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Apalutamide Plus Androgen Deprivation Therapy for Metastatic Castration-Sensitive Prostate Cancer: Analysis of Pain and Fatigue in the Phase 3 TITAN Study

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Abstract

Purpose: Exploratory analysis of prostate cancer–related pain and fatigue on health-related quality of life in patients with metastatic castration-sensitive prostate cancer (mCSPC) receiving apalutamide (240 mg/day) or placebo, with continuous androgen-deprivation therapy (ADT), in the phase 3, randomized, double-blind placebo-controlled TITAN trial (NCT02489318).

Materials and Methods: Patient-reported outcomes for pain and fatigue were evaluated using the Brief Pain Inventory-Short Form (BPI-SF) and Brief Fatigue Inventory (BFI). Time to deterioration (TTD) was estimated by Kaplan-Meier method; hazard ratios and 95% confidence intervals were calculated using Cox proportional-hazards model. General estimating equations for logistic regression estimated treatment-related differences in the likelihood of worsening pain or fatigue.

Results: Compliance for completing the BPI-SF and BFI was high (96% to 97%) in the first year. Median follow-up times were similar between treatments (19 to 22 months). Median pain TTD was longer with apalutamide than placebo for “pain at its least in the last 24 hours” (28.7 vs 21.8 months, respectively; p = 0.0146), “pain interfered with mood” (not estimable [NE] vs 22.4 months; p = 0.0017), “pain interfered with walking ability” (28.7 vs 20.2 months; p = 0.0027), “pain interfered with relations” (NE vs 23.0 months; p = 0.0139), “pain interfered with sleep” (28.7 vs 20.9 months; p = 0.0167). Likelihood for fatigue and worsening fatigue was similar between groups.

Conclusions: mCSPC patients receiving apalutamide plus ADT vs placebo plus ADT reported consistently favorable TTD of pain. No difference for change in fatigue was observed with apalutamide vs placebo.

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INTRODUCTION

Prostate cancer is the second most common cancer in men and the fifth most deadly, accounting for 13.5% of male cancers and 6.7% of male cancer deaths globally.[1]

Pain and fatigue are common symptoms of metastatic prostate cancer.[2] Bone is the most common site of metastasis in patients with metastatic prostate cancer,[3] and pain is the most common indicative symptom, occurring in 75% of patients with bone metastases.[4] Another symptom of metastatic prostate cancer is fatigue, reported in ~73% of patients.[5,6] Fatigue is also a common and substantial adverse effect of androgen-deprivation therapy (ADT).[7] Fatigue and pain can have severe detrimental effects on health-related quality of life (HRQoL).[2,6]

Recent studies have shown that efficacy outcomes, including prolonged survival, are improved if androgen-signaling inhibitors are added to ADT at its initiation or shortly after, while the cancer remains castration sensitive.[8-12] Data show that the addition of these agents to ADT delays worsening of HRQoL compared with ADT alone.[13] Apalutamide is an oral, nonsteroidal androgen receptor inhibitor.[14] In TITAN, apalutamide plus ADT significantly improved overall survival compared with placebo plus ADT and also significantly improved radiographic progression-free survival.[15] Based on the primary results of the TITAN study, apalutamide has been approved in multiple countries, including the United States[16] and the European Union,[17] for the treatment of men with metastatic castration-sensitive prostate cancer (mCSPC).

The effect of apalutamide on HRQoL, as assessed using patient-reported outcomes (PROs), was analyzed in TITAN.[18] In prespecified analyses, patients' experience of pain and fatigue (intensity and interference) did not differ between the apalutamide and placebo groups. HRQoL, as shown by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) and EuroQol 5D questionnaire 5 level (EQ-5D-5L), was preserved in both groups.[18] Herein, we present a post hoc analysis of PROs from the TITAN study that evaluates the likelihood of meaningful deterioration of pain and fatigue.

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MATERIALS AND METHODS

Study Design and Participants

Details of the TITAN study have been published previously.[15,18] Briefly, TITAN is a phase 3, randomized, double-blind placebo-controlled trial conducted in patients with mCSPC and distant metastatic disease documented by at least 1 lesion on bone scanning. Key eligibility criteria included castration sensitivity and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were permitted to have received up to 6 previous cycles of docetaxel, and ADT for ≤6 months for mCSPC or ≤3 years for localized prostate cancer. Treatments for localized disease must have been completed ≥1 year before randomization.

Review boards at all participating institutions approved the study, which was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice and in accordance with the principles of the Declaration of Helsinki. All patients provided written, informed consent.

Procedures

Patients were randomized 1:1 to receive apalutamide 240 mg/day orally or matching placebo, in addition to continuous ADT (fig. 1). Choice of ADT was at the investigator's discretion. Treatment continued until disease progression, withdrawal of consent or unacceptable treatment-related toxicity.

Randomization was stratified by a Gleason score at diagnosis (≤7 vs >7), geographic region (North America and European Union vs all other countries) and previous treatment with docetaxel (yes vs no).

Outcomes

Clinical outcomes of the TITAN study have been reported previously.[15] Outcomes for pain and fatigue were assessed by the Brief Pain Inventory-Short Form (BPI-SF)[19,20] and the Brief Fatigue Inventory (BFI),[21] respectively. The BPI-SF includes 15 questions addressing pain intensity and interference from pain rated from 0 (no pain/interference) to 10 (pain/interference

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as bad as you can imagine) in the last 24 hours and at the time of reporting.[19] The BFI includes 9 questions addressing fatigue and interference from fatigue similar to the BPI-SF described above.

The BPI-SF and BFI were completed at baseline and averaged over 7 consecutive days every 28 days and then again at months 4, 8 and 12 post completion of study treatment. The data cutoff was November 23, 2018.

Median time to deterioration (TTD) and the likelihood of deterioration as a comparison between the apalutamide and placebo groups were assessed for each question in the BPI-SF and BFI. The likelihood of improvement of pain and fatigue was also compared between the 2 groups.

Statistical analysis

Patient compliance was calculated as a percentage of the questionnaires expected vs those received for each visit and for the study. Descriptive statistics are reported for each PRO at baseline and at follow-up assessments by treatment group.

Median TTD for pain and fatigue was estimated using the Kaplan-Meier method, with hazard ratios and 95% confidence intervals (CIs) calculated using the Cox proportional-hazards model. If median values could not be estimated because fewer than 50% of patients had progression, 25th percentiles are reported.

TTD was defined as the time interval from randomization to the first date that a patient experienced a threshold worsening. Time to pain intensity progression (worst pain in the previous 24 hours) was defined as a 30% increase in worst pain, with no decrease in opioid use confirmed, ≥3 weeks apart. A 2-point increase in worst pain confirmed ≥3 weeks apart, with no decrease in opioid use, was conducted as a sensitivity analysis. Time to BPI-SF interference progression was defined as an increase in the patient's score from baseline of half standard deviation (scores confirmed ≥3 weeks apart) with no decrease in opioid use. Time to average pain progression was defined as the elapsed time between randomization and the first postbaseline BPI-SF assessment date that a patient experienced a ≥30% increase from

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baseline in BPI-SF (an average of items 3 to 6) observed at 2 consecutive evaluations ≥3 weeks apart with no decrease in opioid use. Time to fatigue intensity progression was defined as the time interval from randomization to the first date a patient experienced an increase of ≥2 points from baseline in the worst BFI intensity item (item 3) observed at 2 consecutive evaluations ≥3 weeks apart.[22] Fatigue interference progression was defined as an increase of ≥1.25 points from baseline in the average BFI interference score observed at 2 consecutive evaluations ≥3 weeks apart.[22]

For likelihood of improvement end points, patients with no pain improvement or fatigue improvement were censored at the date of the last assessment. General estimating equations for logistic regression were used to estimate longitudinal treatment-related differences and odds ratios for likelihood of worsening in pain or fatigue scores. For pain, the likelihood of a ≥2-point improvement (on a scale of 0 to 10) in the BPI-SF items "worst pain," "average pain" and "pain interference" while on treatment was compared between the apalutamide and placebo groups in patients with pain at baseline. For fatigue, the likelihood of a ≥2-point improvement in the BFI item "worst fatigue" and of a ≥1.5-point improvement in the "fatigue interference" item (on a scale of 0 to 10) while on treatment was compared between the apalutamide and placebo groups in patients with fatigue at baseline.

RESULTS

Patient Baseline Characteristics

Between December 2015 and July 2017, 1,052 eligible patients were enrolled in TITAN and randomized to receive apalutamide (n=525) or placebo (n=527) (supplementary fig. 1).[15,18] Median follow-up for overall survival in the current analysis was 22.7 months (interquartile range [IQR] 19.4–25.8]). Median treatment durations were 20.5 months (IQR 14.9–24.7) for patients in the apalutamide group and 18.3 months (IQR 10.3–22.9) for patients in the placebo group.[15,18]

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TITAN enrolled a broad population of patients with mCSPC at 260 sites across 23 countries, and demographics and baseline characteristics were well balanced between the groups (supplementary table 1). Patient characteristics at baseline have been reported previously.[15,18] Median follow-up times for pain analyses were similar between the apalutamide and placebo groups (table 1).

Compliance for completion of the PRO instruments was 97% for the BPI-SF and 96% to 97% for the BFI across the first year of therapy. Most patients (apalutamide, 75%; placebo, 77%) reported no or mild pain (scores 0 to 3) at baseline (supplementary table 1). Median BPI-SF pain scores for worst pain in the previous 24 hours were 1.14 in the apalutamide group and 1.00 in the placebo group. Similarly, many patients reported no (apalutamide, 32%; placebo, 34%) or only mild (42% in both groups) fatigue in the BFI at baseline (supplementary table 1).

Patient-Reported Pain Outcomes (BPI-SF)

Among patients with pain at baseline, those treated with apalutamide had a greater confirmed risk of improvement than those who received placebo (fig. 2A).[18] Patients in the apalutamide group were 29% more likely to have an improvement in their worst pain than those who received placebo; the difference was statistically significant (p = 0.02). Patients in the apalutamide group also had a 22% greater likelihood of improvement in average pain compared with patients receiving placebo; the difference was not significant (p = 0.16). The likelihood of improvement in pain interference was similar between the apalutamide and placebo groups.

The likelihood of deterioration of BPI-SF pain items is shown in figure 2B. All odds ratios (ORs) favored apalutamide. The risk of deterioration for some individual BPI-SF pain items was significantly lower with apalutamide than with placebo: “pain interfered with mood” (OR 0.73; 95% CI 0.57–0.94; p = 0.0146), “pain interfered with sleep” (OR 0.77; 95% CI 0.60–0.99; p = 0.0444) and “pain interference score” (OR 0.79; 95% CI 0.64–0.98; p = 0.0317).

Median TTD in individual pain items on the BPI-SF was generally similar or prolonged with apalutamide compared with placebo (fig. 2C). Median TTD for pain was significantly longer in

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the apalutamide group than in the placebo group for the BPI-SF items “pain at its least in the last 24 hours” (28.7 vs 21.8 months, respectively; log-rank p = 0.0146), “pain interfered with mood” (not estimable vs 22.4 months; log-rank p = 0.0017), “pain interfered with walking ability” (28.7 vs 20.2 months; log-rank p = 0.0027), “pain interfered with relations” (not estimable vs 23.0 months; log-rank p = 0.0139) and “pain interfered with sleep” (28.7 vs 20.9 months; log-rank p = 0.0167).

Patients with no or mild pain (scores 0 to 3 in FACT-P worst pain in the last 24 hours) at baseline had little change in mean pain scores over the 29 cycles of treatment (supplementary fig. 2). Those with moderate pain (scores 4 to 7) or severe pain (scores >7 to 10) at baseline saw their mean scores improve (decrease) over time during this study.

Individual responses to pain showed that those with no pain or mild pain at baseline had stable scores over time (supplementary fig. 3A, 3B). Those with moderate or severe pain at baseline saw improvement in pain over time (supplementary fig. 3C, 3D).

Patient-Reported Fatigue (BFI)

The likelihood of patients being fatigued or experiencing increased fatigue was not different between the apalutamide and placebo groups (fig, 3A, 3B).

There were no significant differences between treatment groups on mean BFI domain scores (supplementary fig. 4A, 4B) or in TTD for any BFI items (fig. 3C). While apalutamide was associated with longer median TTDs for “fatigue interfered with walking ability,” “fatigue interfered with mood” and “fatigue interfered with relations” compared with placebo, these differences were not statistically significant.

DISCUSSION

Pain and fatigue are common symptoms in advanced prostate cancer and have a strong impact on HRQoL.[23] In this exploratory analysis, pain and fatigue were improved or not worsened in patients with mCSPC treated with apalutamide compared with placebo. Combined with the

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significant improvement in radiographic progression-free survival and overall survival reported in the overall analysis of the study,[15] these findings support the clinical benefit of apalutamide in patients with mCSPC.

Several factors contributed to a heterogeneous range of pain severity levels among patients in the study at baseline, including those with no or mild pain. TITAN had no criteria limiting the pain level a patient could be experiencing at baseline, whereas other studies in metastatic prostate cancer only included patients with mild pain (a maximum score of 3 on the BPI-SF) at baseline as part of the inclusion criteria.[24-27] Patients entering TITAN were to have been receiving ADT for a minimum of 2 weeks and up to 6 months (median duration of ADT therapy was 1.8 months[18]); therefore, it is possible that patients may have benefitted from some pain relief from ADT in advance of starting apalutamide or placebo.

TTD of pain and time to pain interference item scores consistently favored apalutamide over placebo, and the differences between apalutamide and placebo were significant for several individual BPI-SF items (ie, least pain, mood, walking ability, relations and sleep). Patients who received apalutamide consistently had less likelihood of pain deterioration and interference than patients who received placebo. The item that was significant in both analyses was “pain interfered with mood.” Patients with more severe pain at baseline who received apalutamide were significantly more likely to see an improvement in pain than those who received placebo, and this difference was significant for “worst pain.”

Although fatigue is frequently reported with metastatic prostate cancer and ADT treatment, most patients (75%) enrolled in TITAN had no or only mild fatigue at baseline. The addition of apalutamide to ADT did not have a significant effect on fatigue over the course of the study compared with placebo plus ADT. In these analyses, the fatigue experienced by patients in the apalutamide group was no greater than in the placebo group, which supports previous data.[18] The likelihood of fatigue deterioration was also similar between the groups, and, while some

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comparisons for TTD of individual BFI items trended toward favoring apalutamide, there were no significant differences between the groups.

This study is a post hoc analysis and has limitations associated with such. Only 1.8% of the TITAN population were Black or African American and 22% of the patients in TITAN were Asian. Thus, the robustness of the findings presented here in non-white populations may require further study.

CONCLUSIONS

In the phase 3 TITAN study, patients with mCSPC receiving continuous ADT reported consistently favorable pain scores and less interference from pain in their daily lives with the addition of apalutamide than with the addition of placebo. Furthermore, no additional patient-reported fatigue was observed with the addition of apalutamide to ADT relative to placebo. Together with the primary efficacy results from TITAN,[15] these findings demonstrate that while patients benefitted through delayed disease progression, they also maintained HRQoL with no additional pain and fatigue burden. These data represent an important addition to the efficacy and safety data previously reported with the addition of apalutamide to ADT. They highlight the value of gaining an understanding of an individual patient's baseline pain and fatigue and monitoring these through the course of treatment.

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Data sharing policy

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

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

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of, Glactone Pharma; and has 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; and 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/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 and Bayer. 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 and ALG 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. All remaining authors have nothing to disclose.

Author contributions

NA, AB, SC, AJPSG, BHC, MO, AJS, ASM, HU, DY and RG are investigators who participated in the conduct of the study. KNC, KM, BM and ALG designed the study. NA led the

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development of the manuscript. All authors participated in data interpretation, manuscript review and approval of the final version of the manuscript for submission.

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References

1. Bray F, Ferlay J, Soerjomataram I et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; **68**: 394.

2. Holm M, Doveson S, Lindqvist O et al: Quality of life in men with metastatic prostate cancer in their final years before death - a retrospective analysis of prospective data. BMC Palliat Care 2018; **17**: 126.

3. Cathomas R, Bajory Z, Bouzid M et al: Management of bone metastases in patients with castration-resistant prostate cancer. Urol Int 2014; **92**: 377.

4. Ibrahim T, Farolfi A, Mercatali L et al: Metastatic bone disease in the era of bone-targeted therapy: clinical impact. Tumori 2013; **99**: 1.

5. Drudge-Coates L, Oh WK, Tombal B et al: Recognizing symptom burden in advanced prostate cancer: A global patient and caregiver survey. Clin Genitourin Cancer 2018; **16**: e411.

6. Rodriguez Antolin A, Martinez-Pineiro L, Jimenez Romero ME et al: Prevalence of fatigue and impact on quality of life in castration-resistant prostate cancer patients: the VITAL study. BMC Urol 2019; **19**: 92.

7. Downing A, Wright P, Hounsome L et al: Quality of life in men living with advanced and localised prostate cancer in the UK: a population-based study. Lancet Oncol 2019; **20**: 436.

8. Fizazi K, Tran N, Fein L et al: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017; **377**: 352.

9. James ND, de Bono JS, Spears MR et al: Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017; **377**: 338.

10. James ND, Sydes MR, Clarke NW et al: Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016; **387**: 1163.

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11. Kyriakopoulos CE, Chen YH, Carducci MA et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: Long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018; **36**: 1080.

12. Sweeney CJ, Chen YH, Carducci M et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015; **373**: 737.

13. Kretschmer A, Ploussard G, Heidegger I et al: Health-related quality of life in patients with advanced prostate cancer: A systematic review. Eur Urol Focus S2405-4569(20)30064-X.

14. Clegg NJ, Wongvipat J, Joseph JD et al: ARN-509: a novel antiandrogen for prostate cancer treatment. Cancer Res 2012; **72**: 1494.

15. Chi KN, Agarwal N, Bjartell A et al: Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019; **381**: 13.

16. ERLEADA (apalutamide) [prescribing information]. Janssen Pharmaceutical Companies, Horsham, PA; 2019.

17. European Medicines Agency: Erleada (apalutamide). https://www.ema.europa.eu/en/medicines/human/EPAR/erleada. Accessed January 19, 2021.

18. Agarwal N, McQuarrie K, Bjartell A et al: Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study. Lancet Oncol 2019; **20**: 1518.

19. Cleeland CS: Brief pain inventory (short form). http://www.npcrc.org/files/news/briefpain_short.pdf. Accessed April 15, 2020.

20. Cleeland CS, Ryan KM: Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994; **23**: 129.

21. The University of Texas M. D. Anderson Cancer Center. Brief Fatigue Inventory. http://www.npcrc.org/files/news/brief_fatigue_inventory.pdf. Accessed April 15, 2020.

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22. Sternberg CN, Molina A, North S et al: Effect of abiraterone acetate on fatigue in patients with metastatic castration-resistant prostate cancer after docetaxel chemotherapy. Ann Oncol 2013; **24**: 1017.

23. Chen RC, Chang P, Vetter RJ et al: Recommended patient-reported core set of symptoms to measure in prostate cancer treatment trials. J Natl Cancer Inst 2014; **106**.

24. Basch E, Autio K, Ryan CJ et al: Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. Lancet Oncol 2013; **14**: 1193.

25. Loriot Y, Miller K, Sternberg CN et al: Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. Lancet Oncol 2015; **16**: 509.

26. Ryan CJ, Smith MR, Fizazi K et al: Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2015; **16**: 152.

27. Ye D, Huang Y, Zhou F et al: A phase 3, double-blind, randomized placebo-controlled efficacy and safety study of abiraterone acetate in chemotherapy-naive patients with mCRPC in China, Malaysia, Thailand and Russia. Asian J Urol 2017; **4**: 75.

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Figure and Table Captions

Table 1. *Follow-up times*

Figure 1. Design of the TITAN study.

ECOG PS, Eastern Cooperative Oncology Group performance status; *EU*, European Union; *NA*, North America; *OS*, overall survival; *PSA*, prostate-specific antigen; *rPFS*, radiographic progression-free survival.

Figure 2. (A) Likelihood of pain improvement[a]; (B) model-based likelihood of deterioration in BPI-SF scale items[18]; (C) time to deterioration in pain per individual BPI-SF items.

[a]Analysis examined patients with pain at baseline who experienced a ≥2-point improvement on a scale of 0–10 with treatment. *p < 0.05 for apalutamide vs placebo.

APA, apalutamide; *NE*, not estimable; *OR*, odds ratio; *PBO*, placebo; *RR*, risk ratio.

Figure 3. (A) Likelihood of fatigue; (B) model-based likelihood of deterioration in BFI scale items; (C) time to fatigue deterioration.

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Abbreviations and Acronyms

ADT = androgen-deprivation therapy

BFI = Brief Fatigue Inventory

BPI-SF = Brief Pain Inventory-Short Form

CI = confidence interval

EQ-5D-5L = EuroQol 5D questionnaire 5 level

FACT-P = Functional Assessment of Cancer Therapy-Prostate

HRQoL = health-related quality of life

IQR = interquartile range

mCSPC = metastatic castration-sensitive prostate cancer

NE = not estimable

OR = odds ratio

PRO = patient-reported outcome

TTD = time to deterioration

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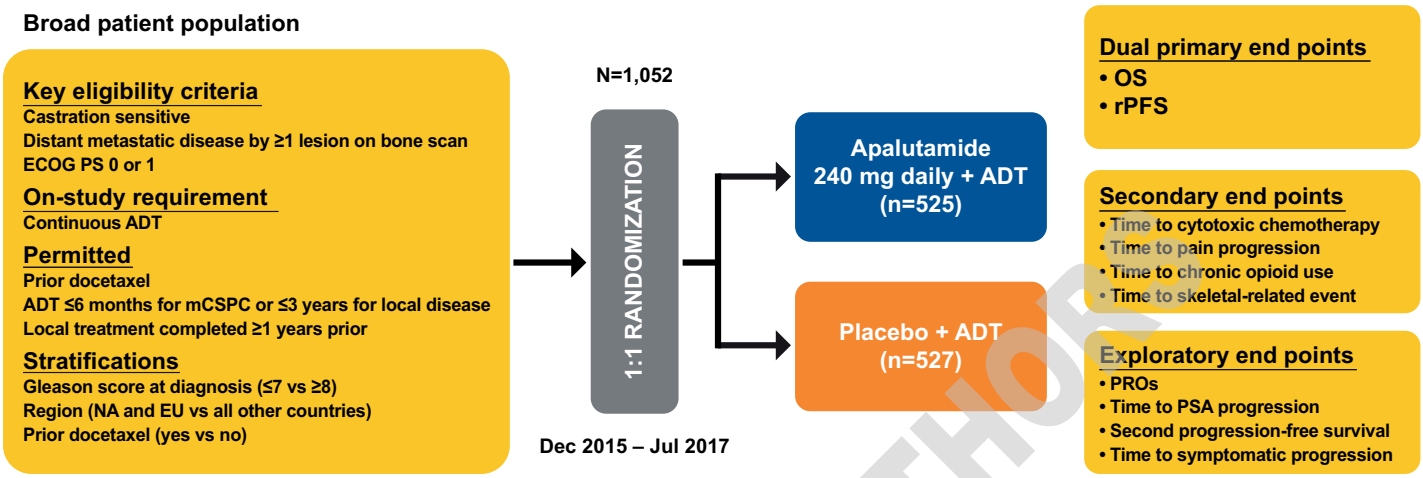
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Table 1. *Follow-up times*

Median (interquartile range), months	Apalutamide (n=525)	Placebo (n=527)
Pain progression	22.1 (18.4–25.6)	21.7 (18.4–24.9)
Worst pain	20.2 (16.6–24.0)	19.4 (14.8–23.4)
Average pain progression	20.3 (16.6–24.0)	19.6 (15.1–23.4)
Pain interference progression	20.3 (16.6–24.6)	19.7 (15.6–24.0)

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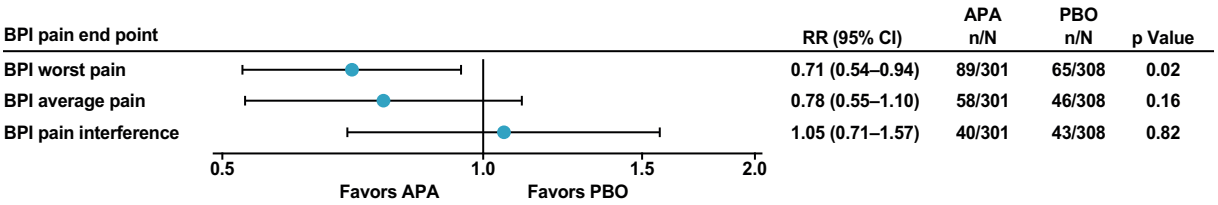
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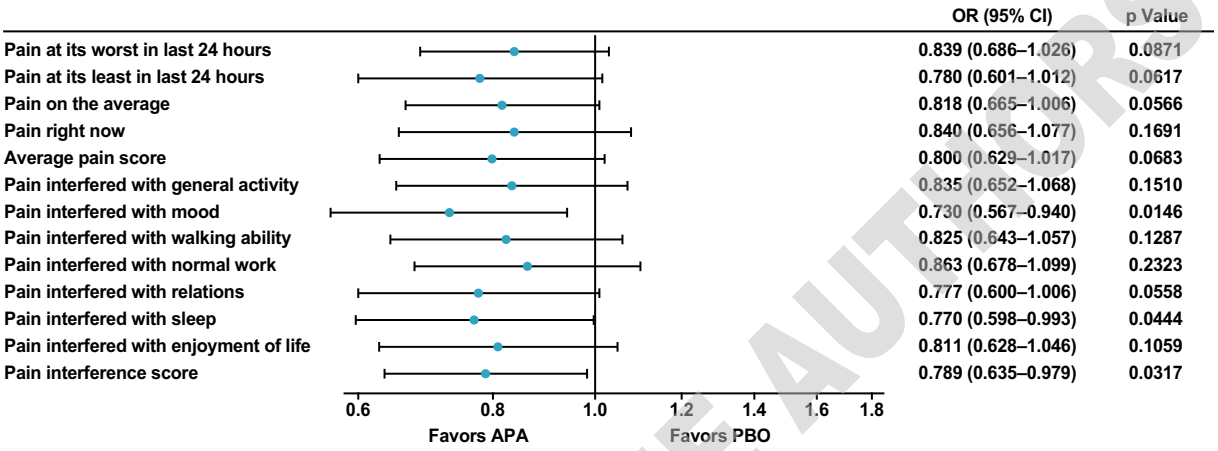
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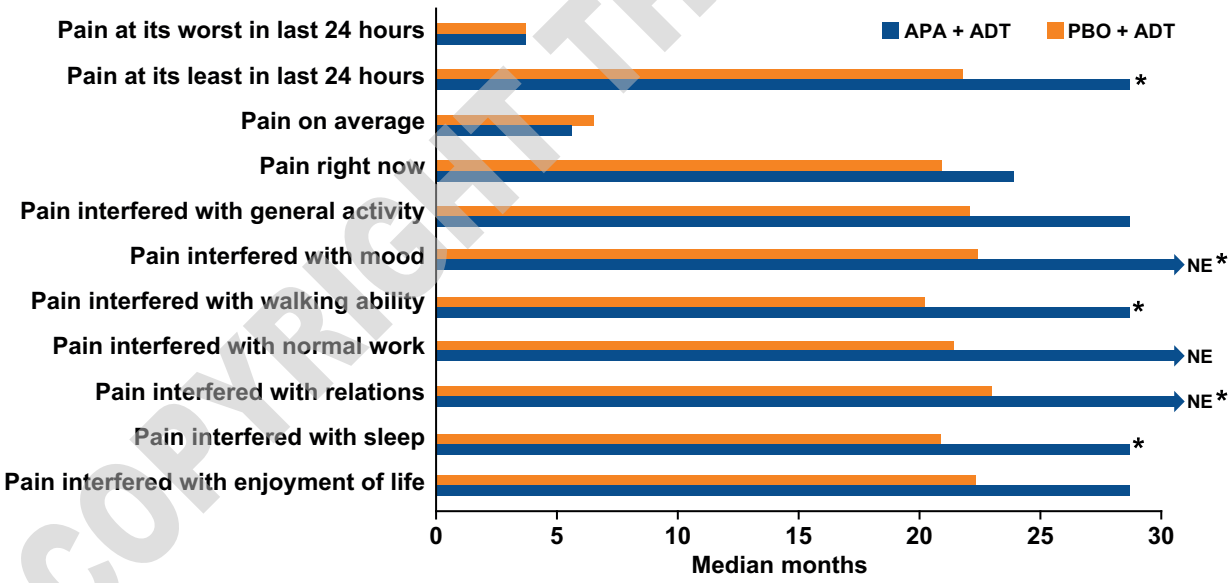
A



B



C

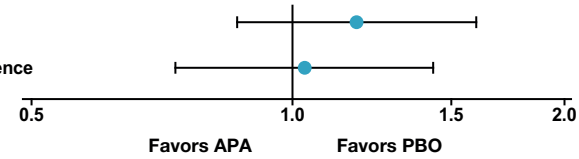


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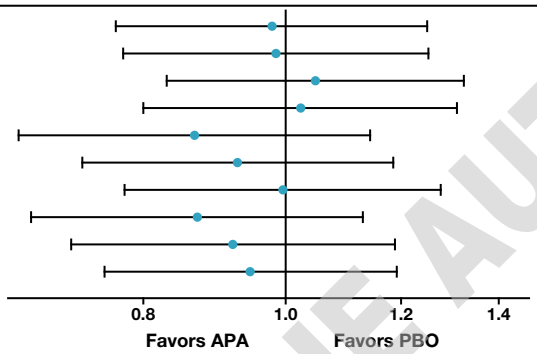
A

BFI fatigue end point	RR (95% CI)	APA n/N	PBO n/N	p Value
BFI worst fatigue	1.18 (0.87–1.60)	61/329	72/331	0.31
BFI fatigue interference	1.03 (0.74–1.43)	58/329	60/331	0.88

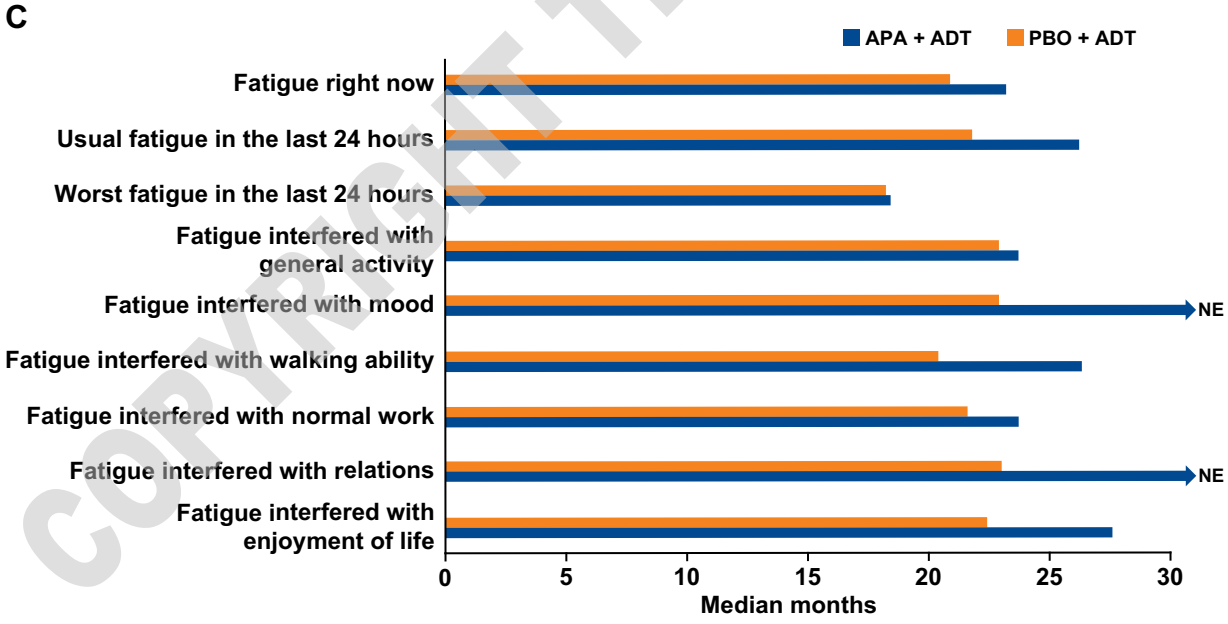


B

	OR (95% CI)	p Value
Fatigue right now	0.979 (0.766–1.250)	0.8631
Usual fatigue in the last 24 hours	0.985 (0.775–1.253)	0.9038
Worst fatigue in the last 24 hours	1.048 (0.830–1.325)	0.6927
Fatigue interfered with general activity	1.024 (0.801–1.310)	0.8485
Fatigue interfered with mood	0.867 (0.658–1.143)	0.3111
Fatigue interfered with walking ability	0.928 (0.727–1.185)	0.5491
Fatigue interfered with normal work	0.996 (0.777–1.277)	0.9755
Fatigue interfered with relations	0.870 (0.671–1.129)	0.2959
Fatigue interfered with enjoyment of life	0.921 (0.714–1.188)	0.5275
BFI fatigue interference progression	0.947 (0.752–1.191)	0.6404



C



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