Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study

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Summary

Background In the phase 3 TITAN study, the addition of apalutamide to androgen deprivation therapy (ADT) significantly improved the primary endpoints of overall survival and radiographic progression-free survival in patients with metastatic castration-sensitive prostate cancer. We aimed to assess health-related quality of life (HRQOL) in TITAN, including pain and fatigue.

Methods In this randomised, placebo-controlled, double-blind, phase 3 study, patients with metastatic castration-sensitive prostate cancer (defined as not receiving ADT at the time of metastatic disease progression) aged 18 years and older, receiving continuous ADT (selected at the investigator's discretion), and with an Eastern Cooperative Oncology Group performance status score of 0 or 1 were randomly assigned (1:1), using an interactive web response system, to receive oral apalutamide (four 60 mg tablets, once daily) or matching placebo. Previous localised disease treatment or previous docetaxel for metastatic castration-sensitive prostate cancer were allowed. Randomisation was stratified by Gleason score at diagnosis, region, and previous docetaxel treatment. Randomisation was done using randomly permuted blocks (block size of four). Investigators, research staff, sponsor study team, and patients were masked to the identities of test and control treatments. Patient-reported outcomes were prespecified exploratory endpoints and were the Brief Pain Inventory-Short Form (BPI-SF), Brief Fatigue Inventory (BFI), Functional Assessment of Cancer Therapy-Prostate (FACT-P), and EuroQoL 5D questionnaire 5 level (EQ-5D-5L). BPI and BFI were completed for 7 consecutive days (days –6 to 1 inclusive of each cycle visit), then at months 4, 8, and 12 in follow-up. FACT-P and EQ-5D-5L were completed during cycles 1–7, then every other cycle until the end of treatment, and at months 4, 8, and 12 in follow-up. Analyses were based on the intention-to-treat population. Missing patient-reported outcome assessments were calculated as the expected number of assessments for a visit minus the actual number of assessments received for that visit. For time-to-event endpoints, when median values could not be calculated because less than 50% of patients had degradation, 25th percentiles were compared. This study is registered with ClinicalTrials.gov, number NCT02489318, and is ongoing.

Findings Between Dec 9, 2015, and July 25, 2017, 1052 eligible patients were enrolled randomly assigned to apalutamide (n=525) or placebo (n=527). Data cutoff for this analysis of patient-reported outcomes was Nov 23, 2018. Median follow-up for time to pain-related endpoints ranged from 19·4 to 22·1 months. Patients were mostly asymptomatic at baseline: on the BPI-SF pain severity scale of 0–10, median pain scores (indicating worst pain in the past 24 h) were 1·14 (IQR 0–3·17) in the apalutamide group and 1·00 (0–2·86) in the placebo group, and median worst fatigue scores on the BFI were 1·29 (IQR 0–3·29) in the apalutamide group and 1·43 (0·14–3·14) in the placebo group. Patient experience of pain and fatigue (intensity and interference) did not differ between the groups for the duration of treatment. Median time to worst pain intensity progression was 19·09 months (95% CI 11·04–not reached) in the apalutamide group versus 11·99 months (8·28–18·46) in the placebo group (HR 0·89 [95% CI 0·75–1·06]; p=0·20). Median time to pain interference progression was not reached in either group (95% CI 28·58–not reached in the apalutamide group; not reached–not reached in the placebo group). 25th percentiles for time to pain interference progression were 9·17 months (5·55–11·96) in the apalutamide group and 6·24 months (4·63–7·43) in the placebo group (HR 0·90 [95% CI 0·73–1·10]; p=0·29). FACT-P total scores and EQ-5D-5L data showed preservation of HRQOL in both groups. The median time to deterioration as determined by FACT-P total score was 8·87 months (95% CI 4·70–11·10) in the apalutamide group and 9·23 months (7·39–12·91) in the placebo group (HR 1·02 [95% CI 0·85–1·22]; p=0·85).

Interpretation Apalutamide with ADT is a well-tolerated and effective option for men with metastatic castration-sensitive prostate cancer. The combination significantly improves survival outcomes compared with ADT alone while maintaining HRQOL despite additive androgen blockade.

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Research in context

Evidence before this study

We searched EMBASE, Medline, and the Cochrane Library, for studies published from inception to Dec 31, 2017, using the terms "prostate cancer", "androgen deprivation therapy (ADT)", "antiandrogen", "androgen blockade/receptor/dependent/ablation/suppression", "anti-androgen", "luteinis(z)ing hormone", "gonadotropin releasing hormone", brand names and generic drug names of multiple treatments, "randomis(z)ed controlled trial", "randomis(z)ation", "controlled trial", "single blind", "double blind", "crossover/cross over procedure", and "placebo". We included case studies, letters, editorials, reviews, and primary data manuscripts. The searches identified 13 unique studies (all randomised controlled trials), with 18 publications reporting on health-related quality of life (HRQOL). The addition of docetaxel or abiraterone acetate plus prednisone to ADT has improved the overall survival and has become a standard approach for patients with metastatic castration-sensitive prostate cancer. However, the addition of docetaxel increases high-grade fatigue and neutropenia, and therefore might not be an optimal treatment option in elderly or frail patients. The frequent laboratory monitoring required with abiraterone acetate plus prednisone might be challenging in patients with comorbid conditions. On the basis of these results and the unmet need for alternative treatment options, the phase 3 TITAN study was done to assess the addition of apalutamide versus placebo to ADT in a broad population of patients with metastatic castration-sensitive prostate cancer. Patient-reported outcome data were prospectively collected and analysed as predefined endpoints.

Added value of this study

In addition to the improved survival that has been reported previously, in the TITAN study, low baseline pain and fatigue levels in patients with metastatic castration-sensitive prostate cancer did not worsen with the addition of apalutamide to ADT, and their overall HRQOL was preserved with no difference versus placebo plus ADT.

Implications of all the available evidence

The improvements in survival and maintenance of HRQOL shown in the TITAN study indicated that treatment with apalutamide plus ADT should be considered a new option for standard of care for a broad range of patients with metastatic castration-sensitive prostate cancer.

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Introduction

Prostate cancer is the second most common cancer in men worldwide, with an estimated 1·28 million new cases and approximately 359 000 deaths in 2018.[1] Up to 6% of patients with prostate cancer in the USA and more than 50% in some regions such as Indonesia have metastatic disease at diagnosis.[2,3] In the USA, between 2009 and 2015, 5-year relative survival was approximately 31% for patients with metastatic disease.[3]

Androgen deprivation therapy (ADT) has long been the standard of care for patients with metastatic prostate cancer.[4] Although patients typically respond to ADT initially, most become castration-resistant within 11 months to 2 years[5,6] and will, at some point, have a higher symptomatic burden associated with disease progression.[7] Studies have shown improved survival in patients treated with ADT in combination with other drugs at the time of initial ADT administration, or shortly after, while the disease remains castration-sensitive.

Apalutamide is an non-steroidal androgen receptor inhibitor, taken orally, that binds directly to the ligand-binding domain of the androgen receptor, preventing androgen receptor nuclear translocation and DNA binding, and impeding androgen receptor-mediated transcription.[8] Apalutamide is approved in several regions around the world, including the USA[9] and the EU,[10] for the treatment of patients with non-metastatic, castration-resistant prostate cancer. The TITAN study investigated apalutamide versus placebo in patients with metastatic castration-sensitive prostate cancer who were receiving concomitant ADT. Substantial benefits were shown for apalutamide plus ADT versus placebo plus ADT on both of the dual primary endpoints of overall survival (hazard ratio [HR] 0·67 [95% CI 0·51–0·89]; p=0·005) and radiographic progression-free survival (HR 0·48 [95% CI 0·39–0·60]; p<0·001),[11] as well as for the time to initiation of cytotoxic chemotherapy (apalutamide *vs* placebo: HR 0·39 [0·27–0·56]; p<0·001).[11] Importantly, TITAN enrolled a broad population of patients with metastatic castration-sensitive prostate cancer, including those with low-volume and high-volume disease, low-risk and high-risk disease, previous docetaxel use, and previous localised disease treatment.[11] On the basis of results from the final analysis for radiographic progression-free survival and the first interim analysis for overall survival, the independent data monitoring committee recommended unblinding the study and allowing patients receiving placebo the opportunity to cross over to apalutamide.

Whether new treatment approaches offer a survival benefit without compromising patient health-related quality of life (HRQOL) is important to investigate.[12] Patient-reported outcomes can provide meaningful data about disease symptoms, treatment tolerance, and overall HRQOL; are essential to clinicians and patients making treatment choices; and have increasing importance to regulatory agencies around the world when approving drug therapies.[13–16] We present the results of the prespecified analysis of patient-reported outcomes in TITAN.

Methods

Study design and participants

TITAN was a phase 3, randomised, double-blind, placebo-controlled study that compared apalutamide with placebo in patients with metastatic castration-sensitive prostate cancer (defined as not receiving ADT at the time of metastatic disease progression) who were receiving ADT. Patients were recruited at 260 sites, including hospitals, and urology and oncology clinics, in 23 countries in Europe, North America, South America, and the Asia-Pacific region (appendix pp 3–7). Eligible patients were aged 18 years or older and had adenocarcinoma of the prostate (confirmed by the investigator), with metastatic disease documented by at least one bone lesion on technetium-99m bone scan, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Permitted previous therapies included six or fewer cycles of docetaxel, and ADT for 6 months or less for metastatic castration-sensitive prostate cancer or 3 years or less for localised prostate cancer. All treatments for localised prostate cancer must have been completed for at least 1 year before randomisation. Patients with unstable angina, myocardial infarction, congestive heart failure, arterial or venous thromboembolic events within 6 months or less of randomisation, known brain metastases, or history of or predisposition for seizure were excluded. Laboratory exclusion criteria included haemoglobin less than 9·0 g/dL, neutrophils less than $1·5 \times 10^9$/L, platelets less than 100×10^9/L, total bilirubin more than 1·5 times the upper limit of normal, alanine aminotransferase or aspartate aminotransferase more than 2·5 times the upper limit of normal, serum creatinine more than 2·0 times the upper limit of normal, and serum albumin less than 3·0 g/dL. Other inclusion and exclusion criteria are described in the appendix (p 8). Review boards at all participating institutions approved the trial, which was done in accordance with International Conference on Harmonisation guidelines for Good Clinical Practice and according to the principles of the Declaration of Helsinki. All patients provided written informed consent.

See Online for appendix

Randomisation and masking

Patients were randomly assigned (1:1) to receive apalutamide or placebo in addition to continuous ADT and stratified according to Gleason score at diagnosis (≤7 *vs* >7), region (North America and the EU *vs* all other countries), and previous docetaxel treatment (yes *vs* no). Randomisation was done using randomly permuted block sizes of four. Patients were assigned unique identifiers via a centralised interactive web response system. Investigators, research staff, sponsor study team, and patients were masked to the identities of test and control treatments. Until unblinding on Jan 28, 2019, only selected individuals unaffiliated with the protocol or independent data safety monitoring committee members (for purposes of efficacy analyses and safety review) were unmasked to individual patient treatment assignments during the study (appendix p 9).

Procedures

Eligible patients were randomly assigned to receive apalutamide (240 mg, given as four 60 mg tablets) or matching placebo, administered orally once daily, with or without food, in addition to continuous ADT.[11] Selection of ADT was at the investigator's discretion; patients had either surgical castration or were on a stable regimen of gonadotropin-releasing hormone agonist or antagonist, which had to be started at least 14 days before randomisation. Each treatment cycle lasted 28 days. Treatment continued until disease progression, withdrawal of consent, or unacceptable treatment-related toxicity. Apalutamide dose interruptions were allowed for grade 3 or worse drug-related toxicities or for grade 2 or worse drug-related rash. Dose reductions of apalutamide to 180 mg or 120 mg were permitted in the event of recurrent grade 3 or worse drug-related toxicities or grade 2 or worse (or symptomatic grade 1) rash.

Efficacy was assessed by investigators according to a modified version of the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, using CT or MRI of the chest, abdomen, and pelvis during screening (≤6 weeks before randomisation) and according to Prostate Cancer Working Group 2[17] criteria, with the use of bone scanning during cycles three and five and every fourth cycle thereafter. Scans from approximately 60% of patients were randomly selected for independent central review.[11] Adverse events and laboratory monitoring (including haematology, liver function, and prostate-specific antigen level) were assessed every cycle until cycle 13, then every two cycles until cycle 25, and every four cycles thereafter, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Clinical outcome assessments are described in the appendix (p 8). Patient-reported outcome instruments were administered allowing patients to report pain, fatigue, prostate cancer symptoms, and HRQOL. Instruments were the Brief Pain Inventory-Short Form (BPI-SF),[18,19] the Brief Fatigue Inventory (BFI),[20] Functional Assessment of Cancer Therapy–Prostate (FACT-P; version 4),[21–23] and the EuroQoL five dimensions, five-levels questionnaire (EQ-5D-5L; appendix p 8).[24,25] BPI and BFI were completed for 7 consecutive days (days –6 to 1 inclusive of each cycle visit), then at months 4, 8, and 12 in follow-up. FACT-P and EQ-5D-5L were completed during cycle one to cycle seven, then every other cycle until the end of treatment, and at months 4, 8, and 12 in follow-up. Because patient-reported outcome assessments were collected by treatment cycle, per the study protocol, the patient-reported outcome results over time are reported in the same manner, by treatment cycle. Because pain can worsen before and after detection of radiographic progression, we assessed patient pain and other aspects of HRQOL after progression.

Outcomes

The primary endpoints in TITAN were overall survival and radiographic progression-free survival, as reported previously.[11] Secondary endpoints were times to pain progression, skeletal-related event, chronic opioid use, and to initiation of cytotoxic chemotherapy.[11] Time to pain or fatigue progression was defined as the time from randomisation to the first date a patient had a worsening of pain or fatigue scores by 2 points or more, observed at two consecutive assessments at least 4 weeks (BPI-SF) or 3 weeks (BFI) apart. We report data from the treatment phase for the prespecified patient-reported outcome exploratory endpoints of pain, fatigue, prostate cancer symptoms, and overall HRQOL.

Statistical analysis

Enrolment of approximately 1000 patients was planned. If the difference in radiographic progression-free survival between the apalutamide and placebo groups was statistically significant, the α was applied to overall survival. An overall type I error of 5% was planned. 368 radiographic progression events were required to provide at least 85% power to detect an HR of 0·67, with a two-tailed significance level of 0·005.[11] For the final overall survival analysis, 410 deaths were required to provide approximately 80% power to detect an HR of 0·75, with a two-tailed significance level of 0·045. Two interim analyses were planned. The protocol was amended on April, 8, 2016, to expand enrolment to include patients with high-volume disease.

The statistical analysis plan for evaluation of patient-reported outcome data in this first, preplanned interim analysis, is available on appendix p 132. Patient-reported outcomes, namely BPI-SF, BFI, FACT-P, and EQ-5D-5L, were prespecified exploratory endpoints of the TITAN clinical study. TITAN was powered for the dual primary endpoints of overall survival and radiographic progression-free survival and was not specifically powered for the exploratory endpoints reported here. Here, patient-reported outcome results from the same data cutoff (Nov 23, 2018) as the first interim analysis for overall survival and final analysis for radiographic progression-free survival, of this ongoing study, are reported.

The intention-to-treat population included all randomly assigned patients, classified according to their assigned treatment group regardless of the actual treatment received. The analysis population for patient-reported outcomes was based on the intention-to-treat population (patients who complied with patient-reported outcome assessments were considered assessable), and patient disposition and efficacy analyses were done in this population.

Descriptive statistics (number of observations, mean [SD], median (IQR), and range) of scores at baseline and at follow-up assessments by treatment group were produced for each prespecified patient-reported outcome scale, and the mean (SD) were calculated over time (appendix p 9). The proportional hazards assumption for the time-to-event outcomes was assessed by verifying that the plots of the complementary log–log survival function between treatment groups over time were approximately parallel. For each patient-reported outcome measure, patient compliance (expected *vs* received) was tabulated and provided as a percentage for each visit and for the study, by treatment group and overall. For BPI-SF and BFI, when at least one patient-reported outcome was available for 7 days, the non-missing data for the cycle were considered. The missing patient-reported outcome assessments were calculated as the expected number of assessments for a visit minus the actual number of assessments received for that visit. Compliance to patient-reported outcome assessments was tabulated by treatment group and overall for baseline and each scheduled visit during the treatment and follow-up phases. In case of a substantial amount of missing data during later treatment cycles, truncation was applied for all subsequent visits at the first visit at which 90% or more of the patients were missing for any endpoint and from either treatment group. Once the truncation cycle was determined, the truncation was applied to both treatment groups.

Time to pain, fatigue, and HRQOL degradation was defined as the time from randomisation to the first date that a patient had a clinically meaningful threshold change in score on a patient-reported outcome scale (appendix p 11).[22] Median time to degradation was estimated for each patient-reported outcome scale using the Kaplan-Meier method, and HRs and 95% CIs were calculated using the Cox proportional hazards model, stratified by baseline stratification factors. When median values could not be calculated because less than 50% of patients had degradation, 25th percentiles were compared. For the pain and fatigue progression endpoints, patients with no pain or fatigue progression were censored at the date of their last assessment. To determine the time of event censoring, assessments in both treatment and follow-up phases were included. Time to pain intensity progression (worst pain in the past 24 h) was defined as an increase of 30% or more in worst pain (item BPI3 of the BPI-SF), without reduction in opioid use, observed at two consecutive assessments at least 3 weeks apart. An additional sensitivity analysis assessed time to pain intensity progression using a two-point increase in worst pain, confirmed at least 3 weeks later without decrease in opioid use. Time to pain interference progression was defined as an increase of half an SD of baseline BPI-SF interference score confirmed at two consecutive evaluations at least 3 weeks apart, without a decrease in opioid use. Time to average pain progression was defined as the elapsed time between randomisation and the first BPI-SF assessment date after baseline when a patient experienced a 30% or more increase from baseline in BPI-SF (average of BPI items 3–6), observed at two consecutive assessments at least 3 weeks apart, without decrease in opioid use.

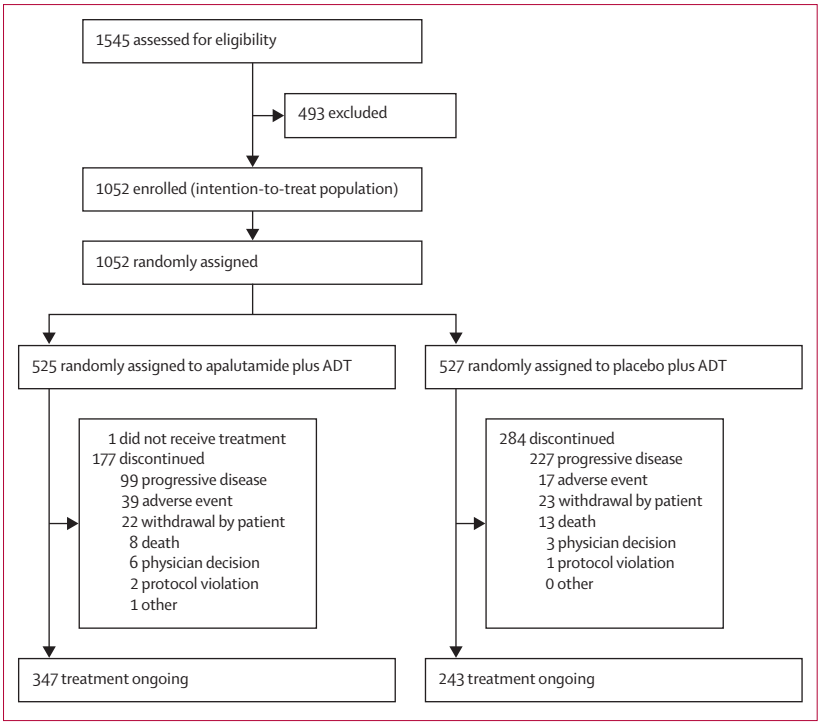


Figure 1: **Trial profile**
ADT=androgen deprivation therapy. Adapted from Chi et al,[11] by permission of Massachusetts Medical Society.

Several sensitivity analyses were done, including elimination of the requirement for an absolute score of greater than 4 on the BPI-SF pain scale, extension of the BPI-SF data collection to 4 days, or removal of the requirement for confirmation of BPI-SF pain score. Time to pain progression was defined as the time from the date of randomisation to the date of the first observation of worsening pain scores by 2 points or more on two consecutive assessments.

Time to fatigue intensity progression was defined as the time from randomisation to the first date with an increase of 2 points or more from baseline in the worst BFI intensity item (item 3) observed at two consecutive assessments 3 weeks or more apart, and fatigue interference progression as an increase of at least 1·25 points from baseline in the average BFI interference score observed at two consecutive assessments 3 weeks or more apart.

Post-hoc analyses included the proportion of patients whose pain intensity remained stable, improved by 1 or 2 points or more, or worsened by 1 or 2 points or more, analyses of patients grouped by no pain (score of 0 on the BPI-SF), mild pain (scores of 1–3), moderate pain (scores of 4–7), or severe pain (scores of 8–10) at baseline, and change from baseline in BPI-SF, BFI, FACT-P, and EQ-5D-5L using a mixed model of repeated measure (appendix p 9).

Major protocol deviations and amendments to the study protocol that might have affected enrolment are described in the appendix (p 9). SAS (version 9.4) was used for all statistical analyses. The appendix contains the TITAN study protocol (p 29) and statistical analysis plan (p 132) for patient-reported outcomes. This study is registered with ClinicalTrials.gov, NCT02489318.

Role of the funding source

This study was designed by employees of the sponsor and academic authors and the protocol steering committee, and data collection was funded by the sponsor, and data were analysed by sponsor-employed statisticians. KM, BM, LD, KD, VN, and ALG had access to the raw data. All authors participated in interpretation of the data and preparation of the manuscript. The manuscript was written with editorial support from medical writers, which was 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 Dec 9, 2015, and July 25, 2017, 1545 patients were assessed for eligibility, of whom 493 patients did not pass screening and were not randomly assigned. 1052 eligible patients were enrolled and randomly assigned to the apalutamide (n=525) or placebo (n=527) groups (figure 1). At the clinical cut-off date (for the primary analysis and the current analysis)—Nov 23, 2018—median follow-up for overall survival was 22·7 months (IQR 19·4–25·8). Clinical results from the first interim analysis have been reported previously.[11] Patients in the apalutamide group received protocol treatment for a median of 20·5 months (IQR 14·9–24·7) and patients in the placebo group were treated for a median of 18·3 months (10·3–22·9). The median time from initiation of ADT to randomisation was 1·8 months (IQR 0·9–3·5) in the apalutamide group and 1·8 months (0·9–3·5) in the placebo group.

Patient demographic and clinical characteristics at baseline were similar between groups (table) and have been reported previously.[11] The median age was 69 years (IQR 63–75) in the apalutamide group and 68 years (62–74) in the placebo group. 719 (68%) of 1052 patients were white; 676 (64%) had an Eastern Cooperative Oncology Group performance status of 0; 660 (63%) had high-volume disease; 173 (16%) had previous prostatectomy or radiotherapy; and 113 (11%) had previous docetaxel treatment. Patients had few pain or fatigue symptoms when they began apalutamide or placebo treatment; 800 (76%) patients had mild or no pain, and 792 (75%) had mild or no fatigue.

The median follow-up time for pain progression was 22·1 months (IQR 18·4–25·6) for the apalutamide group and 21·7 months (18·4–24·9) for the placebo group; for worst pain 20·2 months (16·6–24·0) for the apalutamide group and 19·4 months (14·8–23·4) for the placebo group; for average pain progression 20·3 months (16·6–24·0) for the apalutamide group and 19·6 months (15·1–23·4) for the placebo group; and for pain

interference progression 20·3 months (16·6–24·6) for the apalutamide group and 19·7 months (15·6–24·0) for the placebo group. Cumulative compliance was greater than 95% for BPI-SF and BFI, and 75–85% for FACT-P and EQ-5D-5L during 13 cycles of therapy, and compliance was similar between treatment groups (data not shown). Cumulative patient disposition by treatment group during the first 13 cycles is summarised in the appendix (pp 10, 12). After cycle 13, compliance remained high (approximately 90%) for BPI-SF and BFI and seemed to be associated with clinic visits (data not shown). For cycles that were not associated with clinic visits, compliance ranged from 75% to 85% (data not shown). Compliance for FACT-P and EQ-5D-5L was approximately 80% after cycle 13 (expected compliance and reasons for non-compliance shown in the appendix [p 10]).

Patients had few pain-related symptoms at baseline. Median BPI-SF pain scores indicating worst pain in the past 24 h were 1·14 (IQR 0–3·17) in the apalutamide group and 1·00 (0–2·86) in the placebo group. At baseline, 198 (38%) of 525 patients in the apalutamide group and 200 (38%) of 527 in the placebo group reported no pain, and 195 (37%) in the apalutamide group and 207 (39%) in the placebo group reported mild pain.

Time to pain progression, per BPI-SF, was a secondary endpoint and was reported in the primary efficacy analysis.[11] Briefly, median time to pain progression was not reached in either group (95% CI not reached in both groups); 25th percentiles were 20·53 months (95% CI 16·10–not reached) in the apalutamide group and 14·78 months (11·07–19·81) in the placebo group (HR 0·83 [0·65–1·05]; p=0·12). Results of sensitivity and exploratory analyses were consistent with the time to pain progression endpoint results (figure 2). Median time to worst pain intensity progression was 19·09 months (IQR 1·94–not reached; 95% CI 11·04–not reached) in the apalutamide group and 11·99 months (1·91–not reached; 8·28–18·46) in the placebo group and was similar between groups (HR 0·89 [95% CI 0·75–1·06]; p=0·20).

Median time to pain interference progression was not reached in either group (95% CI 28·58–not reached in the apalutamide group; not reached–not reached in the placebo group). 25th percentiles for time to pain interference progression were 9·17 months (5·55–11·96) in the apalutamide group and 6·24 months (4·63–7·43) in the placebo group. Therefore, time to pain interference progression was similar between groups (HR 0·90 [95% CI 0·73–1·10]; p=0·29). Median time to average pain progression was 22·11 months in the apalutamide group (IQR 2·79–not reached; 95% CI 13·83–not reached [25th percentile 2·79 months; 95% CI 1·91–3·71]) and 14·72 months in the placebo group (IQR 2·66–not reached; 95% CI 10·25–22·05 [25th percentile 2·66 months; 95% CI 1·87–2·79]) and was similar between groups (HR 0·89 [95% CI 0·74–1·05]; p=0·15).

	Apalutamide group (n=525)	Placebo group (n=527)
Age, years		
<65	149 (28%)	182 (35%)
65–69	136 (26%)	108 (20%)
70–74	107 (20%)	124 (24%)
≥75	133 (25%)	113 (21%)
Race		
White	354 (67%)	365 (69%)
Asian	119 (23%)	110 (21%)
Black or African–American	10 (2%)	9 (2%)
Other	24 (5%)	22 (4%)
Not reported	11 (2%)	8 (2%)
ECOG performance status		
0	328 (62%)	348 (66%)
1	197 (38%)	178 (34%)
Gleason score at initial diagnosis		
<7	41 (8%)	39 (7%)
7	133 (25%)	130 (25%)
8	161 (31%)	154 (29%)
9	165 (31%)	174 (33%)
10	25 (5%)	30 (6%)
Subgroup of mCSPC		
High-volume disease	325 (62%)	335 (64%)
Low-volume disease	200 (38%)	192 (36%)
Previous prostate cancer therapy		
Prostatectomy or radiotherapy	94 (18%)	79 (15%)
Hormonal therapy	525 (100%)	527 (100%)
Docetaxel	58 (11%)	55 (10%)
Vandetanib	1 (<1%)	0
BPI-SF pain score*		
N	503 (96%)	513 (97%)
0 (no pain)	198 (38%)	200 (38%)
1–3 (mild)	195 (37%)	207 (39%)
4–7 (moderate)	98 (19%)	95 (18%)
8–10 (severe)	12 (2%)	11 (2%)
BFI fatigue†		
N	503 (96%)	513 (97%)
0 (no fatigue)	170 (32%)	177 (34%)
1–3 (mild)	222 (42%)	223 (42%)
4–7 (moderate)	99 (19%)	96 (18%)
8–10 (severe)	12 (2%)	17 (3%)
FACT-P score		
Median FACT-P total score (IQR)	113 (98–128)	113 (99–127)

Data are n (%), unless otherwise specified. Percentages are based on the intention-to-treat population of each treatment group (as denominator). BFI=Brief Fatigue Inventory. BPI-SF=Brief Pain Inventory-Short Form. ECOG=Eastern Cooperative Oncology Group. FACT-P=Functional Assessment of Cancer Therapy-Prostate. mCSPC=metastatic castration-sensitive prostate cancer. *Worst pain during past 24 h, based on the average of a maximum of the seven records closest to the first dose using a window of 14 days before with a minimum of 1 day. †Worst fatigue during past 24 h.

Table: **Baseline characteristics of the intention-to-treat population**

On the basis of repeated-measures mixed-effects model analysis, mean changes from baseline in pain intensity and pain interference were similar between the groups; differences were not statistically significant (figure 3). Repeated-measures mixed-effects modelling also showed that worst pain intensity

	Events (n/N)		HR (95% CI)
	Apalutamide group	Placebo group	
Pain progression (≥2 points to >4 points, minimum 1 day)	128/525	148/527	0·828 (0·653–1·049)
Pain progression (≥2 points, minimum 1 day)	182/525	207/527	0·853 (0·699–1·042)
Pain progression (≥2 points to >4 points, minimum 4 days)	120/525	143/527	0·803 (0·630–1·024)
Pain progression (≥2 points to >4 points, minimum 1 day no confirm)	190/525	207/527	0·899 (0·738–1·096)
Pain intensity (≥30%)	242/525	271/527	0·890 (0·747–1·062)
Pain intensity (≥2 points)	151/525	173/527	0·862 (0·692–1·074)
Pain interference	176/525	191/527	0·895 (0·728–1·100)
Average pain	237/525	262/527	0·878 (0·735–1·049)

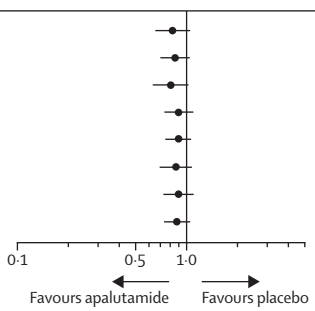
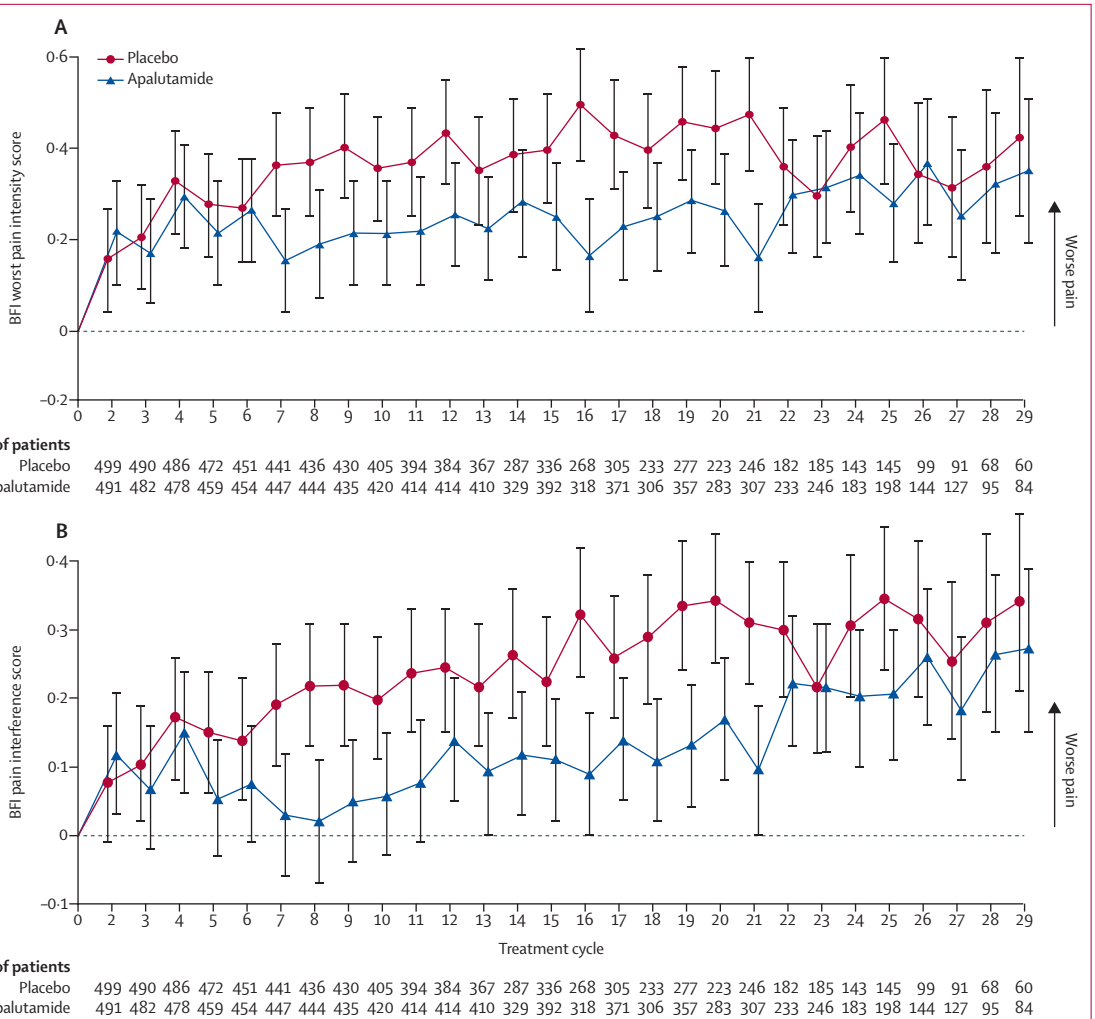


Figure 2: **Forest plot of sensitivity and exploratory analyses of time to pain progression**
HR=hazard ratio. Plotted points are HRs and error bars are 95% CIs.



(Figure 3 continues on next page)

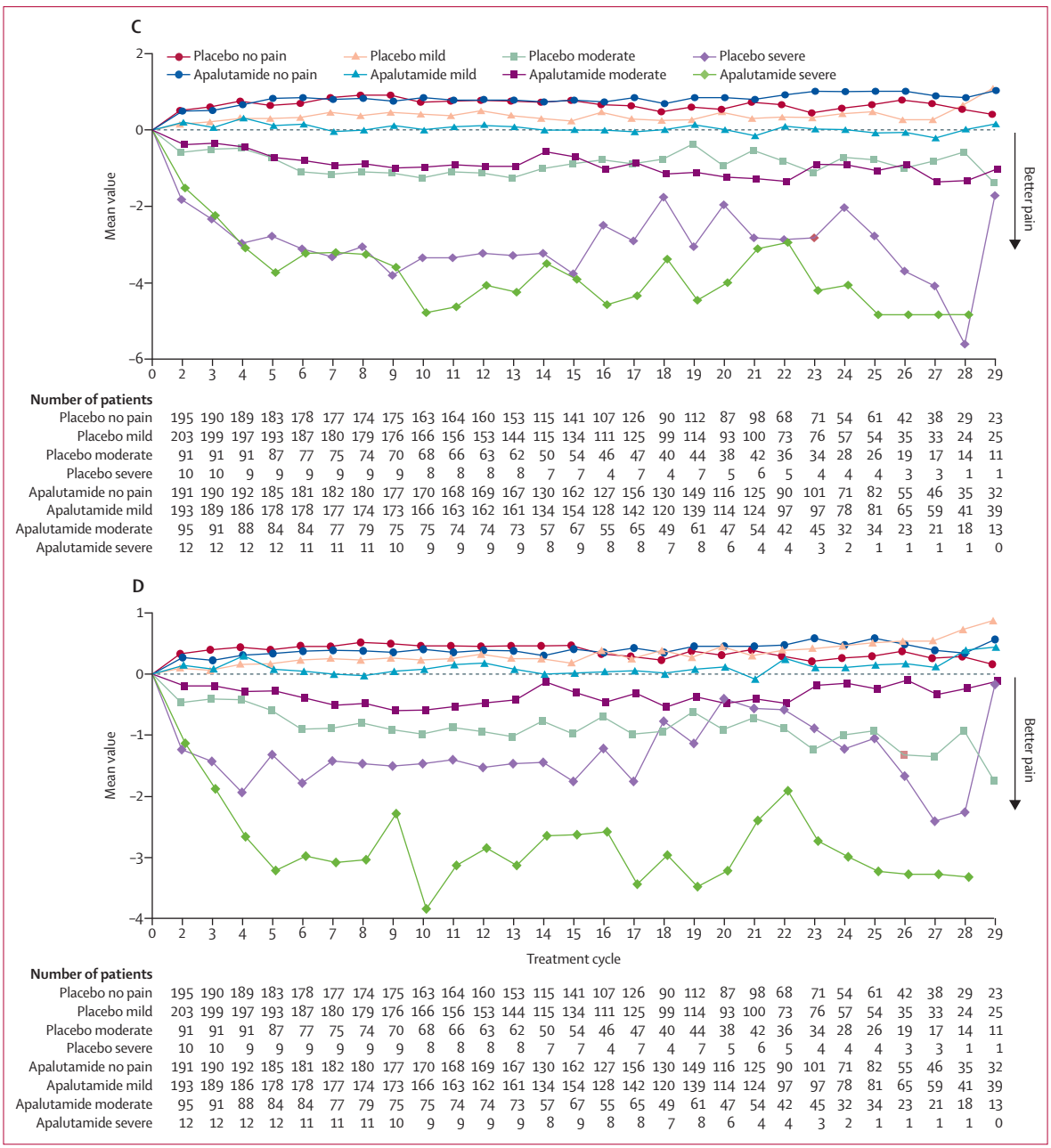


Figure 3: **Patient-reported changes in pain from baseline by BPI-SF**

Error bars are the standard error of the mean. Repeated-measures mixed-effects analyses for mean change from baseline in BPI-SF (A) worst pain intensity, (B) pain interference, (C) worst pain intensity as stratified by baseline worst pain intensity, and (D) mean pain interference as stratified by baseline pain. Data from 29 treatment cycles are presented. BPI-SF=Brief Pain Inventory-Short Form.

was unchanged over time and was similar between groups (appendix p 12).

Incremental improvements corresponding to baseline pain severity were observed in an additional post-hoc analysis done to assess the proportion of patients whose pain remained stable, worsened, or improved, which showed that for most patients pain remained stable or improved. A similar analysis was done with patients grouped by baseline pain level: no pain (score of 0 on the BPI-SF), mild (scores 1–3), moderate (scores 4–7), or severe pain (scores 8–10). The largest proportion of patients had no pain at baseline and remained stable, most patients with mild pain at baseline remained stable or improved, and most with moderate or severe pain at baseline improved by at least 1 point (appendix pp 13–16). Greater proportions of pain intensity improvement were observed in patients who had greater severity of pain at baseline; the proportion of patients with severe pain at

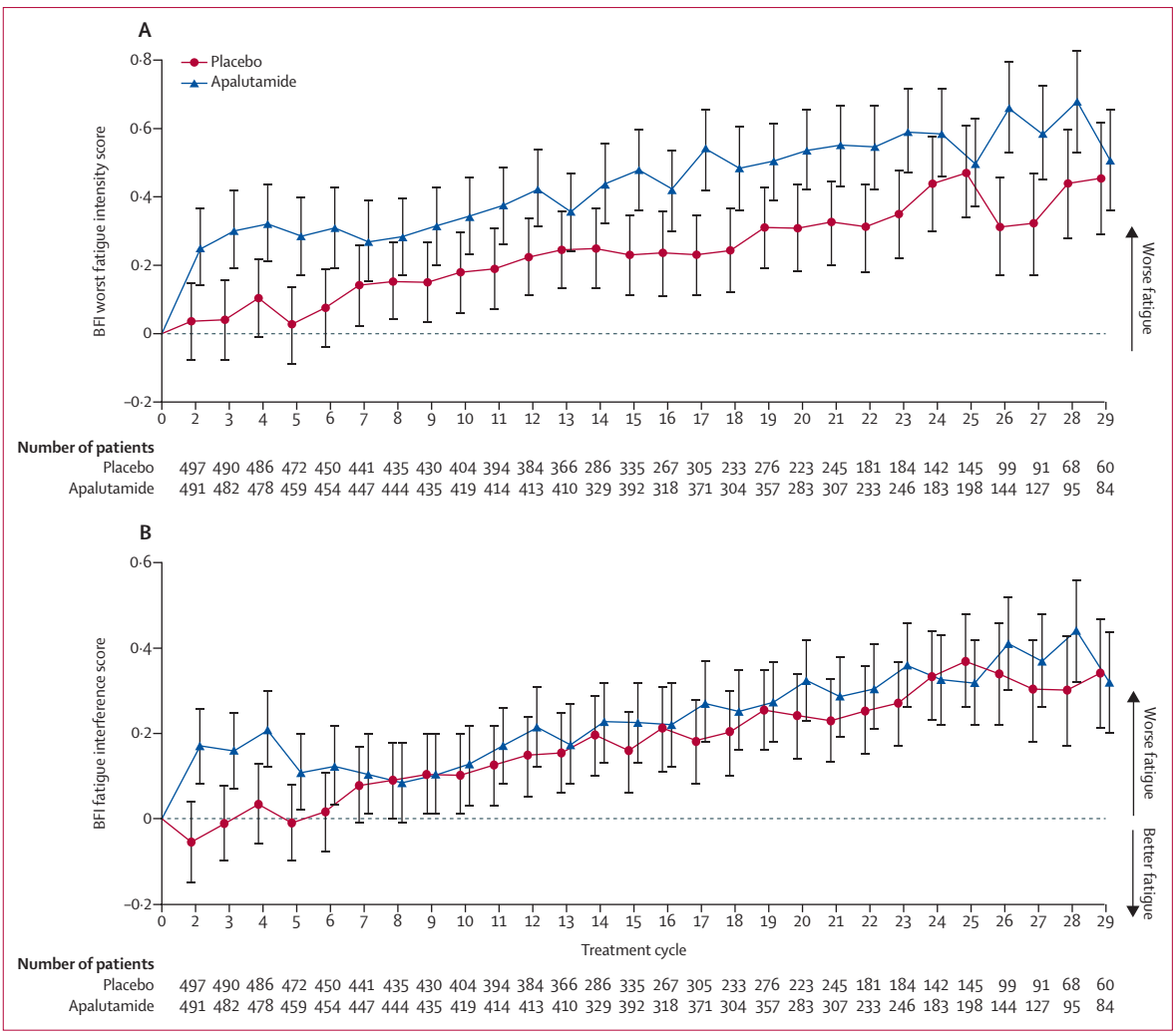


Figure 4: **Patient-reported changes in fatigue by BFI**
Error bars are the standard error of the mean. Repeated-measures mixed-effects analyses for mean change from baseline in BFI (A) worst fatigue intensity and (B) fatigue interference. BFI=Brief Fatigue Inventory.

baseline who had improvement of 2 points or more was greater in the apalutamide group than in the placebo group from cycle 5 to the end of study (appendix pp 13–16).

Patients had few fatigue-related symptoms at baseline; median worst fatigue score on the BFI was 1·29 (IQR 0–3·29) in the apalutamide group and 1·43 (0·14–3·14) in the placebo group. 170 (32%) of 525 patients in the apalutamide group and 177 (34%) of 527 in the placebo group reported no fatigue, and 222 (42%) in the apalutamide group and 223 (42%) in the placebo group reported mild fatigue at baseline. Group mean scores at baseline are described in the appendix (p 11). Similar group mean fatigue intensity and interference scores were observed over time (data not shown).

Median time to worst fatigue intensity was not reached in either group (95% CI not reached–not reached); 25th percentiles were 9·23 months (6·47–12·91) in the apalutamide group and 11·04 months (8·28–14·75) in the placebo group (HR 1·09 [0·88–1·35]; p=0·44). Median time to fatigue interference was also not reached in either group (95% CI not reached–not reached); 25th percentiles were 10·15 months (95% CI 6·64–14·42) in the apalutamide group and 10·51 months (7·39–14·69) in the placebo group (HR 1·01 [0·81–1·26]; p=0·93). Worst fatigue intensity and fatigue interference mean scores, assessed using repeated-measures mixed-effects models, were similar between groups (figure 4). The largest proportion of patients had no fatigue at baseline and remained stable, most patients with mild fatigue at baseline remained stable or improved, and most with moderate or severe fatigue at baseline improved by at least 1 point (appendix pp 18–20).

A post-hoc analysis of change in fatigue from baseline among patients grouped by baseline fatigue scores showed no worsening over time in mean fatigue intensity

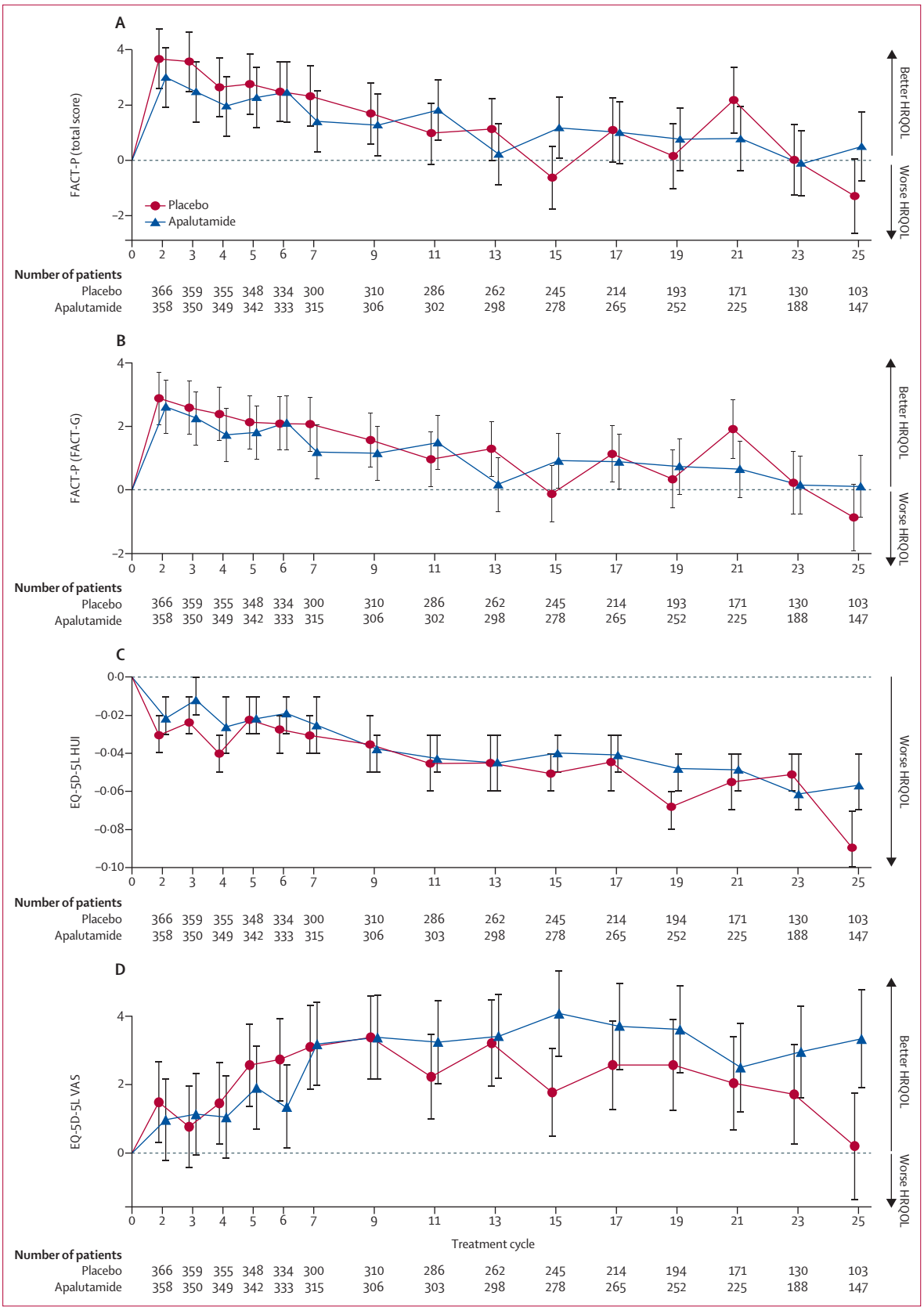


Figure 5: **Patient-reported changes in HRQOL**
Error bars are the standard error of the mean. Repeated-measures mixed-effects analyses for mean change from baseline in (A) FACT-P, (B) FACT-G, (C) EQ-5D-5L HUI, and (D) EQ-5D-5L VAS using repeated-measures mixed-effects analyses. Figure 5A adapted from Chi et al,[11] by permission of Massachusetts Medical Society. EQ-5D-5L=EuroQoL five dimensions, five levels. FACT-G=Functional Assessment of Cancer Therapy-General. FACT-P=Functional Assessment of Cancer Therapy-Prostate. HRQOL=health-related quality of life. HUI=health utility index. VAS=visual analogue scale.

and fatigue interference in most patients, except for fatigue intensity in the apalutamide group in patients with severe baseline fatigue, and particularly those with no fatigue to moderate fatigue at baseline (appendix pp 21, 22).

The presence of few disease symptoms at baseline was supported by the group mean scores for FACT-P and its subscales as well as other patient-reported outcome assessments (appendix pp 23–26). Overall, HRQOL was preserved during the treatment period. Group means for the FACT-P total and all the domains were similar between treatment groups over time.

The median time to deterioration as determined by FACT-P total score was 8·87 months (IQR 1·87–not reached; 95% CI 4·70–11·10) in the apalutamide group and 9·23 months (2·79–24·77; 7·39–12·91) in the placebo group (HR 1·02 [95% CI 0·85–1·22]; p=0·85). There were no differences in the time to HRQOL deterioration between the treatment groups (appendix p 23).

In repeated-measures analyses, the changes from baseline scores in FACT-P, FACT-G, physical wellbeing, functional wellbeing, social and family wellbeing, and emotional wellbeing scores were similar between treatment groups over time (figure 5; appendix p 25). The FACT-P prostate cancer subscale and pain-related subscale were similar between groups (appendix p 26). Differences were not statistically significant in the post-hoc analysis of treatment tolerability based on responses to item GP5 from the FACT-P physical wellbeing domain, "I am bothered by side effects of treatment," and tolerability seemed similar between treatment groups (appendix p 27).

The EQ-5D-5L health utility index declined over time and EQ-5D-5L visual analogue scale scores were maintained over time. Results from both assessments were similar between the two treatment groups (figure 5).

Discussion

This analysis of prespecified patient-reported outcome endpoints in TITAN showed that HRQOL did not worsen with the addition of apalutamide to ADT versus placebo for a broad population of patients with metastatic castration-sensitive prostate cancer, including those with high-volume or low-volume disease, previous docetaxel use, previous treatment for localised disease, and previously or newly diagnosed disease. This maintenance of HRQOL in patients who were mostly asymptomatic at baseline, taken together with the significantly improved radiographic progression-free survival and overall survival, reduced risk of death, delayed time to disease progression, and delayed time to initiation of cytotoxic chemotherapy in TITAN, as reported previously,[11] and tolerability reported by patients, supports the clinical benefit of apalutamide in a broad patient population with metastatic castration-sensitive prostate cancer.[11]

Having already initiated ADT before enrolment as required by the protocol, patients with metastatic castration-sensitive prostate cancer in TITAN had few symptoms at baseline, with low pain and fatigue scores. Patients' pain and fatigue (intensity and interference, per BPI-SF and BFI) remained stable throughout the study or improved and was similar between the treatment groups and across treatment cycles.

Because participants were required to have started treatment with ADT before randomisation, patients were possibly benefiting from ongoing ADT and having ADT-associated adverse events, which might have reduced the magnitude of difference in patient-reported outcomes between groups. Most patients who reported no pain at baseline remained stable, and most with pain at baseline either remained stable or improved, with greater proportions of improvement seen in those who reported greater levels of pain severity at baseline. Similarity in mean changes from baseline in FACT-P and EQ-5D-5L results between treatment groups indicated that the addition of apalutamide to ADT did not result in a decrease in overall HRQOL, despite significantly improving survival outcomes.

In a post-hoc analysis of responses to the FACT-P (GP5) side-effects bother item,[26] most patients indicated they were "not at all" bothered by adverse effects from the treatment, and few patients indicated they were "very much" or "quite a bit" bothered. This result further supports the observation that apalutamide was well tolerated.

This study has several potential limitations. Despite the use of conservative models, missing data over time might have contributed to bias by non-ignorable dropout, and this could have had different effects on the apalutamide and placebo groups. Additionally, clinical study recruitment is subject to selection bias, so the patient population might not be generalisable to the true global population of patients with metastatic castration-sensitive prostate cancer. Prostate cancer occurs more frequently in black patients than in white patients,[27] and only 1·8% of patients in TITAN were black or African–American. Moreover, 22% of patients in TITAN were Asian and might have had more severe disease; some reports indicate lower screening rates in Asian regions resulting in more frequent initial diagnoses of severe disease compared with western countries.[2] The validity of these results in non-white populations might require further study. Among the strengths of this study were the frequent administration of the patient-reported outcome instruments and the high rate of compliance during the study. Despite compelling findings indicating the stability of overall HRQOL with the addition of apalutamide to ADT, adverse events related to apalutamide exist that might affect patient experience (eg, rash). Although rash was not assessed specifically in this study, high compliance rates and the favourable results of the GP5 analysis address this limitation. Additionally, mood disturbance, cognitive function, and sleep quality should be

incorporated in the standardised tool to be assessed in future studies of metastatic prostate cancer.

The use of patient-reported outcome instruments to assess symptoms such as pain and fatigue and overall HRQOL is important to help improve the overall understanding of patients' experience with cancer treatments. The Prostate Cancer Clinical Trials Working Group 3 recognised the importance of reporting quality of life and patient experience as an important goal for patients with prostate cancer.[28] Guidelines such as the National Comprehensive Cancer Network and National Institute for Health and Care Excellence include efficacy, cost, and quality of life in their considerations when assessing the overall value of a particular therapeutic drug. Therefore, the assessment of symptoms and HRQOL of patients in TITAN as well as the previously reported survival benefits was important. The addition of apalutamide did not diminish HRQOL in patients with metastatic castration-sensitive prostate cancer who were enrolled in TITAN. Longer-term assessments are recommended for better precision in measuring preservation of HRQOL.

In conclusion, the results of the TITAN study showed substantial benefits for apalutamide plus ADT for overall survival and radiographic progression-free survival in patients with metastatic castration-sensitive prostate cancer, and overall HRQOL was maintained with the addition of apalutamide to ADT. These data support the addition of apalutamide to ADT for a broad range of patients with metastatic castration-sensitive prostate cancer.

Contributors

NA, AB, SC, AJPdSG, BHC, MO, AJS, ASM, HU, DY, and RG are investigators who participated in the conduct of the study. NA, KNC, KM, BM, LD, KD, VN, and AL-G designed the study. NA led the development of the manuscript. DC and EB provided substantial contributions to the interpretation of the data and critical reviews of the manuscript. All authors participated in data interpretation, manuscript review, and approval of the final version of the manuscript for submission.

Declaration of interests

NA has received advisory board fees from Astellas Pharma, Argos Therapeutics, Foundation Medicine, Genentech, and Pharmacyclics; grant support and advisory board fees from AstraZeneca, Bristol-Myers Squibb, Bayer, Clovis Oncology, Eisai, Exelixis, EMD Serono, Eli Lilly, Merck, Medivation, Novartis, Nektar Therapeutics, and Pfizer; and his institution has received grant support from Bavarian Nordic, Calithera, Celldex Therapeutics, GlaxoSmithKline, NewLink Genetics, Prometheus Laboratories, Rexahn Pharmaceuticals, Sanofi, Takeda, and Tracon Pharmaceuticals. AB has received honoraria, consulting fees, fees for serving on a speakers bureau, and travel support from Janssen and Ipsen; grant support, honoraria, consulting fees, fees for serving on a speakers bureau, and travel support from Astellas Pharma and Bayer; consulting fees and travel support from Incyte; grant support, honoraria, fees for serving on a speakers bureau, and travel support from Ferring Pharmaceuticals; fees for serving as a board member, travel support, and stock options from LIDDS Pharma; grant support, fees for serving as a board member, travel support, and stock options from and serves as cofounder of Glactone Pharma; and stock options from WntResearch. SC has received honoraria, fees for serving on a speakers' bureau, consulting fees, and travel support from Johnson & Johnson, Astellas Pharma, and Sanofi; support, honoraria, fees for serving on a speakers' bureau, consulting fees, and travel support from Clovis Oncology. BHC has received grant support and consulting fees from Janssen; grant support from Bayer, Pfizer, AstraZeneca, Roche, and Myovant Sciences; and consulting fees from Astellas Pharma, Ipsen, JW Pharmaceutical, Takeda, Handok, and Amgen. AJS has received lecture fees and fees for serving on a publication steering committee from Janssen. ASM has received grant support, consulting fees, lecture fees, and fees for serving on a speakers' bureau from Janssen-Cilag, Astellas Pharma, and Roche. HU has received grant support, lecture fees, and fees for serving as a meeting chairman from Janssen and Ono and Bristol-Myers Squibb; grant support from AstraZeneca, Takeda, Astellas Pharma, and Taiho; and lecture fees and fees for serving as a meeting chairman from Pfizer, Bayer, Merck Sharp and Dohme, and Novartis. RG has received fees for serving on a speakers' bureau for Janssen. DC is president of FACIT.org; has received research funding to his institution from AbbVie, Amgen, Astellas, AstraZeneca, Bristol-Myers Squibb, Clovis, Janssen, GlaxoSmithKline, Novartis, and Pfizer; and has received consulting honoraria from Astellas, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, and Pfizer. EB has received fees for serving on the scientific advisory boards for CareVive Systems, Sivan Healthcare, and Self Care Catalysts; fees for serving on the editorial board of the *Journal of the American Medical Association*; and fees for consulting on research projects for Memorial Sloan Kettering Cancer Center, Dana-Farber Cancer Institute, and Research Triangle Institute. KM, BM, LD, KD, VN, and AL-G are employed by Janssen Research & Development or Janssen Global Services and hold stock in Johnson & Johnson. KNC has received grant support, consulting fees, and lecture fees from Janssen, Astellas Pharma, and Sanofi; and grant support and consulting fees from Essa Pharma, Bayer, Roche, and AstraZeneca. AJPdsG, MO, and DY declare no competing interests.

Data sharing

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available online. As noted on this website, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project online.

For **Janssen's data sharing policy** see https://www.janssen.com/clinical-trials/transparency

For the **YODA Project** see http://yoda.yale.edu

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