Effect of apalutamide on health-related quality of life in patients with non-metastatic castration-resistant prostate cancer: an analysis of the SPARTAN randomised, placebo-controlled, phase 3 trial

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Lancet Oncol 2018; 19: 1404–16

Published Online September 10, 2018 http://dx.doi.org/10.1016/S1470-2045(18)30456-X

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Summary

Background In the SPARTAN trial, addition of apalutamide to androgen deprivation therapy, as compared with placebo plus androgen deprivation therapy, significantly improved metastasis-free survival in men with non-metastatic castration-resistant prostate cancer who were at high risk for development of metastases. We aimed to investigate the effects of apalutamide versus placebo added to androgen deprivation therapy on health-related quality of life (HRQOL).

Methods SPARTAN is a multicentre, international, randomised, phase 3 trial. Participants were aged 18 years or older, with non-metastatic castration-resistant prostate cancer, a prostate-specific antigen doubling time of 10 months or less, and a prostate-specific antigen concentration of 2 ng/mL or more in serum. Patients were randomly assigned (2:1) to 240 mg oral apalutamide per day plus androgen deprivation therapy, or matched oral placebo plus androgen deprivation therapy, using an interactive voice randomisation system. Permuted block randomisation was used according to the three baseline stratification factors: prostate-specific antigen doubling time (>6 months *vs* ≤6 months), use of bone-sparing drugs (yes *vs* no), and presence of local-regional nodal disease (N0 *vs* N1). Each treatment cycle was 28 days. The primary endpoint was metastasis-free survival. The trial was unblinded in July, 2017. In this prespecified exploratory analysis we assessed HRQOL using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) and EQ-5D-3L questionnaires, which we collected at baseline, day 1 of cycle 1 (before dose), day 1 of treatment cycles 1–6, day 1 of every two cycles from cycles 7 to 13, and day 1 of every four cycles thereafter. This study is registered with ClinicalTrials.gov, number NCT01946204.

Findings Between Oct 14, 2013, and Dec 15, 2016, we randomly assigned 1207 patients to receive apalutamide (n=806) or placebo (n=401). The clinical cutoff date, as for the primary analysis, was May 19, 2017. Median follow-up for overall survival was 20·3 months (IQR 14·8–26·6). FACT-P total and subscale scores were associated with a preservation of HRQOL from baseline to cycle 29 in the apalutamide group; there were similar results for EQ-5D-3L. At baseline, the mean for FACT-P total score in both the apalutamide and placebo groups were consistent with the FACT-P general population norm for US adult men. Group mean patient-reported outcome scores over time show that HRQOL was maintained from baseline after initiation of apalutamide treatment and was similar over time among patients receiving apalutamide versus placebo. Least-squares mean change from baseline shows that HRQOL deterioration was more apparent in the placebo group.

Interpretation In asymptomatic men with high-risk non-metastatic castration-resistant prostate cancer, HRQOL was maintained after initiation of apalutamide treatment. Considered with findings from SPARTAN, patients who received apalutamide had longer metastasis-free survival and longer time to symptomatic progression than did those who received placebo, while preserving HRQOL.

Funding Janssen Research & Development.

Introduction

Androgen deprivation therapy with or without an antiandrogen has been the standard treatment approach for men with metastatic prostate cancer, and is also used to treat non-metastatic prostate cancer.[1] Men with high-risk non-metastatic castration-resistant prostate cancer, which is characterised by rapidly rising prostate-specific antigen concentrations in the absence of detectable metastases despite castrate levels of testosterone, are at significant risk for development of metastases and prostate-cancer-specific death.[2] Nearly all patients with non-metastatic prostate cancer have a response to androgen deprivation therapy, with or without an antiandrogen.[1,3] Within a few years, most patients progress to castration-resistant prostate cancer.[4] Men with high-risk, non-metastatic castration-resistant

Research in context

Evidence before this study

At the time the trial was designed, the optimum management of patients with high-risk non-metastatic castration-resistant prostate cancer was undefined. We comprehensively reviewed the scientific literature for English-langage publications published up to the end of 2017, to identify patient-reported outcomes in prostate cancer. Data about health-related quality of life (HRQOL) in men with non-metastatic castration-resistant prostate cancer are scarce. In a phase 2 study of men with high-risk non-metastatic castration-resistant prostate cancer, treatment with apalutamide, an androgen receptor inhibitor, was associated with a decrease of at least 50% in prostate-specific antigen in 89% of patients at 12 weeks. On the basis of these results and the unmet need for treatment options for patients with high-risk non-metastatic castration-resistant prostate cancer, we did the phase 3 SPARTAN study to investigate the addition of apalutamide to androgen deprivation therapy compared with androgen deprivation therapy plus placebo in this setting. Results from SPARTAN showed that treatment with apalutamide versus placebo extended median metastasis-free survival by 2 years (hazard ratio [HR] for metastasis or death 0·28; 95% CI 0·23–0·35; p<0·0001) and time to symptomatic progression (HR 0·45; 95% CI 0·32–0·63; p<0·0001).

Added value of this study

We present HRQOL data that were prospectively collected and analysed as exploratory endpoints in the SPARTAN study. In asymptomatic men with high-risk non-metastatic castration-resistant prostate cancer, HRQOL was maintained after initiation of treatment with apalutamide, with a trend towards deterioration in HRQOL from baseline in the placebo group, and there was similar tolerability between treatment with apalutamide and placebo. HRQOL continued to be similar between treatment groups in the post-progression follow-up. There were similar declines in HRQOL associated with symptomatic progression. The decrease in HRQOL for patients treated with apalutamide was delayed, consistent with the longer time to symptomatic progression identified in the SPARTAN study, based on group mean scores of any available patient-reported outcome data post-progression. To our knowledge, this is the first report of HRQOL associated with a novel treatment that has been shown to significantly delay metastases and prolong metastasis-free and symptomatic progression-free survival in this patient population.

Implications of all the available evidence

Apalutamide was approved by the US Food and Drug Administration in 2018, for the treatment of patients with high-risk non-metastatic castration-resistant prostate cancer, on the basis of data from SPARTAN. Maintaining patient HRQoL after initiation of a new effective treatment added to current standard of care is an advance for patients with non-metastatic castration-resistant prostate cancer and the clinicians who treat them. Future research is needed on cognitive assessments for patients treated with androgen receptor inhibitors.

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prostate cancer, which is characterised by rapidly increasing prostate-specific antigen concent rations in the absence of detectable metastases, are at substantial risk of developing metastases and prostate-cancer-specific death.[2] The effect of metast ases and disease progression on patients' functional and emotional wellbeing (eg, increased anxiety about mortality, loss of wellbeing) shows that disease progression is a constant concern for patients with non-metastatic castration-resistant prostate cancer.[5–7] Additionally, anxiety among men with prostate cancer can be substantially higher in patients whose prostate-specific antigen concentrations are changing, versus those with stable prostate-specific antigenconcen trations.[8]

Patient-reported outcome data are increasingly important as health-care systems across the world place greater emphasis on patients' experience of treatment, and there is a growing interest in incorporating patient-reported outcomes into the care of patients with cancer.[9–11] Patient-reported outcomes allow patients to report issues related to their physical and psychological wellbeing, and can help patients and their clinicians make informed decisions about care. Patient-reported physical functioning can provide meaningful information about patients' physical fitness and tolerance of treatment. Studies of several cancers show that patient-reported outcomes are associated with important clinical outcomes, such as treatment tolerability, hospital admissions, and survival.[11,12] Knowledge about health-related quality of life (HRQOL) can inform clinicians and patients about the benefits and risks of drug treatments in terms of patients' physical, social, emotional, and functional wellbeing.[10] Androgen deprivation therapy can have negative effects on HRQOL in patients with prostate cancer, including loss of libido and erectile dysfunction, and impaired memory, attention, and executive functions.[13] Previous studies in metastatic castration-resistant prostate cancer have shown improvement in overall HRQOL in patients treated with androgen receptor inhibitors,[14,15] although an increase in fatigue has been reported.[16,17] Data about the effect of these drugs on HRQOL in men with non-metastatic castration-resistant prostate cancer are scarce because this patient population has historically been understudied, which represents an area of unmet medical need.

Apalutamide is an androgen receptor inhibitor approved for the treatment of non-metastatic castration-resistant prostate cancer.[18] Apalutamide binds directly to the ligand-binding domain of the androgen receptor and prevents androgen receptor translocation, DNA binding,

and androgen receptor-mediated transcription.[19] In the placebo-controlled phase 3 Selective Prostate AR Targeting with ARN-509 (SPARTAN) trial, apalutamide treatment significantly improved metastasis-free survival, time to metastasis, progression-free survival, and time to symptomatic progression in men with non-metastatic castration-resistant prostate cancer.[20] In this prespecified exploratory analysis, we compared the patient-reported outcomes of HRQOL in men with high-risk, non-metastatic castration-resistant prostate cancer treated with apalutamide plus androgen deprivation therapy, versus those of men treated with placebo plus androgen deprivation therapy.

Methods

Study design and participants

The SPARTAN study is a phase 3, multicentre, randomised, double-blind, placebo-controlled study comparing apalutamide plus androgen deprivation therapy with placebo plus androgen deprivation therapy in high-risk patients with non-metastatic castration-resistant prostate cancer. Patients were recruited at 332 sites in 26 countries in North America, Europe, and the Asia-Pacific region (appendix pp 3–11). Eligible patients were aged 18 years or older and had histologically confirmed adenocarcinoma of the prostate, without neuroendocrine differentiation or small-cell features. Eligible patients also had progressive disease despite castrate concentrations of testosterone (defined as three increases in prostate-specific antigen concentrations at least 1 week apart, with the last prostate-specific antigen concentration ≥2 ng/mL), and were at high risk for the development of metastases, defined by a prostate-specific antigen doubling time of 10 months or less during continuous androgen deprivation therapy (bilateral orchiectomy or treatment with a gonadotropin releasing hormone analogue). Patients with pelvic lymph nodes smaller than 2 cm in the short axis (N1) located below the iliac bifurcation were eligible for enrolment. Patients maintained castrate concentrations of testosterone (<50 ng/dL [1·72 nmol/L]) within 4 weeks of randomisation and throughout the study. Patients were excluded if they had distant metastases detected by technetium-99m bone scan or CT scans of the pelvis, abdomen, chest, and brain; if they had received previous treatment with next-generation antiandrogens, CYP17 inhibitors, or previous chemotherapy for prostate cancer, except if administered in the adjuvant or neoadjuvant setting; or if they had a history of seizure or a condition that could predispose to seizure. Details about study design, ethical conduct, previous treatments, patient comorbidities, and eligibility criteria in SPARTAN were reported in the primary publication.[20] The review boards at all participating institutions approved the study, which was done in accordance with current 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

After eligibility criteria were met, patients were randomly assigned with an interactive voice randomisation system (2:1) to receive apalutamide plus androgen deprivation therapy or placebo plus androgen deprivation therapy.[20] We used permuted block randomisation according to three baseline stratification factors. Patients were stratified according to prostate-specific antigen doubling time (>6 months *vs* ≤6 months), use of bone-sparing drugs (yes *vs* no), and presence of local-regional nodal disease (N0 *vs* N1) at the time of study entry. The identities of test and control treatments were not known to investigators, research staff, the sponsor study team, or patients. Only selected individuals not affiliated with the protocol or members of the independent data safety and monitoring committee were unmasked to individual patient treatment assignment during the trial, for the purposes of efficacy analyses and safety review. Patients, trial staff, and sponsor representatives were masked to the patients' prostate-specific antigen values until after the study was unblinded in July, 2017. The randomisation codes and all datasets were stored in a secure area accessible only to these individuals, and only released after completion of the study and after the study database had been locked.

Procedures

Eligible patients were randomly assigned to receive apalutamide (240 mg per day) plus androgen deprivation therapy or matched placebo plus androgen deprivation therapy, administered orally on a continuous daily dosing regimen. Each treatment cycle was 28 days. Dose interruptions or reductions were permitted (appendix pp 96–97) provided that study treatment discontinuation criteria were not met. Treatment continued until masked independent central review confirmed distant metastases or adverse events, or if patients withdrew consent. Possible reasons for early discontinuation of study treatment included disease progression, any episode of seizure, any other adverse event that could not be adequately managed with dose modifications, a protocol violation requiring discontinuation of study treatment, non-compliance with study procedures, loss to follow-up, or patient withdrawal of consent (appendix pp 114–15). Interventions required to manage symptoms from local-regional disease were allowed while patients received study treatment. Subsequent therapy was at the discretion of the investigator. Patients who met the primary study endpoint were eligible to receive sponsor-provided abiraterone acetate plus prednisone as a treatment option for metastatic castration-resistant prostate cancer as part of the study, at the treating physician's discretion, for a duration according to prescribing information in the country of residence.

Disease assessments, including technetium-99m bone scans and CT or MRI of the pelvis, abdomen, and chest, were done every 16 weeks and at additional timepoints if distant metastases were suspected. Evidence of distant

metastases on imaging was determined on the basis of Response Evaluation Criteria in Solid Tumors (version 1.1).[21] All imaging studies were assessed prospectively by means of masked independent central review. Symptomatic progressive disease was defined as development of a skeletal-related event, initiation of new systemic anticancer treatment because of pain or worsening of disease-related symptoms, or development of clinically significant symptoms due to local-regional tumour progression requiring surgery or radiation.

We used the Functional Assessment of Cancer Therapy-Prostate (FACT-P) patient-reported outcome questionnaire to assess prostate cancer symptoms, pain-related symptoms, and overall HRQOL (appendix pp 13, 36–41). We used the EuroQol five-dimension, three-level questionnaire (EQ-5D-3L) to assess mobility, self-care, usual activities, pain, discomfort, and anxiety or depression (appendix pp 13, 42–43). Patients were required to complete the two paper, self-administered patient-reported outcome questionnaires before any other interventions or examinations on the day of the clinic visit. FACT-P and EQ-5D-3L were given and collected during the treatment phase at baseline, on day 1 of cycle 1 (before dose), day 1 of cycles 2–6, day 1 of every two cycles starting at cycle 7 to cycle 13, then day 1 of every four cycles, unless otherwise specified (appendix p 14). This frequency enabled us to assess treatment tolerability and patients' HRQOL over time. In patients who developed metastases and moved on to the post-progression follow-up phase, FACT-P and EQ-5D-3L were given at the end-of-treatment visit and at 4, 8, and 12 months from start of post-progression follow-up. We collected post-progression data to compare the experience in the post-metastatic period for patients originally assigned to receive apalutamide plus androgen deprivation therapy versus patients given placebo plus androgen deprivation therapy. By the first post-progression assessment, most patients were receiving subsequent approved treatment for metastatic castration-resistant prostate cancer.[20]

FACT-P is a 39-item questionnaire that was developed and validated specifically in patients with prostate cancer.[22–24] The scores for five FACT-P subscales (physical wellbeing [seven items], social and family wellbeing [seven items], emotional wellbeing [six items], functional wellbeing [seven items], and prostate cancer subscale [12 items]) can be added together to make a single overall score (appendix pp 36–41). The FACT-P overall score ranges from 0 to 156. Higher values of FACT-P total and all subscales indicate a higher HRQOL. Because items are worded in either a positive or negative direction, negatively worded values are subtracted from 4 before scoring to maintain consistency in higher scores that indicate a better HRQOL. According to standard practice, the FACT-P subdomains were scored when a response for at least one item was completed.

FACT-General (FACT-G) is made up of 27 items in FACT-P and measures general HRQOL in patients with cancer, which was the focus of our prespecified analysis. The overall score of FACT-G ranges from 0 to 108, with higher values indicating a higher general HRQOL.[23] To calculate FACT-G total and subscale scores we added the item responses for each subscale, and took the FACT-G total score as the sum of the four subscale scores from the physical wellbeing, social and family wellbeing, emotional wellbeing, and functional wellbeing domains. We assessed the effect of adverse events on HRQOL by analysing responses to the question, "I am bothered by side-effects of treatment", an item (GP5) of the FACT-P physical wellbeing domain. The response to this question is correlated with the FACT-G total score and has been used in various studies in oncology.[25,26]

The EQ-5D-3L is a general preference-based HRQOL instrument intended to complement other patient-reported outcome instruments.[27] EQ-5D-3L comprises five items that ask patients to rate their perceived health state on the day of the questionnaire, including mobility, self-care, usual activities, pain or discomfort, and anxiety or depression (appendix pp 42–43). These domains are scored on a Likert-type scale, with scores ranging from 1 to 3, with 1 indicating no problems, 2 indicating some problems, and 3 indicating extreme problems. We included the EQ-5D-3L visual analogue scale to measure current general health status from 0 to 100, in which 0 represents worst imaginable health state and 100 represents best imaginable health state. The EQ-5D-3L health utility index is calculated from scores of the five health state domains and is scored between –1 (worst imaginable health state) and 1 (best imaginable health state), with 0 representing a health state equivalent to death.

In July, 2017, the independent data and safety monitoring committee concluded that the efficacy and safety data constituted compelling evidence of a clinical benefit in the apalutamide group, and the committee unanimously recommended that the trial be unblinded.

Outcomes

The primary endpoint in SPARTAN was metastasis-free survival, as reported previously.[20] Secondary endpoints were time to symptomatic progression, time to metastasis, progression-free survival, overall survival, and time to the initiation of cytotoxic chemotherapy. In this study, we report data from the treatment phase and the post-progression follow-up phase for the prespecified patient-reported outcome exploratory endpoints, to assess HRQOL for participants in the SPARTAN study by use of the FACT-P and EQ-5D-3L questionnaires.

Statistical analysis

The statistical analysis plan for the assessment of patient-reported outcomes is in the appendix (p 28). The trial was powered for the primary endpoint (metastasis-free survival), and was not specifically powered for the exploratory endpoints reported here.

	Apalutamide (n=806)	Placebo (n=401)
Median age, year	74 (68–80)	74 (68–80)
Race		
White	524 (65%)	276 (69%)
Asian	93 (12%)	47 (12%)
Black or African American	48 (6%)	20 (5%)
Not reported	135 (17%)	57 (14%)
Region		
Europe	395 (49%)	204 (51%)
North America	285 (35%)	134 (33%)
Asia-Pacific	126 (16%)	63 (16%)
Eastern Cooperative Oncology Group performance status score		
0	623 (77%)	311 (78%)
1	183 (23%)	89 (22%)
Bone-sparing drug use		
Yes	82 (10%)	39 (10%)
No	724 (90%)	362 (90%)
Local-regional disease at study entry		
N0	673 (83%)	336 (84%)
N1	133 (17%)	65 (16%)
Previous prostate cancer treatment*		
Surgery only	159 (20%)	69 (17%)
Radiotherapy only	157 (19%)	85 (21%)
Surgery and radiotherapy	301 (37%)	153 (38%)
Gonadotropin-releasing hormone analogue agonist	780 (97%)	387 (97%)
First-generation antiandrogen drug (flutamide, bicalutamide, or nilutamide)	592 (73%)	290 (72%)
Orchiectomy	47 (6%)	24 (6%)
Other hormonal therapy	17 (2%)	9 (2%)
Chemotherapy (adjuvant or neoadjuvant)	17 (2%)	7 (2%)
Other prostate cancer therapy	64 (8%)	32 (8%)

(Table 1 continues in next column)

(Continued from previous column)

	Apalutamide (n=806)	Placebo (n=401)
Baseline FACT-P scores		
Number of patients	797/803 (99%)	395/398 (99%)
Mean total FACT-P score	117·2 (19·2)	116·6 (19·3)
Mean total FACT-G score	84·1 (14·4)	83·4 (14·2)
Mean physical wellbeing subscale score	24·8 (3·4)†	24·8 (3·4)‡
Mean social and family wellbeing subscale score	20·9 (5·8)†	20·8 (5·4)‡
Mean emotional wellbeing subscale score	18·4 (4·1)§	18·1 (4·0)¶
Mean functional wellbeing subscale score	20·3 (5·9)§	20·0 (6·0)¶
Prostate cancer subscale	33·3 (6·5)‖	33·4 (6·4)¶
Mean pain-related score	12·4 (3·7)†	12·8 (3·7)
Baseline EQ-5D-3L scores		
Number of patients	782/803 (97%)	391/398 (98%)
Mean health utility index score	0·85 (0·17)	0·86 (0·17)
Number of patients	787/803 (98%)	390/398 (98%)
Mean health status score (VAS)	76·2 (17·3)	76·8 (16·9)

Data are n (%), n/N (%), median (IQR), or mean (SD). Denominators are the number of patients with patient-reported outcome data at baseline. FACT-P=Functional Assessment of Cancer Therapy-Prostate. FACT-G=Functional Assessment of Cancer Therapy-General. EQ-5D-3L=EuroQol five-dimension, three-level questionnaire. VAS=visual analogue scale. *Apalutamide, n=803; duration of androgen-deprivation therapy was not collected. †Apalutamide, n=796. ‡Placebo, n=394. §Apalutamide, n=793. ¶Placebo, n=393. ‖Apalutamide, n=792.

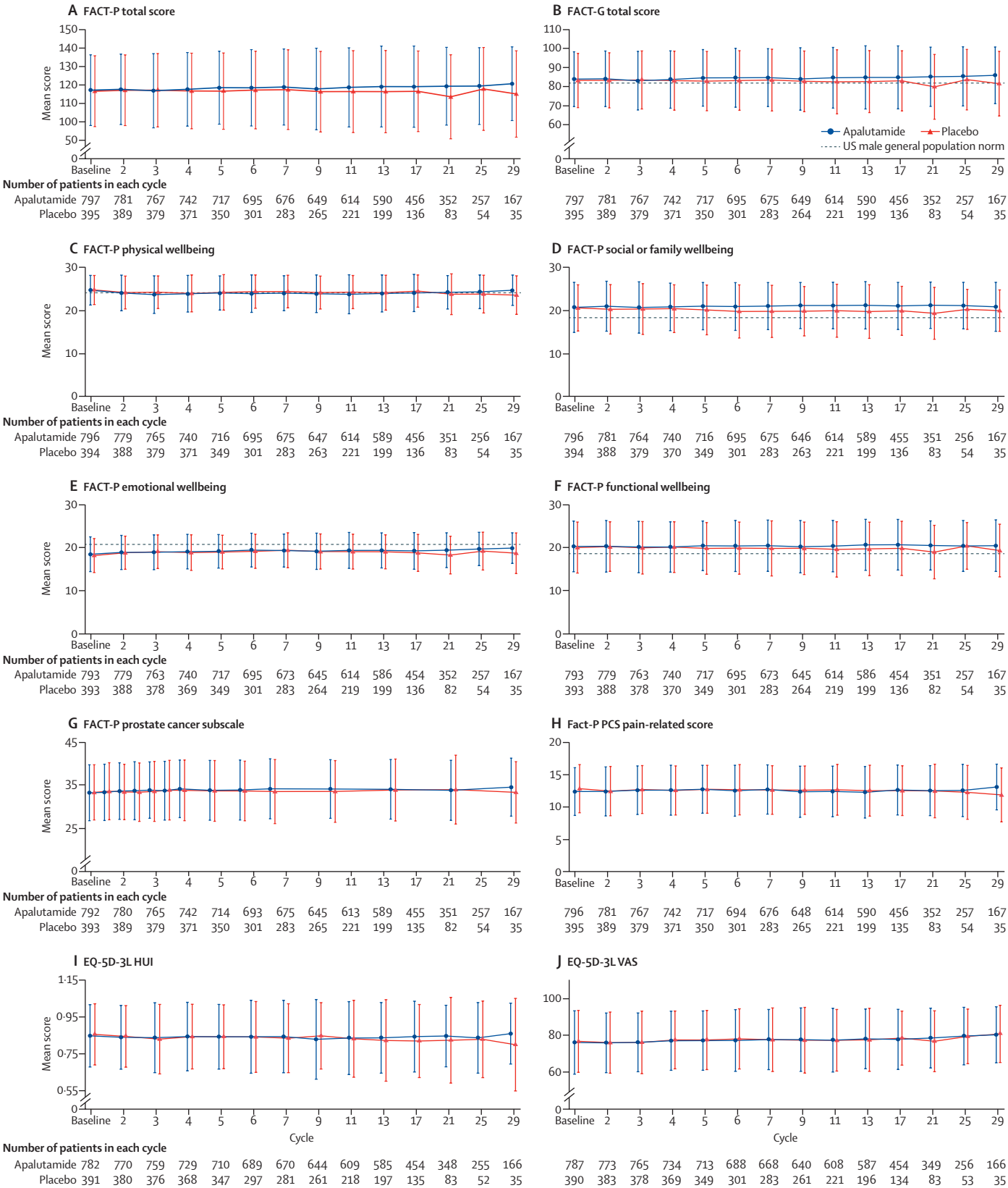
Table 1: **Baseline demographic and clinical characteristics**

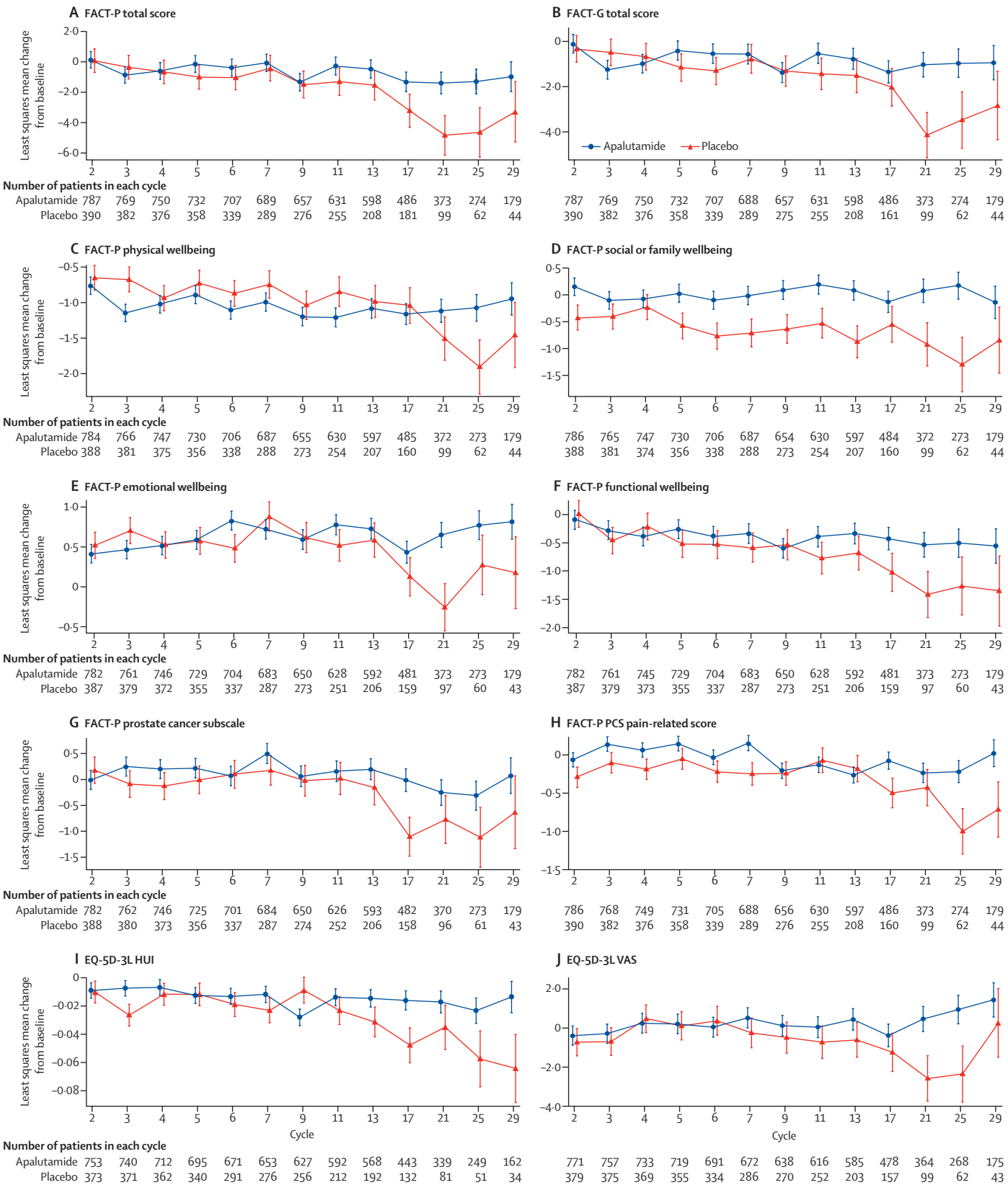
The intention-to-treat population was defined as all patients randomly assigned to one of the study groups. The analysis population for patient-reported outcomes was defined as the patients in the intention-to-treat population who had completed baseline assessment and at least one post-baseline assessment of either FACT-P or EQ-5D-3L. We analysed all FACT-P and EQ-5D-3L data from the patient-reported outcome population.

We calculated compliance with the planned assessment schedule for patient-reported outcomes at baseline and for each treatment cycle as the proportion of patients still receiving study treatment at that timepoint. We determined the expected number of assessments per visit by patient-level study completion status. We calculated missing patient-reported outcome assessments as the expected number of assessments for a particular visit minus the actual number of assessments received for that visit, and tabulated the proportions of received and missing patient-reported outcome assessments by treatment group, at baseline and at each scheduled visit during the treatment phase. In a post-hoc analysis, we assessed the compliance rate for completion of at least 50% of the items in FACT-P and EQ-5D-3L. We censored at randomisation any patients who did not have baseline or any post-baseline patient-reported outcome assessments.

For the prespecified analysis of mean subscale scores by treatment group over time, we produced descriptive statistics (number of observations, mean, SD, minimum, maximum) of scores at baseline and each scheduled visit during the treatment phase by treatment group for each patient-reported outcome scale, censored at the time of subsequent therapy, and not statistically tested. We derived group mean scores during the treatment phase at each treatment cycle after baseline to cycle 29. During the treatment phase, patients were censored at the time of subsequent therapy.

Figure 1: **Group mean FACT-P total (A), FACT-G total (B), FACT-P subscale scores (C–H), and EQ-5D-3L (I, J) scores by treatment group over time**
Data from the post-progression phase are shown in tables 2 and 3. Error bars show SD. FACT-P=Functional Assessment of Cancer Therapy-Prostate. FACT-G=Functional Assessment of Cancer Therapy-General. HUI=health utility index. VAS=visual analogue scale.


A FACT-P total score
Mean score
150
140
130
120
110
100
50
0
Baseline 2 3 4 5 6 7 9 11 13 17 21 25 29
Number of patients in each cycle
Apalutamide 797 781 767 742 717 695 676 649 614 590 456 352 257 167
Placebo 395 389 379 371 350 301 283 265 221 199 136 83 54 35
B FACT-G total score
110
100
90
80
70
60
0
Apalutamide
Placebo
US male general population norm
797 781 767 742 717 695 675 649 614 590 456 352 257 167
395 389 379 371 350 301 283 264 221 199 136 83 54 35
C FACT-P physical wellbeing
30
20
10
0
796 779 765 740 716 695 675 647 614 589 456 351 256 167
394 388 379 371 349 301 283 263 221 199 136 83 54 35
D FACT-P social or family wellbeing
796 781 764 740 716 695 675 646 614 589 455 351 256 167
394 388 379 370 349 301 283 263 221 199 136 83 54 35
E FACT-P emotional wellbeing
793 779 763 740 717 695 673 645 614 586 454 352 257 167
393 388 378 369 349 301 283 264 219 199 136 82 54 35
F FACT-P functional wellbeing
793 779 763 740 717 695 673 645 614 586 454 351 257 167
393 388 378 370 349 301 283 264 219 199 136 82 54 35
G FACT-P prostate cancer subscale
45
35
25
0
792 780 765 742 714 693 675 645 613 589 455 351 257 167
393 389 379 371 350 301 283 265 221 199 135 82 54 35
H Fact-P PCS pain-related score
20
15
10
5
0
796 781 767 742 717 694 676 648 614 590 456 352 257 167
395 389 379 371 350 301 283 265 221 199 135 83 54 35
I EQ-5D-3L HUI
1·15
0·95
0·75
0·55
0
Cycle
782 770 759 729 710 689 670 644 609 585 454 348 255 166
391 380 376 368 347 297 281 261 218 197 135 83 52 35
J EQ-5D-3L VAS
100
80
60
0
787 773 765 734 713 688 668 640 608 587 454 349 256 166
390 383 378 369 349 301 283 261 221 196 134 83 53 35


A FACT-P total score
B FACT-G total score
C FACT-P physical wellbeing
D FACT-P social or family wellbeing
E FACT-P emotional wellbeing
F FACT-P functional wellbeing
G FACT-P prostate cancer subscale
H FACT-P PCS pain-related score
I EQ-5D-3L HUI
J EQ-5D-3L VAS
Least squares mean change from baseline
Apalutamide
Placebo
Cycle
Number of patients in each cycle
Apalutamide 787 769 750 732 707 689 657 631 598 486 373 274 179
Placebo 390 382 376 358 339 289 276 255 208 181 99 62 44
Apalutamide 787 769 750 732 707 688 657 631 598 486 373 274 179
Placebo 390 382 376 358 339 289 275 255 208 161 99 62 44
Apalutamide 784 766 747 730 706 687 655 630 597 485 372 273 179
Placebo 388 381 375 356 338 288 273 254 207 160 99 62 44
Apalutamide 786 765 747 730 706 687 654 630 597 484 372 273 179
Placebo 388 381 374 356 338 288 273 254 207 160 99 62 44
Apalutamide 782 761 746 729 704 683 650 628 592 481 373 273 179
Placebo 387 379 372 355 337 287 273 251 206 159 97 60 43
Apalutamide 782 761 745 729 704 683 650 628 592 481 373 273 179
Placebo 387 379 373 355 337 287 273 251 206 159 97 60 43
Apalutamide 782 762 746 725 701 684 650 626 593 482 370 273 179
Placebo 388 380 373 356 337 287 274 252 206 158 96 61 43
Apalutamide 786 768 749 731 705 688 656 630 597 486 373 274 179
Placebo 390 382 376 358 339 289 276 255 208 160 99 62 44
Apalutamide 753 740 712 695 671 653 627 592 568 443 339 249 162
Placebo 373 371 362 340 291 276 256 212 192 132 81 51 34
Apalutamide 771 757 733 719 691 672 638 616 585 478 364 268 175
Placebo 379 375 369 355 334 286 270 252 203 157 99 62 43

For each patient-reported outcome scale, we fitted the mixed model for repeated measures to estimate the mean patient-reported outcome scores at each scheduled visit during the treatment phase. In this model, the dependent variable was the change in patient-reported outcome score from baseline. Fixed effects for the model included treatment and visit number as discrete parameters, and interaction between time and treatment. Patients were included as random effects. Mixed-effect modelling assumed that missing data were missing at random and we used a serial correlation structure for repeated measures. A serial correlation matrix of first-order autoregression was assumed to account for the correlations between repeated measures for each patient. We plotted least squares mean (SE) of change from baseline for each patient-reported outcome scale by visit and treatment group. We selected the mixed model for repeated measures because compliance was high for both treatment groups.[28] We did a time to deterioration analysis using the FACT-P total and subdomain scores.

We used a mixed-effects model on change from baseline in FACT-P score. We fitted the model, adjusting for the baseline covariates of age, race, geographic region, previous surgery, previous radiotherapy Eastern Cooperative Oncology Group performance status, prostate-specific antigen doubling time, use of bone-sparing drug, and classification of local or regional nodal disease.

In a post-hoc analysis of subgroups of patients with metastases or symptomatic progressive disease, we compared overall group means and SE at baseline, before and after metastases, and before and after symptomatic progressive disease. For patients with metastases, we derived overall group mean scores for the treatment phase from the average of cycle 2 to end of treatment. Post-progression patient-reported outcome scores for these patients were calculated as the mean of the scores at months 4, 8, and 12 of the post-progression follow-up phase.

In a post-hoc analysis, we assessed the responses to the FACT-P items GP5 ("I am bothered by side-effects of treatment") and GP1 ("I have lack of energy") by calculating the proportions of patients who felt "not at all", "a little bit", "somewhat", "quite a bit", and "very much" bothered by side-effects or had lack of energy over time.

For the primary analysis, FACT-P was scored when at least one item was completed. In a sensitivity analysis, we determined a least squares mean change from baseline on the basis of missingness rules of 80% for FACT-P and FACT-G total scores and 50% for FACT-P subdomain scores, as recommended by the Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System (version 4.0, November, 1997).[22] We did all statistical analyses using SAS (version 9.2).

SPARTAN is registered with ClinicalTrials.gov, number NCT01946204.

	Apalutamide			Placebo		
	Baseline (N=797)	Before metastasis (N=772)	After metastasis* (N=157)	Baseline (N=396)	Before metastasis (N=384)	After metastasis* (N=184)
FACT-P total						
Number of patients	175	175	157	190	191	184
Group mean (SE)	115·9 (1·5)	117·9 (1·4)	112·5 (1·9)	119·3 (1·3)	117·9 (1·3)	114·5 (1·6)
FACT-G total						
Number of patients	175	175	157	190	191	184
Group mean (SE)	83·5 (1·1)	84·4 (1·0)	80·7 (1·3)	84·8 (1·0)	84·1 (1·0)	81·8 (1·1)
Physical wellbeing						
Number of patients	175	175	157	189	191	184
Group mean (SE)	24·5 (0·3)	24·0 (0·3)	22·9 (0·4)	25·1 (0·2)	24·4 (0·2)	23·5 (0·3)
Social wellbeing						
Number of patients	175	175	157	189	191	184
Group mean (SE)	21·3 (0·4)	21·4 (0·4)	21·1 (0·4)	21·3 (0·4)	20·9 (0·4)	21·0 (0·4)
Emotional wellbeing						
Number of patients	174	175	157	190	191	184
Group mean (SE)	18·0 (0·3)	18·8 (0·3)	18·0 (0·4)	18·4 (0·3)	19·0 (0·3)	18·2 (0·3)
Functional wellbeing						
Number of patients	174	175	157	190	191	184
Group mean (SE)	20·0 (0·4)	20·3 (0·4)	19·1 (0·5)	20·3 (0·4)	20·0 (0·4)	19·5 (0·4)
Prostate cancer subscale						
Number of patients	174	175	157	190	191	184
Group mean (SE)	32·6 (0·5)	33·6 (0·5)	32·0 (0·6)	34·5 (0·5)	33·8 (0·4)	32·8 (0·5)
Pain-related subscale						
Number of patients	175	175	157	190	191	184
Group mean (SE)	12·5 (0·3)	12·9 (0·2)	12·1 (0·3)	13·3 (0·3)	12·9 (0·2)	12·5 (0·3)

Data are from a cross-sectional analysis, showing the group mean of the available patient-reported outcome data at these timepoints. Baseline patient-reported outcome data were not available from one patient in the placebo group. Patient-reported outcome data were not available from 25 patients (n=18 in the apalutamide group, n=7 in the placebo group) of the 366 patients with metastases. FACT-P=Functional Assessment of Cancer Therapy-Prostate. FACT-G=Functional Assessment of Cancer Therapy-General. *Includes patients with and without subsequent approved treatment for metastatic castration-resistant prostate cancer.

Table 2: **Group mean FACT-P total, FACT-G total, and FACT-P subscale scores in patients with distant metastases**

Role of the funding source

The funder of the study had a role in study design, data analysis, data interpretation, and writing of the report. The funder had no role in data collection. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 14, 2013, and Dec 15, 2016, 1207 patients were randomly assigned to the treatment groups (n=806 to the apalutamide group, n=401 to the placebo group;

Figure 2: **Least squares mean change from baseline in FACT-P total score (A), FACT-G total (B), FACT-P subscale scores (C–H), and EQ-5D-3L (I, J), repeated measures mixed effect modelling**
Error bars show SE.

	Apalutamide			Placebo		
	Baseline (n=64)	Before symptomatic progressive disease (n=64)	After symptomatic progressive disease* (n=30)	Baseline (n=63)	Before symptomatic progressive disease (n=63)	After symptomatic progressive disease* (n=30)
FACT-P total	115·2 (2·5)	117·0 (2·4)	108·6 (3·7)	117·8 (2·0)	114·5 (2·2)	105·6 (4·3)
FACT-G total	84·4 (1·9)	84·2 (1·7)	78·6 (2·9)	85·2 (1·5)	82·6 (1·7)	75·3 (3·4)
Physical wellbeing	24·2 (0·5)	23·5 (0·4)	20·8 (0·8)	24·8 (0·4)	24·0 (1·0)	21·3 (1·0)†
Social wellbeing	22·1 (0·8)	21·9 (0·6)	22·9 (0·8)	21·3 (0·5)	20·4 (0·6)	20·8 (1·1)
Emotional wellbeing	18·2 (0·5)	19·0 (0·5)	17·4 (0·9)	18·5 (0·4)	18·9 (0·4)	18·2 (0·9)
Functional wellbeing	19·8 (0·7)	19·8 (0·7)	17·8 (1·1)	20·7 (0·6)	19·8 (0·6)	18·3 (1·0)
Prostate cancer subscale	31·3 (0·8)‡	32·8 (0·8)	30·0 (1·2)	32·6 (0·8)	32·3 (0·7)	30·3 (1·3)
Pain-related subscale	11·6 (0·4)	12·0 (0·4)	10·3 (0·7)	12·9 (0·4)	12·6 (0·4)	11·3 (0·8)

Data are group mean (SE). Data are from a cross-sectional analysis, showing the group mean of the available patient-reported outcome data at these timepoints. Patient-reported outcome data were not available for 13 patients at the time of symptomatic progression, because the symptomatic progression occurred after month 12 of the post-progression follow-up phase. FACT-P=Functional Assessment of Cancer Therapy-Prostate. FACT-G=Functional Assessment of Cancer Therapy-General. *Includes patients with and without subsequent approved treatment for metastatic castration-resistant prostate cancer. †n=29. ‡n=63.

Table 3: **Group mean FACT-P total, FACT-G total, and FACT-P subscale scores in patients with symptomatic progressive disease**

appendix p 12). At the clinical cutoff date, which was the same as for the primary analysis (May 19, 2017), the median follow-up for overall survival was 20·3 months (IQR 14·8–26·6).[20] Patients in the apalutamide group received median treatment of 16·9 months (11·1–24·2), whereas those in the placebo group received median treatment of 11·2 months (4·9–17·7). Patient demographic and baseline characteristics were well balanced between treatment groups and have been reported previously.[20] The median age was 74 years and 317 (26%) of 1207 patients were aged 80 years or older. Baseline FACT-P total and subscale scores, and EQ-5D-3L scores, were well balanced between groups (table 1).

As compared with the number of patients expected to complete the questionnaires at the scheduled visit, the compliance rate for completion of at least one item in FACT-P or EQ-5D-3L was 95·4% or higher at all treatment phase assessment visits in each group.

Compared with apalutamide, more patients in the placebo group discontinued treatment early because of disease progression (appendix pp 17–18).

Patient-reported outcome data are shown for 29 cycles, approximately 25·8 months from the start of treatment; data from subsequent treatment cycles were not interpretable because fewer than 20 patients remained in the placebo group. Generally, the total and subscale scores for FACT-P were maintained with apalutamide from baseline until treatment cycle 29 (figure 1). There were similar data showing this preservation of HRQOL from baseline EQ-5D-3L (figures 1I, 1J). Maintenance of HRQOL was also observed with placebo (figure 1).

There was a greater decrease in HRQOL in the placebo group compared with the apalutamide group, as shown by the mean changes from baseline in FACT-P total score, FACT-G, FACT-P subscale scores, and EQ-5D-3L (figure 2). Across most of the patient-reported outcome scales, there were numerical separations, beginning at cycle 11 and continuing until cycle 29, in favour of apalutamide, suggestive of greater deterioration in FACT-P total, FACT-G, FACT-P subscale scores, and EQ-5D-3L in the placebo group. In the time to deterioration analysis of the FACT-P total and subdomain scores, there was no difference between treatment groups based on the confidence intervals (data not shown).

366 patients developed distant metastases. Group mean patient-reported outcome scores after the date of diagnosis of first metastases were available for 341 patients (table 2). These scores were similar between patients in the apalutamide and placebo groups up to 12 months after metastasis (table 2). Group mean patient-reported outcome scores were available from 60 patients after symptomatic progressive disease (table 3). As reported previously, treatment with apalutamide had longer time to symptomatic progression compared with placebo (hazard ratio [HR] 0·45, 95% CI 0·32–0·63; p<0·0001).[20] In this analysis, there were similar decreases in HRQOL from baseline for both treatment groups after post-symptomatic progression was reached (table 3).

Figure 3A shows the distribution of answers to the question (GP5) from the FACT-P physical wellbeing domain, "I am bothered by side-effects of treatment." The proportion of patients who reported that they were "not at all" bothered by side-effects ranged (from low to high) from 384 (60%) of 635 patients at cycle 9 to 588 (78%) of 757 patients at baseline in the apalutamide group, and from 234 (64%) of 365 patients at cycle 4 to 27 (79%) of 34 patients at cycle 29 in the placebo group (appendix p 19). The distribution of responses and distribution of change from baseline (stable, improved, and worsened) were comparable between treatment groups (figure 3A). To better understand the patients' perspective on fatigue, we analysed answers to the question (GP1) from the FACT-P physical wellbeing

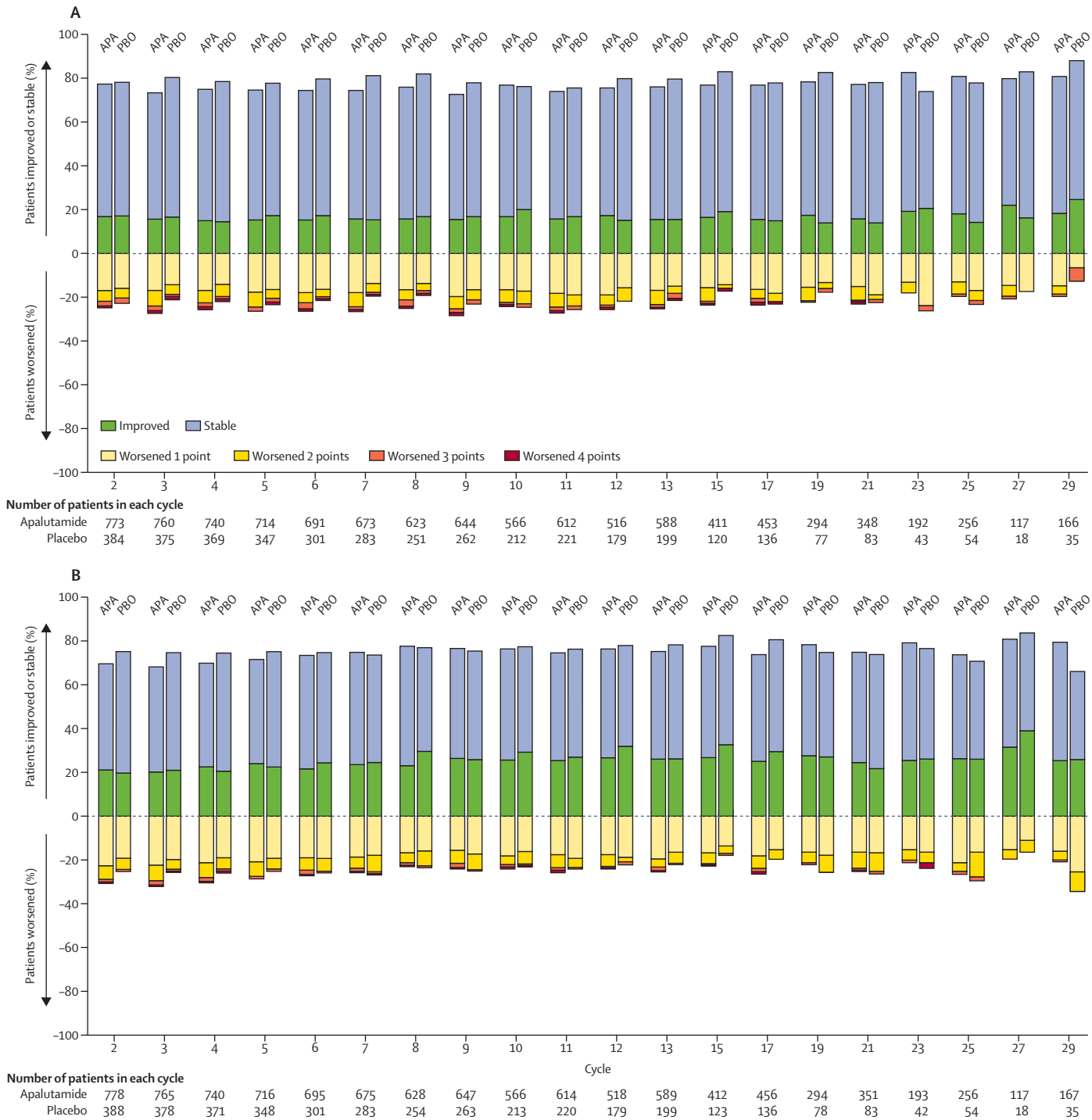


Figure 3: **Post-hoc analysis for FACT-P single items**
Data are change from baseline in each response category for the FACT-P single items "I am bothered by side-effects of treatment" (A) and "I have lack of energy" (B). APA=apalutamide. PBO=placebo.

domain, "I have lack of energy" (figure 3 B; appendix p 20). The proportion of patients who reported that they "quite a bit or very much" had lack of energy ranged from 15 (9%) of 163 patients at cycle 29 to 124 (17%) of 753 patients at cycle 3 in the apalutamide group, and from 15 (7%) of 216 patients at cycle 11 to 7 (13%) of 53 patients at cycle 25 in the placebo group (appendix p 20). It should be noted that data were available from

53 patients at cycle 25 in the placebo group versus 163 patients in the apalutamide group at cycle 29. The distribution of responses and distribution of change from baseline (stable, improved, and worsened) were comparable between treatment groups (figure 3B).

In a post-hoc analysis, the compliance rate for completion of at least 50% of the items in FACT-P and EQ-5D-3L was 95·4% or higher at all treatment phase assessment visits (appendix pp 15–16, 26). In a sensitivity analysis, results for FACT-P total, FACT-G, FACT-P subscale scores, and EQ-5D-3L were similar between treatment groups when the FACT-P analysis was based on all cases who answered at least one item or when based on the FACT-P 50%/80% scoring rules (appendix pp 19–22).

Discussion

In exploratory analysis from the SPARTAN trial, comparing apalutamide versus placebo in addition to androgen deprivation therapy, we assessed HRQOL in men with non-metastatic castration-resistant prostate cancer, a previously under-characterised patient population. Across treatment groups, rates of compliance with the patient-recorded outcome assessments remained high throughout the treatment phase. Analysis of FACT-P and FACT-G total scores and subscale scores, and EQ-5D-3L scores, shows that HRQOL was maintained in these generally asymptomatic patients despite treatment with an androgen receptor inhibitor, which has been shown to negatively affect HRQOL in men with prostate cancer. By analysing the data longitudinally we gained insights into the patients' perspective on their HRQOL. Group mean scores for patient-reported outcomes show that overall HRQOL (including physical, social and family, emotional, and functional wellbeing) was maintained from baseline after the initiation of treatment with apalutamide until treatment cycle 29, for those who remained on therapy. With a median treatment duration of 16·9 months (IQR 11·1–24·2), mean changes from baseline in the FACT-P subscales were similar in both treatment groups, indicating that the addition of apalutamide to androgen deprivation therapy did not result in a decrease in HRQOL. Results were consistent across FACT-P total, FACT-G total, all FACT-P subscales, and the EQ-5D-3L health utility index and visual analogue scale. Findings from the EQ-5D-3L health utility index indicated that patients believed their abilities to walk about, wash and dress themselves, and perform their usual activities were maintained after initiation of study treatment. Additionally, maintenance of EQ-5D-3L visual analogue scores indicated that patients' general health was preserved from baseline throughout assessment. Patients treated with apalutamide had a similar HRQOL after metastasis compared with those who received placebo. A decrease in HRQOL was associated with symptomatic progressive disease in both treatment groups.

Most patients in SPARTAN were asymptomatic at study entry, and patient-reported outcome questionnaires were administered frequently to try to proactively assess HRQOL and any changes in HRQOL after treatment initiation. Generally, mean scores at baseline for the FACT-P subscales and FACT-G were similar to or numerically higher than the US general population norm (appendix p 25). Although median prostate-specific antigen concentrations at 12 weeks had decreased by 89·7% with apalutamide and had increased by 40·2% with placebo,[20] patients and site staff were masked to prostate-specific antigen values. Thus, patient-reported outcome scores in either treatment group would not be expected to reflect the anxiety that typically occurs when patients see their prostate-specific antigen concentrations incease.[8] Patients' mean scores at baseline for the FACT-P emotional wellbeing subscale were below the US general population norm (appendix p 25).[29] In addition to the emotional impact of having cancer, this observation could reflect the uncertainty of receiving active versus placebo treatment, being masked to their prostate-specific antigen concentration, and the tolerability of treatment.

Single-item data from the FACT-G items "I am bothered by side effects of treatment" and "I have lack of energy" further support the observation that apalutamide and placebo had similar tolerability in this patient population. The single FACT-G item "I am bothered by side-effects of treatment" is significantly associated with cancer patients' ability to enjoy life.[25] Most patients in both treatment groups reported that they were "not at all" bothered by side-effects from treatment. The proportion of patients who felt "quite a bit" or "very much" bothered was low, suggesting that apalutamide treatment was generally well tolerated. The proportion of patients who felt that they had lack of energy "quite a bit or very much" was similar between treatment groups (9–17% of patients in the apalutamide group and 7–13% of those in the placebo group). Changes from baseline in these single items showed that the majority of patients remained stable or improved from baseline in these domains.

The use of patient-reported outcome instruments to assess HRQOL has been well established in clinical trials of prostate cancer,[15,23,30] and assessment of changes in patient-reported outcomes is important to help improve clinical understanding of patients' cancer experiences and treatment. The Prostate Cancer Clinical Trials Working Group 3 recognises the importance of reporting patient experience as an essential therapeutic objective in people with prostate cancer.[31] The results from our study show that HRQOL was not impaired after initiation of apalutamide—treatment that improved median metastasis-free survival by more than 2 years (40·5 months *vs* 16·2 months; HR 0·28; 95% CI 0·23–0·35; p<0·0001) and improved time to symptomatic progression, compared with placebo.[20] Although patients in the placebo group had shorter median metastasis-free survival

compared with those in the apalutamide group,[20] HRQOL did not decrease during the treatment phase in our dataset. One possible explanation for this observation is that many metastases were detected in asymptomatic men by masked independent central review. Having blinded prostate-specific antigen values avoids the psychological effect of increasing prostate-specific antigen in asymptomatic men; thus an effect on HRQOL would not be expected. In this generally asymptomatic patient population, we did not anticipate linear change in patient-reported outcome scores because of disease progression during the treatment phase of the study. We used the mixed model of repeated measures rather than the slope model—which is used when there is a constant rate of deterioration and can increase when disease progression is non-linear—because we felt that it was a more appropriate model for use in an asymptomatic patient population in whom linear disease progression was unlikely. Because the mixed model for repeated measures is a conservative approach, the analysis might favour the patient-reported outcome data from the placebo group.

Studies in several cancers have shown that patient-reported outcomes are associated with key clinical outcomes such as treatment tolerability, hospital admission, and survival.[11,12] However, to our knowledge, there are no published reports of HRQOL for asymptomatic men with non-metastatic castration-resistant prostate cancer. The observation that FACT-G total scores at baseline in our patients were consistent with the FACT-G general population norm for US adult men provides corroboration of patient HRQOL status among patients with non-metastatic castration-resistant prostate cancer, since this patient population has historically been under-studied, and shows that HRQOL is preserved after initiation of treatment with apalutamide.

Our study has several potential limitations. First, missing data over time might have contributed to bias by non-ignorable dropout, which could have had different effects on the treatment groups. Second, clinical trial recruitment is subject to selection bias, and therefore our study sample might not be representative of all patients with non-metastatic castration-resistant prostate cancer. Third, the study included only a small number of non-white patients so the results might not be generalisable to minority populations, which requires further study. Finally, FACT-P threshold values are based on research in metastatic disease, so their relevance in the non-metastatic setting is unclear. A strength of the study is that compliance with patient-reported outcome assessments was high and outcomes were assessed over a long period. Future studies should include detailed assessments of pain and functional status, particularly after disease progression. Additionally, future studies should assess cognitive function in patients treated with androgen receptor inhibitors.

These analyses of patient-reported outcome data from SPARTAN indicate that overall HRQOL was maintained among patients treated with apalutamide in addition to androgen deprivation therapy for high-risk non-metastatic castration-resistant prostate cancer. Changes from baseline in patient-reported outcomes suggest that there was a greater decrease in HRQOL in the placebo group. Moreover, no differences were observed between treatment groups in perceived burden of side-effects. Patients treated with apalutamide had a longer metastasis-free survival than those treated with placebo, and both groups had similar HRQOL after metastasis. The fact that a novel, efficacious treatment can be added to current standard of care while maintaining patient HRQOL is a substantial advance for patients with non-metastatic castration-resistant prostate cancer and the clinicians who treat them. The extension of median metastasis-free survival by 2 years shown in SPARTAN, and maintenance of HRQOL from treatment initiation in this mostly asymptomatic population, suggests that apalutamide provides clinical benefit in the treatment of men with non-metastatic castration-resistant prostate cancer.

Contributors

FS, BAH, PNM, SO, JNG, EJS, and MRS participated in the conduct of the study. EJS and MRS designed the study. All authors participated in data interpretation, manuscript review, and approval of the final version of the manuscript for submission.

Declaration of interests

FS reports grants, personal fees, and non-financial support from Janssen, Astellas, Sanofi, and Bayer. DC is a consultant to AbbVie, Astellas, Bayer, Bristol-Myers Squibb, Daiichi Sankyo Inc, Evidera, GlaxoSmithKline, Helsinn, Ipsen, Janssen Research & Development, and Novartis, and is the president of FACIT.org. BAH reports grants from German Cancer Aid, German Research Foundation, and Profound Medical; grants, personal fees, and non-financial support from Janssen; personal fees and non-financial support from Astellas and Bayer; and grants and personal fees from Uromed. PNM reports personal fees from XING Technologies P/L, Ipsen, Janssen, Novartis, Pfizer, and Roche; grants and personal fees from Merck; and has a patent pending with XING Technologies P/L. SO reports personal fees from Janssen, Sanofi, Astellas, Bayer, and Merck. JNG reports grants and personal fees from Janssen, Sanofi, and Astellas; personal fees from Bayer and Dendreon; and grants from Merck and Bristol-Myers Squibb. SH reports consulting fees from Janssen. MRS reports grants and personal fees from Janssen; and personal fees from Astellas and Bayer. KM, SL, JL, AL-G, and MKY are employed by Janssen Research & Development, and hold stock in Johnson & Johnson. EB and EJS declare no competing interests.

Acknowledgments

This study was funded by Janssen Research & Development. Editorial assistance was provided by Ann P Tighe, PhD, of PAREXEL (Hackensack, NJ, USA), with funding from Janssen Global Services LLC (Raritan, NJ, USA).

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