were based on previous reports; threshold values used for ascertaining time to deterioration were predefined on the basis of changes that had been previously shown to be meaningful to patients.[14,18–23] Patients without baseline or on-study assessments were censored at the date of randomisation and included in the analysis as being in the study for 1 day without an event. In cases for which median values could not be determined because less than 50% of patients had deterioration, 25th percentiles were compared instead.

Repeated-measures analyses of changes from baseline (measurement at screening or day 1 before treatment)

were done at multiple time points according to the planned assessment schedule to estimate mean changes in worst pain intensity, pain interference, and average pain progression (BPI-SF); mean changes in worst fatigue intensity and fatigue interference (BFI); mean changes in FACT-P total score and subscales; and mean changes in EQ-5D-5L VAS health status and health utility scores. Patients were considered assessable if results for a given measurement were evaluable. No adjustments for multiplicity were made; instead, a serial correlation was assumed on the basis of previous simulation and comparison between repeated measures within patients. Pre-defined thresholds shown to be meaningful to patients[14,18–23] were used as a reference to define progression in pain (as evaluated by BPI-SF), fatigue (as evaluated by BFI), and HRQOL (as evaluated by FACT-P), and are in the appendix (p 19). To exclude any effect present at baseline, change from baseline was used to fit the repeated-measures model.

Compliance with the planned assessment schedule for PROs was calculated at baseline and for each treatment cycle as the proportion of patients still on study at that particular timepoint. No formal imputation for missing data was done and reasons for missing data were not centrally recorded.

A sensitivity analysis was done for time to worst pain intensity progression, assessed by the BPI-SF. An increase of 2 or more points from baseline in the relevant BPI-SF items, rather than an increase of 30% or more, was tested. All statistical analyses were done with SAS software, version 9.2.

This study is registered with Clinicaltrials.gov, number NCT01715285.

	ADT plus abiraterone acetate and prednisone group (n=597)	ADT plus placebos group (n=602)
Median age, years (range)	68 (38–89)	67 (33–92)
Gleason score at initial diagnosis		
<7	4 (1%)	1 (<1%)
7	9 (2%)	15 (2%)
≥8	584 (98%)	586 (97%)
ECOG performance status at baseline		
0	326 (55%)	331 (55%)
1	245 (41%)	255 (42%)
2	26 (4%)	16 (3%)
Patients with ≥3 bone metastases at screening	586 (98%)	585 (97%)
Extent of disease		
Number of patients	596	600
Bone	580 (97%)	585 (98%)
Liver	32 (5%)	30 (5%)
Lungs	73 (12%)	72 (12%)
Node	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 BPI-SF scores		
Number of patients	570	579
Worst pain in the past 24 h	2·2 (2·5)	2·2 (2·4)
Least pain in the past 24 h	1·2 (1·7)	1·2 (1·8)
Average pain in the past 24 h	1·8 (1·9)	1·9 (1·9)
Pain at time of survey	1·4 (1·9)	1·3 (1·9)
Percentage of pain relief in the past 24 h with use of medication*	35·8 (40·5)	37·5 (41·4)
Pain interference subscale score	1·5 (2·0)	1·5 (2·0)
(Table 1 continues in next column)		

	ADT plus abiraterone acetate and prednisone group (n=597)	ADT plus placebos group (n=602)
(Continued from previous column)		
Baseline BFI scores		
Number of patients	568	578
Worst fatigue in the past 24 h	2·2 (2·6)	2·2 (2·5)
Average fatigue in the past 24h	1·8 (2·1)	1·8 (2·1)
Fatigue at the time of survey	1·6 (2·1)	1·7 (2·2)
Baseline FACT-P scores		
Number of patients	568	579
Total FACT-P score	113·2 (20·0)	112·4 (20·0)
Prostate cancer-specific subscale score	32·1 (7·0)	32·2 (7·2)
FACT-G subscale score	81·1 (14·8)	80·2 (14·7)
Pain-related subscale score	11·7 (4·1)	11·6 (4·0)
Trial outcome index	73·8 (15·3)	73·7 (15·4)
Emotional wellbeing subscale score	18·5 (4·1)	18·2 (4·2)
Functional wellbeing subscale score	18·3 (6·2)	18·3 (6·2)
Physical wellbeing subscale score	23·4 (4·6)	23·2 (4·5)
Social and family wellbeing subscale score	20·9 (5·9)	20·6 (6·1)
Baseline EQ-5D-5L scores		
Number of patients	570	578
Health status score (VAS)	73·9 (17·6)	74·2 (16·8)
Health utility index	0·8 (0·2)	0·8 (0·2)

Data are n (%) or mean (SD), unless otherwise stated. Not all patients are included in the assessment of extent of disease, since data were not available for three patients. PROs=patient-reported outcomes. ADT=androgen deprivation therapy. BPI-SF=Brief Pain Inventory-Short Form. BFI=Brief Fatigue Inventory. FACT-P=Functional Assessment of Cancer Therapy-Prostate. FACT-G=Functional Assessment of Cancer Therapy-General subscale. EQ-5D-5L=EuroQol five-dimension, five-level questionnaire. VAS=visual analogue scale. *Calculation based on responses to BPI-SF question 7 (asking patients to state what treatments or medications they have used for their pain) and BPI-SF question 8 ("In the last 24 hours, how much relief have pain treatments or medications provided?"; the patient marks one choice among the following: 0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%).

Table 1: Baseline characteristics and PROs

Role of the funding source

This study was designed by employees of the sponsor and academic authors, and data collection was funded by the sponsor. Data analyses were done by statisticians employed by the sponsor. All authors employed by the sponsor and academic authors participated in interpretation of the data and preparation of the manuscript. The manuscript was written with editorial support from medical writers funded by the sponsor. All authors had full access to the data, and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Feb 12, 2013, and Dec 11, 2014, 1209 patients were assessed for eligibility; ten patients were excluded and 1199 were randomly allocated (597 to ADT plus abiraterone acetate and prednisone, 602 to ADT plus

placebos) and comprised the intention-to-treat and safety populations (appendix p 8). At the cutoff date for the first interim analysis and after 406 deaths, the median follow-up for all patients was 30·4 months (IQR 18·4–32·2). Patients in the ADT plus abiraterone acetate and prednisone group received a median of 25 treatment cycles (range 1–47; IQR 13–33) during a median follow-up of 30·9 months (IQR 21·2–33·2), versus a median of 15 cycles (range 1–47; IQR 8–25) during a median follow-up of 29·7 months (IQR 16·1–31·3) in the ADT plus placebos group. Demographic characteristics of patients, and baseline pain, fatigue, and functional status scores were well balanced between treatment groups (table 1).

Compliance was 90% or higher for all PRO measurement tools in all treatment cycles in both treatment groups (appendix p 20). Approximately 10% of data were missing, although the reasons were not
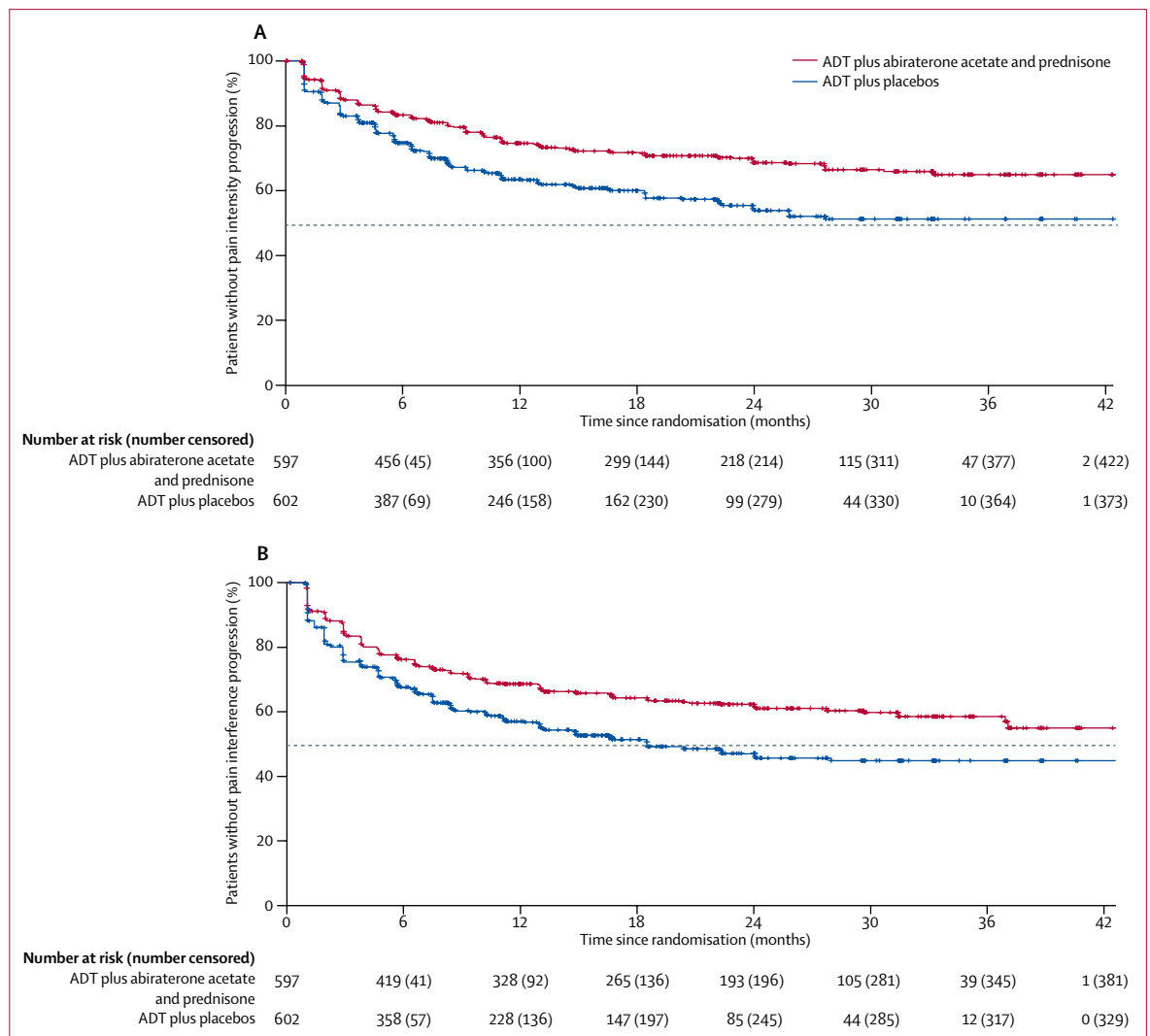

Figure 1 continued on next page

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centrally recorded. Sensitivity analyses did not identify a large effect caused by the missing data (data not shown).

Based on data from the BPI-SF questionnaire, patients in the ADT plus abiraterone acetate and prednisone group had a longer median time to worst pain intensity progression (not reached [95% CI not reached to not reached]; 25th percentile 11·07 months [95% CI 9·23–18·43]) than did patients in the ADT plus placebos group (not reached [95% CI not reached to not reached]; 25th percentile 5·62 months [95% CI 4·63–7·39]; HR 0·63 [95% CI 0·52–0·77]; p<0·0001; figure 1A). Median time to pain interference progression was not reached in the ADT plus abiraterone acetate and prednisone group (not reached [95% CI not reached to not reached]; 25th percentile 6·5 months [95% CI

4·6–9·2]) and was 18·4 months (95% CI 14·5–27·7; 25th percentile 3·7 months [95% CI 2·8–4·6]) in the ADT plus placebos group (HR 0·67 [95% CI 0·56–0·80]; p<0·0001; figure 1B). Median time to average pain progression was not reached in either treatment group (not reached [95% CI not reached to not reached]; 25th percentile not reached [95% CI not reached to not reached] in the ADT plus abiraterone and acetate group and not reached [95% CI not reached to not reached]; 25th percentile 30·3 months [95% CI 18·7–not reached] in the ADT plus placebos group) and did not significantly differ between treatment groups (HR 0·90 [95% CI 0·69–1·16]; p=0·41; appendix p 9). Based on repeated-measures mixed-effects model data, mean changes from baseline in worst pain intensity, pain interference, and average pain progression
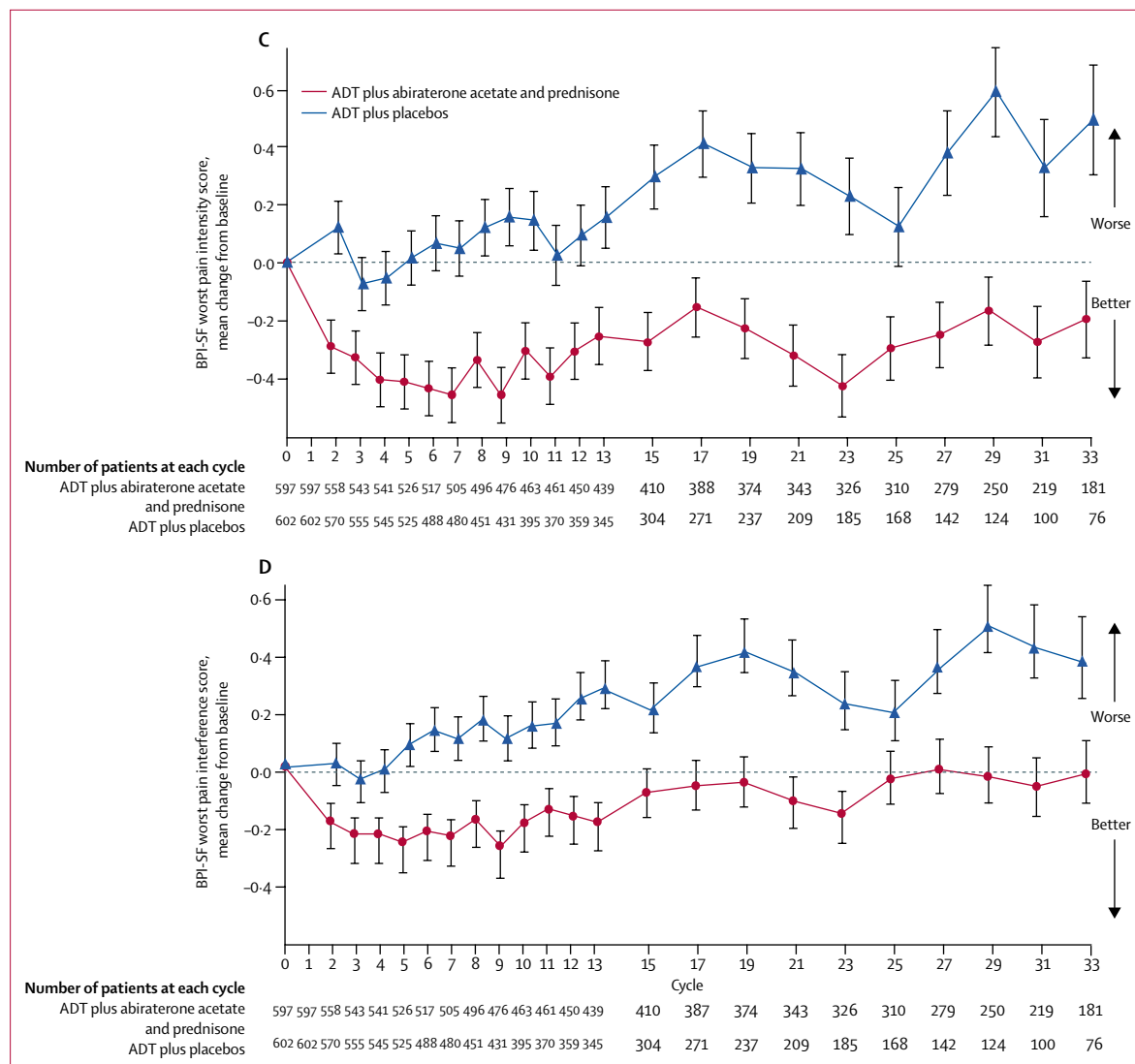
Figure 1: **Patient-reported pain progression**
Error bars are SEM. Kaplan-Meier curves for time to worst pain intensity progression (A) and time to pain interference progression (B) assessed by the BPI-SF. Mean change from baseline in worst pain intensity score (C) and pain interference score (D) by repeated-measures mixed-effects analyses. Each cycle was 28 days long. ADT=androgen deprivation therapy. BPI-SF=Brief Pain Inventory Short Form.
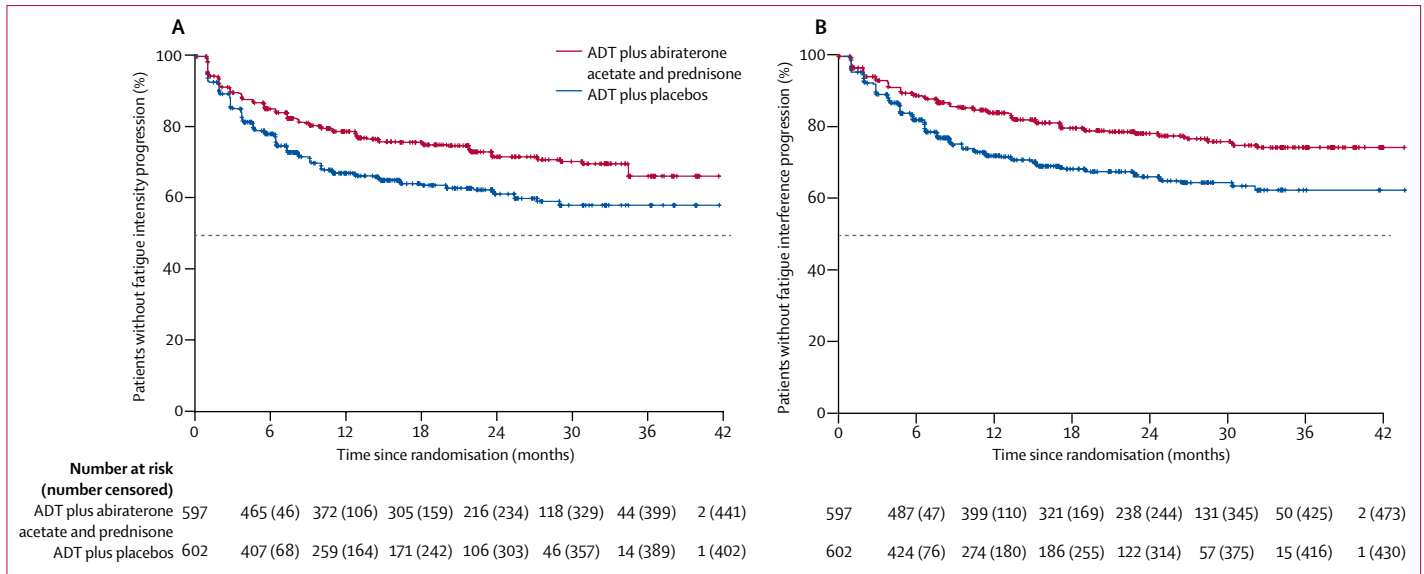
Figure 2: Patient-reported fatigue progression
Kaplan-Meier curves for time to worst fatigue intensity progression (A) and time to fatigue interference progression (B) assessed by BFI. ADT=androgen deprivation therapy. BFI=Brief Fatigue Inventory.

improved with ADT plus abiraterone acetate and prednisone compared with ADT plus placebos at most time points evaluated (figure 1C, D; appendix p 10). Mean change in score was improved in the ADT plus abiraterone acetate and prednisone group as early as cycle 2 and maintained through cycle 33 for all BPI-SF measurements examined except at two data points: cycle 3 for average pain progression and cycle 25 for pain interference (figure 1C, D; appendix p 10).

Median time to worst fatigue intensity was not reached in either the ADT plus abiraterone acetate and prednisone group (not reached [95% CI not reached to not reached]; 25th percentile 18·4 months [95% CI 12·9–27·7]) or the ADT plus placebos group (not reached [95% CI not reached to not reached]; 25th percentile 6·5 months [95% CI 5·6–9·2]; HR 0·65 [95% CI 0·53–0·81]; p=0·0001; figure 2A). Median time to fatigue interference progression was also not reached in either group (for ADT plus abiraterone acetate and prednisone, not reached [95% CI not reached to not reached]; 25th percentile 31·3 months [95% CI 22·1–not reached]; and for ADT plus placebos, not reached [95% CI not reached to not reached]; 25th percentile 9·2 months [95% CI 7·4–12·9]; HR 0·59 [95% CI 0·47–0·75]; p<0·0001; figure 2B). Changes from baseline in worst fatigue intensity and fatigue inteference mean scores, calculated with the repeated-measures mixed-effect model, were improved with ADT plus abiraterone acetate and prednisone compared with ADT plus placebos as early as cycle 5 and maintained through cycle 33 except at two timepoints (cycle 27 for worst fatigue intensity and cycles 19 and 27 for fatigue interference; appendix pp 11–12).

The median time to deterioration ascertained by FACT-P total score was 12·9 months (95% CI 9·0–16·6) in the ADT plus abiraterone acetate and prednisone group versus 8·3 months (95% CI 7·4–11·1) in the ADT plus placebos group (HR 0·85 [95% CI 0·74–0·99]; p=0·032; figure 3A). Table 2 shows the median times to deterioration for all the FACT-P subscales: there were significant differences between the treatment groups for the prostate cancer-specific, pain-related, trial outcome index, and physical wellbeing subscales, while there were no significant differences between groups for the FACT-G general function, emotional, functional, and social and family wellbeing subscales. In repeated-measures analyses using the mixed-effect model, patients in the ADT plus abiraterone acetate and prednisone group had similar or better FACT-P total and subscale scores at most timepoints compared with baseline than did patients in the ADT plus placebos group (figure 3B; appendix pp 13–17).

EQ-5D-5L data indicated better general health status scores (assessed by the EQ-VAS) and health utility scores in patients in the ADT plus abiraterone acetate and prednisone group than in patients in the ADT plus placebos group (figure 4). These improvements were observed throughout the study.

The sensitivity analysis for time to worst pain intensity progression with a threshold of an increase of 2 or more points from baseline in the relevant BPI-SF items, rather than an increase of 30% or more, showed that time to worst pain intensity progression was longer among patients in the ADT plus abiraterone acetate and prednisone group than in those in the ADT plus placebos group (medians were not reached [95% CI not reached to not reached] in both groups; 25th percentiles were
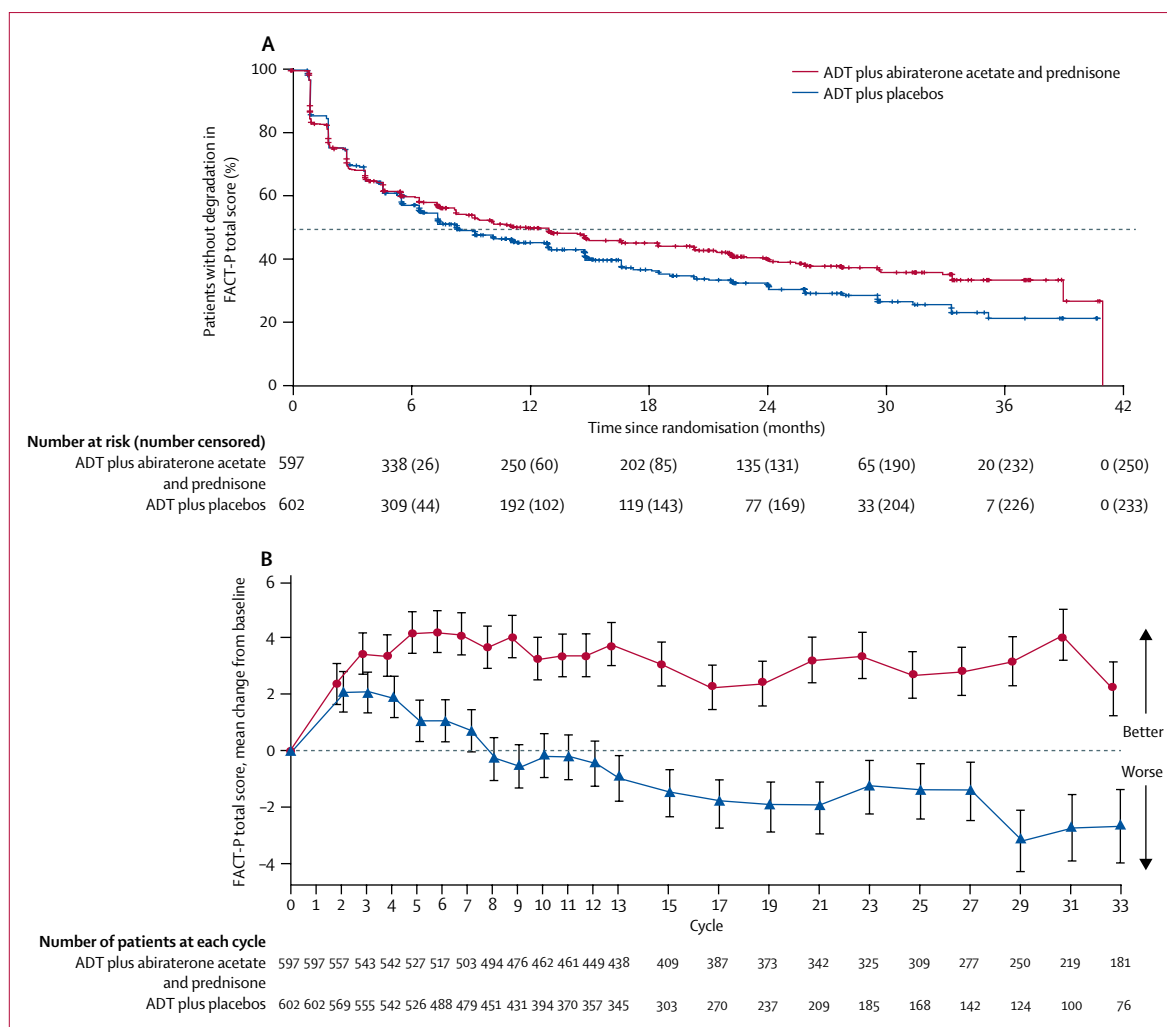
Figure 3: **Patient-reported changes in functional status by FACT-P total score**
Error bars are SEM. Kaplan-Meier curve for time to functional status deterioration assessed by the FACT-P total score (A) and repeated-measures mixed-effects analyses for mean change from baseline in FACT-P total score (B). Each cycle was 28 days long. FACT-P=Functional Assessment of Cancer Therapy-Prostate. ADT=androgen deprivation therapy.

11·1 months [95% CI 9·2–18·4] in the ADT plus abiraterone acetate and prednisone group and 5·6 months [95% CI 4·6–7·4] in the ADT plus placebos group; HR 0·63 [95% CI 0·52–0·77]; p<0·0001).

Discussion

Our PRO analysis from the randomised, phase 3 LATITUDE study shows that ADT plus abiraterone acetate and prednisone consistently improves pain and fatigue symptoms, and overall HRQOL, when compared with those for ADT plus placebo, in patients with newly diagnosed, high-risk metastatic castration-naive prostate cancer. Patients treated with ADT plus abiraterone acetate and prednisone showed significantly longer median time to worst pain intensity progression, worst fatigue intensity progression, and functional deterioration status as assessed by the FACT-P total score or the

prostate cancer-specific subscale than those for patients treated with ADT plus placebo, and maintained or improved HRQOL. Treatment with ADT plus abiraterone acetate and prednisone led to longer median time to deterioration of physical wellbeing; however, median time to deterioration of functional, emotional, and social and family wellbeing did not differ significantly between treatment groups. These results might have been anticipated since wellbeing domains are qualitative and affected by multiple aspects of life and are therefore less likely to be dependent on disease and treatment factors. The collection of PROs from the follow-up period of the study is currently ongoing and additional overall HRQOL results assessed by the EQ-5D-5L might be reported in the future. Because patients who discontinued treatment also discontinued completion of all PRO assessments except for EQ-5D-5L, the comparisons of outcomes

	ADT plus abiraterone acetate and prednisone (n=597)	ADT plus placebos (n=602)	HR (95% CI)	p value
FACT-P total score	12·9 (9·0–16·6)	8·3 (7·4–11·1)	0·85 (0·74–0·99)	0·032
FACT-G general function subscale including physical, social and family, emotional, and functional wellbeing items	12·9 (9·3–18·4)	8·3 (7·4–11·1)	0·87 (0·75–1·01)	0·058
Trial outcome index including physical, functional, and prostate cancer-specific items	18·4 (14·4–22·6)	9·2 (7·4–11·2)	0·73 (0·63–0·85)	0·0001
Pain-related subscale including 4 pain-specific items: GP4 and P1–P3	10·2 (8·3–14·8)	6·5 (5·6–7·5)	0·76 (0·66–0·88)	0·0001
Prostate cancer-specific subscale including additional concerns section items	8·3 (6·5–11·1)	5·6 (4·6–7·3)	0·81 (0·70–0·93)	0·0025
Emotional wellbeing including items GE1–GE6	16·1 (10·2–20·7)	10·2 (8·3–14·8)	0·92 (0·79–1·08)	0·31
Functional wellbeing including items GF1–GF7	7·4 (5·6–9·2)	5·5 (3·8–6·4)	0·89 (0·78–1·03)	0·11
Physical wellbeing including items GP1–GP7	14·4 (10·2–18·2)	7·4 (6·5–9·2)	0·75 (0·65–0·87)	0·0001
Social and family wellbeing including items GS1–GS7	3·8 (2·9–4·7)	5·5 (4·6–6·4)	1·06 (0·92–1·23)	0·38

Data are median (95% CI). ADT=androgen deprivation therapy, HR=hazard ratio. FACT-P=Functional Assessment of Cancer Therapy-Prostate. FACT-G=Functional Assessment of Cancer Therapy-General.

Table 2: Median time to deterioration of functional status (months) in FACT-P total and subscale scores

presented herein are between patients who had not progressed or received subsequent therapies.

This study has several limitations. First, as in any randomised, controlled trial, patients were selected on the basis of specific criteria and the results might not be generalisable to other populations. Second, several PRO measures were collected at different time points and multiplicity could be an issue, although we used repeated-measures analyses to adjust for this over time. Third, there were missing PRO data, and the reasons for this were not centrally recorded. It is possible there were challenges associated with collection of information from this elderly population. No formal imputations for missing data were done, although a sensitivity analysis did not identify a large effect caused by the missing data. Among the strengths of the study, rates of compliance with PRO assessments were high, which we believe might be because of the use of electronic tablets to administer the assessment tools at clinical sites.

The use of PRO assessment tools has been well established in clinical trials of prostate cancer.[14,24,25] Pain, fatigue, specific prostate cancer symptoms (including urination difficulties and sexual dysfunction), and deterioration of overall HRQOL are common problems associated with prostate cancer,[7] and many of these symptoms are also linked to clinical progression. The PRO results described in this analysis are consistent with the primary efficacy analysis of LATITUDE, in which ADT plus abiraterone acetate and prednisone significantly improved overall survival compared with that for ADT plus placebos (median not reached *vs* 34·7 months) and radiographic progression-free survival (33·0 months *vs* 14·8 months).[9] The benefit of adding abiraterone acetate and prednisone to ADT was also shown in results from the STAMPEDE trial,[26] which included 1917 patients with high-risk, locally advanced, or metastatic castration-naive prostate cancer. At a median

follow-up of 40 months, 3-year overall survival rate was 83% with the addition of abiraterone acetate and prednisone to ADT versus 76% with ADT alone (HR 0·63 [95% CI 0·52–0·76]; p<0·001).[26] The improvements in overall survival reported in the LATITUDE trial[9] and in 3-year overall survival in STAMPEDE[26] as well as improvements in HRQOL in LATITUDE reported here indicate that treatment with ADT plus abiraterone acetate and prednisone should be considered as a new option for standard of care for patients with metastatic castration-naive prostate cancer.

The results observed with ADT plus abiraterone acetate and prednisone compare favourably with those reported by patients receiving ADT plus docetaxel, in whom HRQOL is not consistently improved. In the CHAARTED trial,[27] HRQOL was worse in patients with metastatic castration-naive prostate cancer 3 months after ADT plus docetaxel compared with ADT alone and was not improved until the 12-month timepoint, reflecting the minimum time required to recover from treatment. This treatment burden might influence patients' preference for a less toxic therapy option. However, prospective studies have not yet been done to directly compare ADT plus abiraterone acetate and prednisone versus ADT plus docetaxel. Ongoing trials might provide additional insights in this regard.[26]

The improvements in PROs and survival observed with the addition of abiraterone acetate and prednisone to ADT in patients with metastatic castration-naive prostate cancer in the LATITUDE study complement the benefits observed with abiraterone acetate plus prednisone for patients with metastatic castration-resistant prostate cancer.[19,24,28–30] In the phase 3 COU-AA-301 trial in 1195 patients with metastatic castration-resistant prostate cancer who were previously treated with docetaxel, abiraterone acetate and prednisone significantly improved overall survival compared with that for placebo plus prednisone
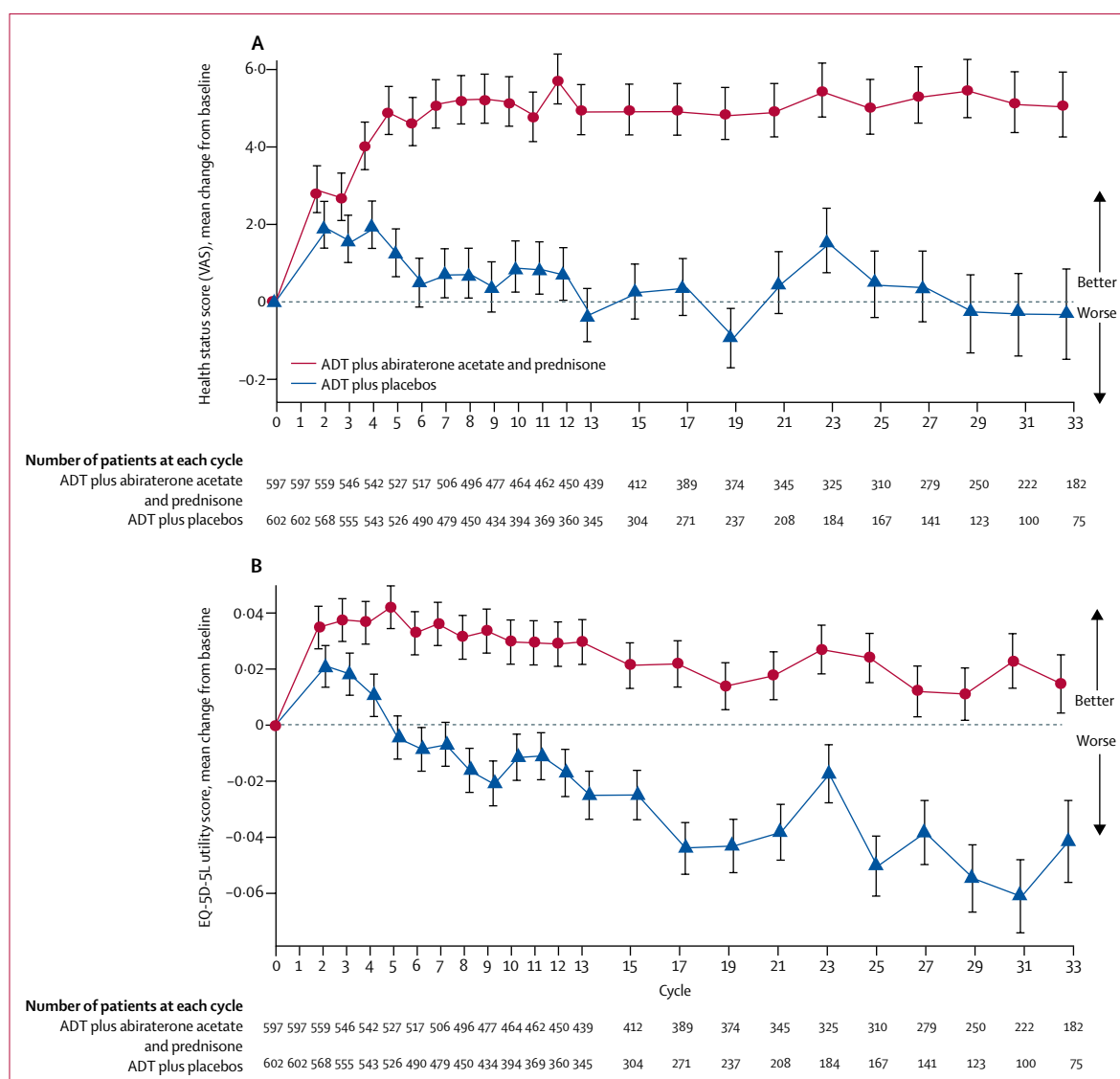
***Figure 4:* Patient-reported changes in HRQOL**
Error bars are SEM. Repeated-measures mixed-effects analyses for health status score assessed by the visual analogue scale (EQ-VAS) of the EQ-5D-5L (A) and health utility score of the EQ-5D-5L (B). Each cycle was 28 days long. ADT=androgen deprivation therapy. EQ-5D-5L=EuroQol five-dimensions, five-levels questionnaire.

(15·8 months *vs* 11·2 months; HR 0·74 [95% CI 0·64–0·86]; p<0·0001).[31] Treatment with abiraterone acetate plus prednisone also resulted in greater pain relief, longer time to pain progression, prevention of skeletal-related events, and a more favourable HRQOL than treatment with prednisone alone.[29] In the phase 3 COU-AA-302 trial, in 1088 patients with chemotherapy-naive metastatic castration-resistant prostate cancer, treatment with abiraterone acetate and prednisone resulted in longer radiographic progression-free survival compared with that for placebo plus prednisone (median 16·5 months *vs* 8·2 months; HR 0·53 [95% CI 0·45–0·61]; p<0·0001) and longer median time to patient-reported pain interference (10·3 months *vs*

7·4 months; 0·80 [0·68–0·93]; p=0·005), median time to deterioration in FACT-P total score (12·7 months *vs* 8·3 months; 0·79 [0·67–0·93]; p=0·005), FACT-P general score (16·6 months *vs* 11·1 months; 0·76 [0·64–0·91]; p=0·002), prostate cancer-specific subscale (11·1 months *vs* 5·8 months; 0·72 [0·61–0·84]; p<0·0001), and trial outcome index (13·9 months *vs* 9·3 months; 0·77 [0·65–0·91]; p=0·002).[30]

Several studies have shown a link between PROs and survival outcomes. Pain in treatment-naive patients with prostate cancer and bone metastases is associated with increased risk of progression to castration-resistant prostate cancer.[32] Therefore, delayed pain progression might be a meaningful clinical benefit indicator. In a

multivariate analysis in patients with prostate cancer, after adjusting for treatment history and disease stage, fatigue (assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire [EORTC-QLQ-C3]) was significantly associated with overall survival,[33] further emphasising the clinical importance of our findings. Meaningful temporal relationships between PROs and survival outcomes have also been shown in patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate and prednisone.[34] In the COU-AA-301 trial, patients with improvements in PRO scores had reduced risk of death and radiographic progression compared with patients with worsening or stable PROs (p<0·0001). Likewise, patients in the COU-AA-302 trial who had worsening PROs had greater risk of radiographic progression compared with patients with improved or stable PROs (p≤0·02). Moreover, results of a trial[35] comparing overall survival in patients with metastatic cancers undergoing chemotherapy who were randomly assigned to either have PROs collected or have routine care showed that active monitoring of PROs was associated with longer survival than was routine care (median overall survival 31·2 months vs 26·0 months; p=0·03). Taken together, these data show the increasing importance and clinical relevance of monitoring PROs in clinical trials.

In conclusion, our findings in combination with the efficacy results from the LATITUDE trial[9] indicate that treatment with ADT plus abiraterone acetate and prednisone could be considered a new option for standard of care for patients with metastatic castration-naive prostate cancer.

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