

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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Study Need and Importance: Patients with advanced prostate cancer commonly experience pain and fatigue, and these symptoms can have a dramatic impact on health-related quality of life. In TITAN, a randomized, double-blind placebo-controlled study in metastatic castration-sensitive prostate cancer (mCSPC), apalutamide plus androgen deprivation therapy (ADT) significantly improved overall survival and radiographic progression-free survival compared with placebo plus ADT while maintaining health-related quality of life. In this exploratory analysis of TITAN, we evaluated the likelihood of clinically meaningful deterioration of patient-reported pain and fatigue with apalutamide vs placebo.

What We Found: Among patients with baseline pain (609), those receiving apalutamide were 29% more likely to have an improvement in their worst pain than those receiving placebo ($p=0.02$). Median time to deterioration of pain (Brief Pain Inventory-Short Form items) was longer with apalutamide than placebo for “pain at its least in the last 24 hours,” “pain interfered with mood,” “pain interfered with walking ability,” “pain interfered with relations” and “pain interfered with sleep” (all $p < 0.05$; see figure). Patient-reported fatigue was not increased with addition of apalutamide to ADT.

Limitations: Limitations include the post hoc nature of the analysis.

Interpretation for Patient Care: New treatments for advanced cancer should improve survival and symptoms of cancer without increasing the fatigue patients with prostate cancer frequently endure. This study demonstrates that patients with mCSPC who received apalutamide in addition to standard ADT report longer time to pain worsening, and no worsening of patient-reported fatigue than those who received placebo plus ADT. Combined with its survival benefits, these findings support the clinical benefit of apalutamide in patients with mCSPC.

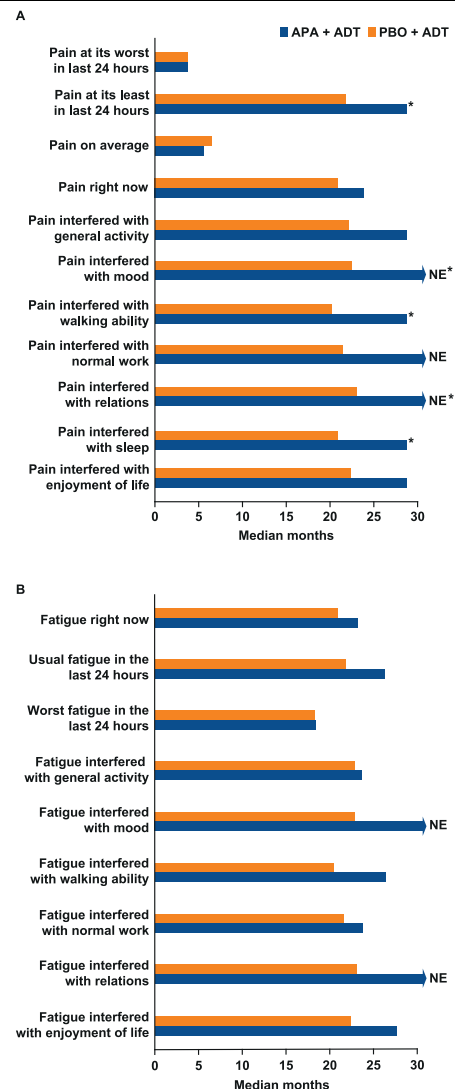


Figure. Time to deterioration in pain (A) and fatigue (B) based on individual questions from Brief Pain Inventory-Short Form questionnaire administered to patients (TITAN study). * $p < 0.05$ for apalutamide (APA) vs placebo (PBO). NE, not estimable.

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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Purpose: We performed an exploratory analysis of prostate cancer-related pain and fatigue on health-related quality of life in patients with metastatic castration-sensitive prostate cancer 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 and Brief Fatigue Inventory. 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 Brief Pain Inventory-Short Form and Brief Fatigue Inventory was high (96% to 97%) in the first year. Median followup 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 vs 22.4 months; $p=0.0017$), “pain interfered with walking ability”

Abbreviations and Acronyms

ADT = androgen deprivation therapy

BFI = Brief Fatigue Inventory

BPI-SF = Brief Pain Inventory-Short Form

FACT-P = Functional Assessment of Cancer Therapy-Prostate

HRQoL = health-related quality of life

mCSPC = metastatic castration-sensitive prostate cancer

NE = not estimable

PRO = patient-reported outcome

TTD = time to deterioration

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(28.7 vs 20.2 months; $p=0.0027$), “pain interfered with relations” (not estimable vs 23.0 months; $p=0.0139$) and “pain interfered with sleep” (28.7 vs 20.9 months; $p=0.0167$). Likelihood for fatigue and worsening fatigue were similar between groups.

Conclusions: Patients with metastatic castration-sensitive prostate cancer 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.

Key Words: apalutamide, quality of life, prostatic neoplasms, neoplasm metastasis

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 States¹⁶ 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, was preserved in both groups.¹⁸ Herein, we present a post hoc analysis of PROs from the TITAN study, which evaluated the likelihood of meaningful deterioration of pain and fatigue.

MATERIALS AND METHODS

Study Design and Participants

Details of the TITAN study have been published previously (NCT02489318).^{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 Harmonization 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 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

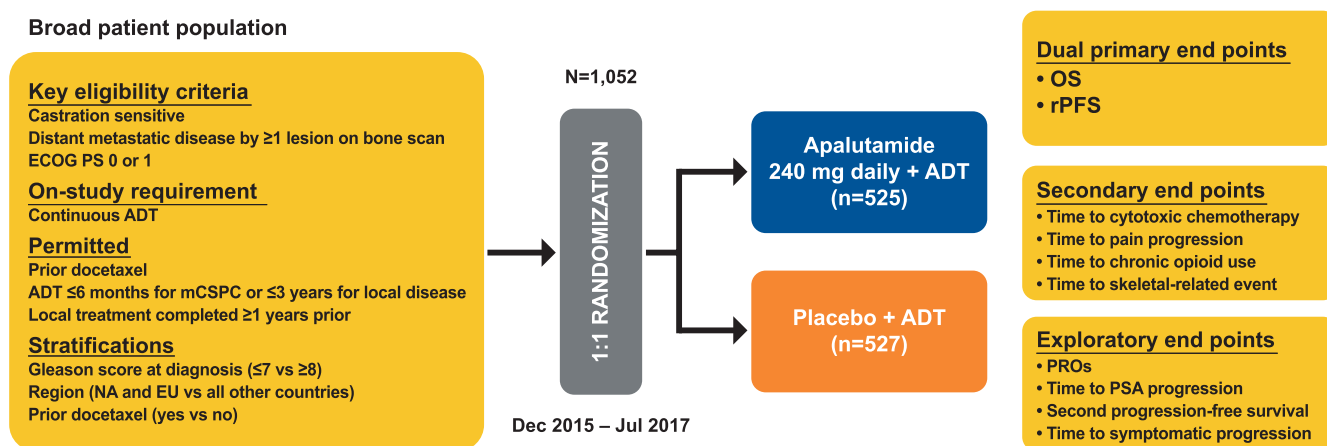


Figure 1. Design of TITAN study. ECOG PS, Eastern Cooperative Oncology Group performance status. EU, European Union. NA, North America. OS, overall survival. PSA, prostate specific antigen. rPFS, radiographic progression-free survival.

and for the study. Descriptive statistics are reported for each PRO at baseline and at followup assessments by treatment group.

Median TTD for pain and fatigue was estimated using the Kaplan-Meier method, with hazard ratios and 95% confidence intervals 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 post-baseline BPI-SF assessment date that a patient experienced a $\geq 30\%$ increase from 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 (525) or placebo (527; supplementary fig. 1, <https://www.jurology.com>).^{15,18} Median followup for overall survival in the current analysis was 22.7 months (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}

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 (see supplementary table, <https://www.jurology.com>). Patient characteristics at baseline have been reported previously.^{15,18} Median followup times for pain analyses were similar between the apalutamide and placebo groups (see table).

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 (see supplementary table, <https://www.jurology.com>). Median BPI-SF pain scores for worst pain in the previous 24 hours were 1.14 in the apalutamide

Followup times

	Median Mos (IQR)	
	Apalutamide (525 pts)	Placebo (527 pts)
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)
Av 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)

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 (see supplementary table, <https://www.jurology.com>).

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. 2, A).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 2, part B. All odds ratios 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. 2, C). Median TTD for pain was significantly longer in 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, <https://www.jurology.com>). 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. 3, A and B, <https://www.jurology.com>). Those with moderate or severe pain at baseline saw improvement in pain over time (supplementary fig. 3, C and D, <https://www.jurology.com>).

Patient-Reported Fatigue (BFI)

The likelihood of patients being fatigued or experiencing increased fatigue was not different between the apalutamide and placebo groups (fig. 3, A and B). There were no significant differences between treatment groups on mean BFI domain scores (supplementary fig. 4, A and B, <https://www.jurology.com>) or in TTD for any BFI items (fig. 3, C). 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 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 months¹⁸); 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

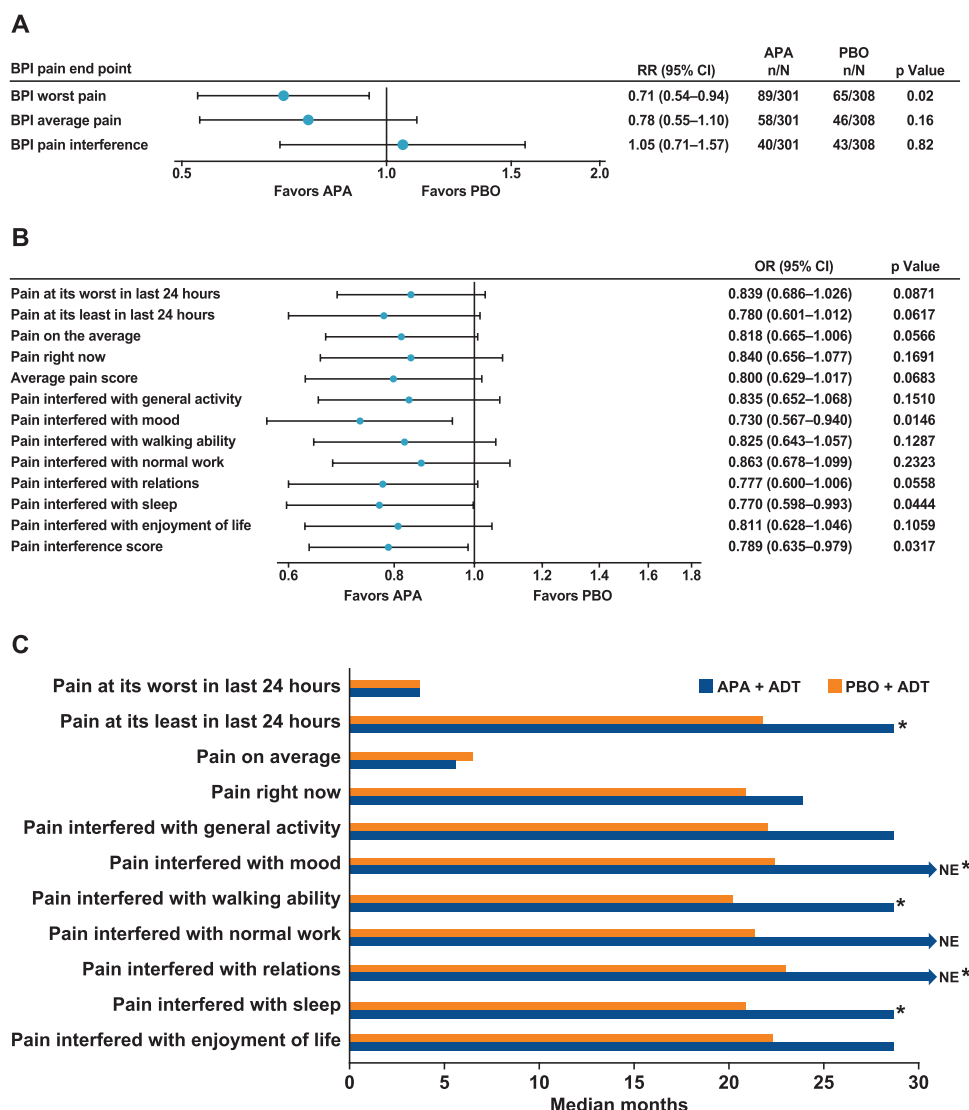


Figure 2. A, likelihood of pain improvement. Analysis examined patients with pain at baseline who experienced a ≥ 2 -point improvement on scale of 0–10 with treatment. B, model-based likelihood of deterioration in BPI-SF scale items.¹⁸ C, time to deterioration in pain per individual BPI-SF items. * $p < 0.05$ for apalutamide vs placebo. APA, apalutamide. PBO, placebo. n/N, number/total number. RR, risk ratio.

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 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 nonwhite 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

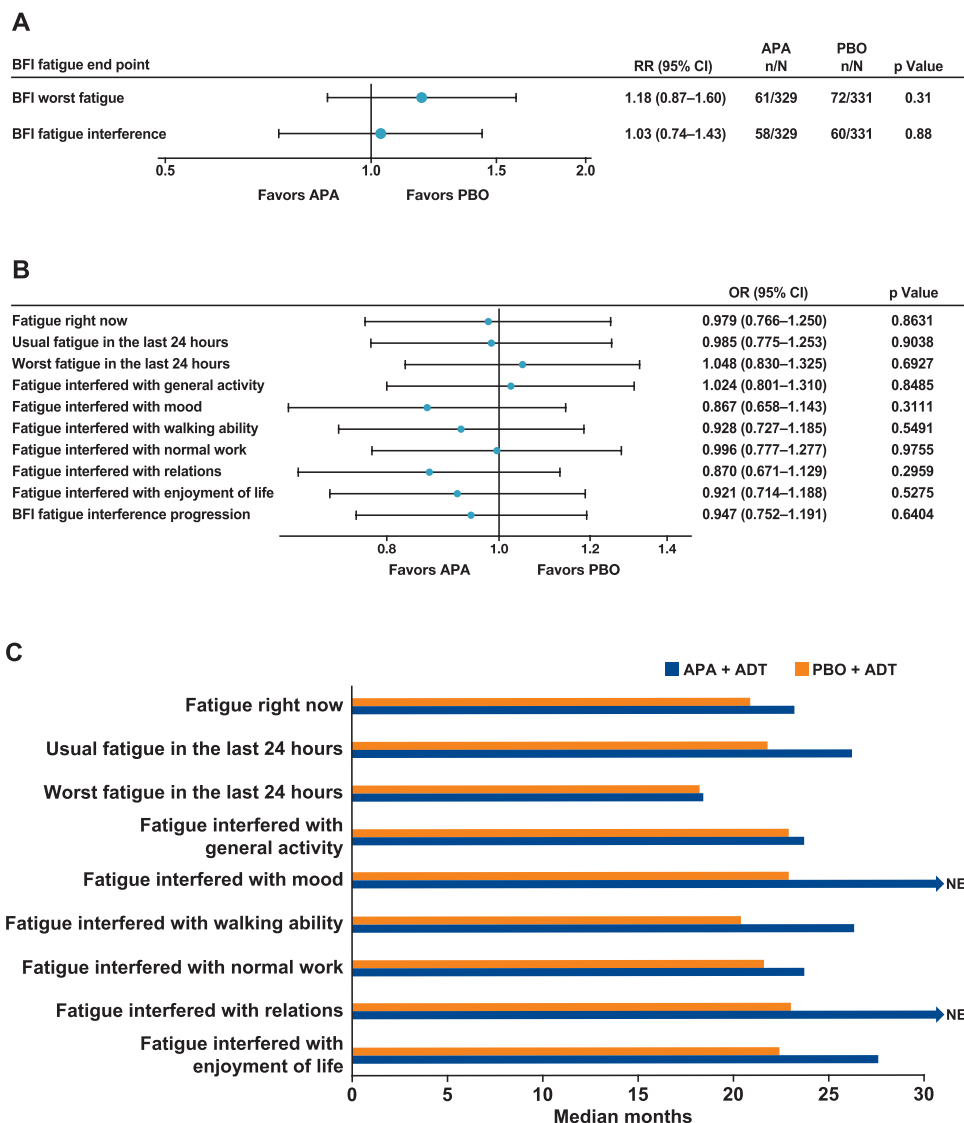


Figure 3. A, likelihood of fatigue. B, model-based likelihood of deterioration in BFI scale items. C, time to fatigue deterioration. APA, apalutamide. PBO, placebo. n/N, number/total number. RR, risk ratio.

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.

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, New-Link Genetics, Prometheus Laboratories, Rexahn Pharmaceuticals, Sanofi, Takeda and Traccon 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 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

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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 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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EDITORIAL COMMENTS

The assessment of PROs, such as HRQoL or patient-reported symptoms, is part of the usual approval process for new treatments and strongly influences the clinical decision-making pathway. Previous studies suggested a significant improvement in HRQoL among mCSPC patients receiving androgen-signaling inhibitors in addition to ADT compared to ADT alone.^{1,2} Furthermore, the TITAN study, a phase 3, randomized, double-blind trial, has recently assessed an overall survival benefit from apalutamide plus ADT compared to placebo plus ADT among mCSPC patients (reference 15 in article).

Considering these promising oncologic results, Agarwal et al performed an exploratory analysis of PROs from the TITAN study, focusing on the likelihood of meaningful deterioration of pain and fatigue among a cohort of 1,052 mCSPC patients. At baseline analysis, 75% of individuals receiving apalutamide and 77% receiving placebo reported no/mild pain, while moderate/severe pain was recorded in 21% and 20% of individuals, respectively. Among patients experiencing pain at baseline analysis, individuals treated with apalutamide showed a significant improvement in worst pain

compared to those receiving placebo ($p=0.02$) within a median followup of 20 months. Similarly, pain interfering with mood or sleep was significantly lower following apalutamide ($p=0.01$ and $p=0.04$, respectively). Furthermore, improvement was greater among patients with moderate/severe pain at baseline, compared to those with no/mild pain. Conversely, the likelihood of fatigue did not differ according to the treatment received.

The authors should be praised for their substantial contribution to the ongoing debate with this large sample size cohort and a high level of evidence deriving from the randomized design of the study. However, the high percentage of patients with no/mild pain partially limits the strength of these findings. Taken together, the present study should be interpreted as a remarkable starting point for additional research efforts in this field.

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Agarwal et al provide a useful contribution for the daily use of apalutamide in combination with androgen deprivation in metastatic castrate-sensitive prostate cancer patients. The authors present a post hoc analysis of pain and fatigue within the TITAN trial (NCT02489318).

Despite the relative short followup with 19–22 months, the compliance for completing the questionnaires after one year was astonishingly high (96% to 97%). The results demonstrate that the addition of apalutamide to androgen deprivation improved the time to deterioration in pain, eg for “pain at its least in the last 24 hours,” median time to deterioration was 28.7 vs 21.8 months for apalutamide vs placebo ($p=0.0146$). Furthermore, the authors could demonstrate that the benefit of apalutamide did not compromise fatigue rates compared to placebo.

Thus, the current study underlines that the combination of apalutamide and androgen deprivation is well tolerated in everyday life and can maintain the quality of life of our patients. This said, in addition to the well-known oncologic advantages, it further supports the use of apalutamide as combination therapy in metastatic castration-sensitive prostate cancer patients (reference 15 in article). This study underpins the importance of a combined therapy as the standard of care for the treatment of metastatic castrate-sensitive prostate cancer patients, and that nearly all patients should be offered these therapeutic options if they qualify for such a treatment.¹

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REPLY BY AUTHORS

We appreciate the comments from Preisser and Mandel, and Lonati and Mattei on data from analysis of pain and fatigue with apalutamide in the TITAN trial. In this context, we would like to highlight the recently published results from the final survival analysis of the TITAN study after a longer median followup of 44 months.¹ When compared to placebo, addition of apalutamide to ADT continues to show significantly decreased risk of death by 35%. Risk of death with apalutamide was further reduced by 48% after crossover of the 40% of patients on placebo to apalutamide was taken into account (HR 0.52; 95% CI 0.42–0.64; $p < 0.0001$). Treatment with apalutamide also maintained the favorable baseline patient-reported HRQoL per the FACT-P score.

Secondary end points of time to pain progression and time to chronic opioid use also favored apalutamide over placebo, although they did not cross the level of statistical significance. The cumulative incidence of any-grade treatment-emergent fatigue, falls and fracture were also similar between both groups.

Changes in bone pain and fatigue are important surrogates for efficacy and toxicity, respectively, of a therapeutic agent, are easy to measure in a busy clinic and are one of the most relevant components of patients' quality of life. Having improved survival outcomes significantly without compromising quality of life, apalutamide has clearly emerged as one of the most pertinent treatment options for men with metastatic castration-sensitive prostate cancer.

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