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ORIGINAL ARTICLE

Tumor burden and heterogenous treatment effect of apalutamide in metastatic castration-sensitive prostate cancer

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Abstract

Background: Investigation remains incomplete regarding potential variations in the effect of androgen receptor pathway inhibitors, including apalutamide, based on baseline tumor burden in patients with metastatic castration-sensitive prostate cancer (mCSPC).

Methods: The authors analyzed individual participant-level data from 1052 patients with mCSPC who were randomized in the TITAN trial (apalutamide vs. placebo, both with androgen-deprivation therapy). Outcomes included radiographic progression-free survival (PFS), second PFS (PFS2), and overall survival (OS). Multivariable Cox proportional hazards regression models, with and without restricted cubic splines, were used to determine the association between apalutamide benefit and bone metastasis count or visceral metastasis. Subgroup treatment effects were quantified based on inverse probability of treatment weighting-adjusted hazard ratios (HRs).

Results: Analysis using restricted cubic splines indicated that apalutamide provided less benefit for PFS2 and OS in patients with fewer bone metastases. The authors also found evidence of a heterogeneous effect of apalutamide on PFS2 and OS between patients with two or less bone metastases and those with three or more bone metastases. In patients who had two or less bone metastases, there was no evidence of a benefit from apalutamide for radiographic PFS (HR, 0.65; 95% confidence interval [CI], 0.35–1.22), PFS2 (HR, 1.18; 95% CI, 0.66–2.12), or OS (HR, 1.05; 95% CI, 0.60–1.83). No evidence of an association was noted between visceral metastasis and apalutamide benefit.

Conclusions: The addition of apalutamide to androgen-deprivation therapy may provide less benefit in patients with mCSPC who have fewer bone metastases.

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Counting baseline bone metastases may help identify optimal candidates for apalutamide treatment of mCSPC.

Clinical trials registration: NCT02489318

Plain language summary

- In an analysis of individual participant data from a trial (the TITAN trial) in patients with metastatic (spreading) castration-sensitive prostate cancer, treatment intensification based on the addition new drugs to standard androgen-deprivation therapy (ADT) was analyzed and compared with the effects in patients who received only standard ADT.
- Compared with ADT alone, the survival benefit of adding the new drug apalutamide to standard ADT varied according to the number of bone metastases, but no association was observed between the spread of cancer to soft tissues and organs and a survival benefit from adding apalutamide.
- The results indicate that counting the number of bone metastases may help identify which patients with metastatic castration-sensitive prostate cancer are optimal candidates for treatment intensification with the addition of apalutamide to standard ADT.

KEYWORDS
apalutamide, castration-sensitive prostate cancer, heterogeneity in treatment effect, prostate cancer

INTRODUCTION

Prostate cancer is the most frequently diagnosed cancer in men and the second most frequent cause of death in men in 2023.[1] Data also have indicated that the incidence of metastatic prostate cancer is increasing.[2] After the addition of docetaxel to androgen-deprivation therapy (ADT) in metastatic castration-sensitive prostate cancer (mCSPC),[3] treatment intensification based on the addition to ADT of several new androgen-receptor pathway inhibitors (ARPIs), including abiraterone acetate,[4] apalutamide,[5] darolutamide,[6] and enzalutamide, has been shown to improve the survival of patients with mCSPC.[7,8]

In mCSPC, baseline disease volume is often compared with the outcomes of patients who receive ADT plus ARPIs and/or docetaxel. Criteria from the CHAARTED trial (ClinicalTrials.gov identifier NCT00309985), established by data from the ADT era, provide the most widely accepted standard for assessing disease volume.[3] These criteria define high-volume disease as the presence of visceral metastases or four or more bone lesions with one or more located external to the vertebral bodies and pelvis. The subgroup analysis of several randomized controlled trials (RCTs) showed no evidence of the heterogeneous effect of ARPIs based on the CHAARTED-defined disease volume in mCSPC.[9–11] In contrast, meta-analysis of individual participant data indicated that the addition of docetaxel to ADT may provide a range of effects based on baseline mCSPC tumor burden, suggesting that in-depth evaluation of the association between tumor burden and effect of treatment intensification based on RCT data might uncover heterogeneous effects of ARPIs in mCSPC.

Therefore, in this post-hoc analysis of individual participant data from the TITAN trial (ClinicalTrials.gov identifier NCT02489318), we investigated the detailed effects of bone metastasis count and the presence of visceral metastasis on the benefit of adding apalutamide to ADT in patients with mCSPC.

MATERIALS AND METHODS

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology Statement.[12]

Data sources and study population

This cohort study accessed individual participant-level data from the TITAN trial, which is an international, double-blind, placebo-controlled, phase 3 randomized trial that evaluated the efficacy of adding apalutamide to ADT in patients with mCSPC.[5] Eligible participants included those who had adenocarcinoma of the prostate and distant metastatic disease, evidenced by at least one lesion on technetium-99 bone scintigraphy, with or without visceral or lymph node metastasis. The cancer was required to be castration-sensitive. Participants were assigned randomly at a 1:1 ratio to receive either apalutamide (apalutamide group) or placebo (placebo group) along with ADT, which continued until patients developed either clinical progression or the emergence of unacceptable treatment-related adverse events.

The interim and final analysis efficacy results have been reported in earlier publications.[5,13] This study analyzed the final analysis data set of the TITAN trial.[5] We conducted data analysis from April 2024 to May 2024. The intention-to-treat population of the TITAN trial ($N = 1052$) was eligible for this study.

Exposures and variable definitions

The baseline bone metastasis count and the presence of visceral metastasis were evaluated within 6 weeks of randomization. The following covariates were included: age at randomization, Eastern Cooperative Oncology Group (ECOG) performance status, the Brief Pain Inventory-Short Form (BPI-SF) pain score, prior docetaxel use, metastatic stage at initial diagnosis, evidence of visceral metastasis, baseline hemoglobin concentration, baseline lactate dehydrogenase (LDH), and baseline prostate-specific antigen (PSA).

Outcomes

The outcomes included radiographic progression-free survival (rPFS), second progression-free survival (PFS2), and overall survival (OS), defined according to the trial protocol.[5] In brief, rPFS was determined as the interval from the date of randomization to the date of radiographic progression or all-cause death, whichever occurred first. PFS2 was defined as the interval from the date of randomization to the date of investigator-determined disease progression (PSA progression, radiographic progression, or clinical progression) on first subsequent therapy for prostate cancer or all-cause death, whichever occurred first. OS was defined as the interval from the date of randomization to the date of all-cause death. Patients without the event of interest were censored at the time they were last known to be event-free.

Statistical analysis

To handle missing baseline data, we used random forest-based imputation using R package *missForest* (The Comprehensive R Archive Network).[14] This method uses random forest algorithms to predict and impute missing values in the data set, generating a single imputed data set. The imputed data set was used for the following analysis. Cox proportional hazards regression models with a treatment × bone metastasis count interaction term were used to assess the effect of bone metastasis count on the benefit of apalutamide through the R package *interactionRCS*, and the results are shown as hazard ratios (HRs) with 95% confidence intervals (CIs). Models were adjusted for age at randomization (younger than 75 years or 75 years and older), ECOG performance status (0 or 1–2), BPI-SF item 3 scores (<4 or ≥4), prior docetaxel use (yes/no), metastatic stage at initial diagnosis (M0 or M1), evidence of visceral metastasis (yes/no), baseline hemoglobin concentration, baseline LDH, and baseline PSA. Models with three-knot, four-knot, and five-knot restricted cubic splines and linear functions of bone metastasis counts as a continuous scale were used to evaluate possible linear or nonlinear associations between the effect of apalutamide and bone metastasis counts. Among these models, the model with the lowest Akaike information criterion was selected.[15] The association between the effect of apalutamide and bone metastasis count was evaluated based on the CIs depicted in the plot. Simultaneously, we evaluated the proportional hazards assumption using the global Schoenfeld test.[16] If the results of the interaction analysis suggested that the effect of apalutamide varied depending on bone metastasis count, we categorized the bone metastasis count at the data-driven cutoff and assessed the effect of adding apalutamide to ADT in the subgroups.

Furthermore, to validate the results of restricted cubic spline analysis, we checked the effect of apalutamide based on HRs within the subgroups, which were stratified by bone metastasis count and analyzed on a quarterly basis. Because of the limited number of events and patients in each subgroup, covariate balances were adjusted based on inverse probability of treatment weighting (IPTW). This was estimated from the propensity scores, which were calculated based on a multivariable logistic regression model using the R package *WeightIt* with the following covariates: age at randomization, ECOG performance status, BPI-SF item-3 scores, prior docetaxel use, metastatic stage at initial diagnosis, evidence of visceral metastasis, baseline hemoglobin concentration, baseline LDH, and baseline PSA.[17] Standardized mean differences (SMDs) were used to assess the covariate balance within each subgroup, with SMDs <0.1 indicating sufficient balance.[18]

In the sensitivity analysis, we checked the robustness of our findings based on the following two analyses. First, to provide clinically meaningful measures of the effect of apalutamide within each subgroup, we assessed the differences in the restricted mean survival times (RMSTs), which represent the mean differences in survival time up to the truncation time point.[19] The truncation time was the minimum of the longest observation time among the subgroups. The covariates were adjusted by the IPTWs used in the above-mentioned four-subgroup analysis. Second, we also assessed HRs for PFS2 and OS based on a univariable rank-preserving structural failure time model to adjust the effect of treatment switching from placebo to apalutamide in the placebo group based on bone metastasis count using R package *rpsftm*.[20] Because of the limited number of events in the subgroups, multivariable analysis was not conducted.

In addition, we examined whether the effect of apalutamide varied based on the presence of visceral metastasis by using multivariable Cox proportional hazards regression models with a treatment × visceral metastasis interaction term. Covariates included age at randomization, ECOG performance status, BPI-SF item-3 scores, prior docetaxel use, previous therapy for localized prostate cancer, bone metastasis count, baseline hemoglobin concentration, baseline LDH, and baseline PSA. We did not adjust p values for multiplicity because these analyses were exploratory rather than confirmatory.

When assessing an interaction, we considered a p value $< .1$ to indicate evidence of an effect modification because testing for

interactions has limited statistical power.[21,22] The other statistical tests were two-sided, and a p value < .05 was considered statistically significant. All statistical analyses were performed using R version 4.3.0 (The Comprehensive R Archive Network).

RESULTS

Baseline characteristics

Between December 15, 2015, and July 25, 2017, 525 patients were assigned to the apalutamide group, and 527 were assigned to the placebo group. The median follow-up was 44.0 months. In total, 39.5% of patients (208 of 527) in the placebo group switched from placebo to apalutamide because of the crossover. Baseline characteristics are summarized in Table 1. The most common missing baseline characteristic was the metastatic stage at initial diagnosis, which was absent in 56 of 1052 patients (5.3%). The baseline characteristics of the imputed data set are shown in Table S1. Figure S1 displays the histograms of bone metastasis counts. In total, 126 of 1052 bone metastasis counts (12.0%) were truncated as *>50*, and those values were treated as 50. The median number of bone metastases was seven (interquartile range [IQR], three to 22 bone metastases) in the apalutamide group and six (IQR, three to 20 bone metastases) in the placebo group.

Association between bone metastasis count and benefit of apalutamide

Among the four models evaluated, the Akaike information criterion analysis determined that four-knot restricted cubic spline interaction models for rPFS, PFS2, and OS were the best fits for the data set (see Table S2). The splines are shown in Figure 1. Although the spline for rPFS demonstrated a consistent effect of apalutamide across all bone metastasis counts, the splines for PFS2 and OS indicated that the effect of apalutamide began to decrease in patients who had five or less bone metastases (Figure 1). Furthermore, the upper CIs exceeded an HR for OS of 1.0 in patients who had two or less bone metastases, suggesting a lower benefit for apalutamide versus placebo (Figure 1C). No violation of the proportional hazards assumptions for the rPFS model (p = .27), the PFS2 model (p = .69), of the OS model (p = .28) was identified.

By dividing the bone metastasis count into two or less and three or more, the application of IPTWs achieved sufficient covariate balance between the groups (all SMDs < 0.1; see Table S3). The crude and IPTW-adjusted Kaplan–Meier curves are shown in Figure 2 and Figure S2. We observed that the addition of apalutamide was associated with lower hazards for rPFS, PFS2, and OS in patients who had at least three bone metastases (Figure 2). However, patients who had two or less bone metastases exhibited no evidence of benefit from apalutamide for these outcomes (Figure 2). We found evidence of the heterogeneous effect of apalutamide on PFS2 (p for interaction = .02) and OS (p for interaction = .053) based on bone metastasis count. This heterogeneity was not observed for rPFS (p for interaction = .38).

To check the findings from restricted cubic spline interaction models, we further analyzed the benefit of apalutamide within four subgroups based on the bone metastasis count: from the minimum to the first quartile (Q1; bone metastasis count of one or two; N = 249), from Q1 to the second quartile (Q2; bone metastasis count, three to six; N = 281), from Q2 to the third quartile (Q3; bone metastasis count, seven to 20; N = 253), and from Q3 to the maximum (bone metastasis count, 21 to 50; N = 269). The baseline characteristics of all subgroups according to treatment regimen are summarized in Table S4. The application of IPTW achieved adequate balance between the apalutamide group and the placebo group across all subgroups (all SMDs < 0.1; see Table S5). We observed similar associations between the effect of apalutamide and bone metastasis count (Figure 3).

Association between visceral metastasis and benefit of apalutamide

Overall, 56 of 1052 patients (10.7%) in the apalutamide group and 72 of 1052 (13.7%) in the placebo group had evidence of visceral disease. We found no evidence of an interaction between the presence of visceral metastasis and the benefit of apalutamide for rPFS (p for interaction = .15), PFS2 (p for interaction = .57), or OS (p for interaction = .59). There was no evidence of any violation of the proportional hazards assumption for rPFS (p = .11), PFS2 (p = .64), or OS (p = .35).

Sensitivity analysis

We further assessed the association between the difference in RMSTs between the apalutamide group and the placebo group based on bone metastasis count. The crude and IPTW-adjusted Kaplan–Meier plots of all subgroups are illustrated in Figures S3 and S4. The minimum of the longest observation times among the subgroups was 25.9 months for rPFS, 46.9 months for PFS2, and 47.6 months for OS. Within these truncation times, we observed that the results of the IPTW-adjusted RMST analysis within each subgroup corresponded to those from the restricted cubic spline interaction models (Figure 4).

In addition, we also observed a similar association between apalutamide benefit and bone metastasis count in rank-preserving structural time models for PFS2 and OS (see Figure S5).

DISCUSSION

In this secondary analysis of the TITAN trial, we investigated the effects of bone metastasis counts and visceral metastases on the benefit of apalutamide in patients with mCSPC. We reached several main findings.

TABLE 1 Baseline characteristics.

Characteristic	No. (%)[a]	
	Placebo, *N* = 527	Apalutamide, *N* = 525
Age at randomization, years		
<75	414 (78.6)	392 (74.7)
≥75	113 (21.4)	133 (25.3)
ECOG performance status		
0	348 (66.0)	328 (62.5)
1	178 (33.8)	197 (37.5)
2	1 (0.2)	0 (0.0)
Gleason grade group		
1–4	165 (31.8)	172 (33.0)
5	354 (68.2)	350 (67.0)
Missing	8	3
Prior docetaxel		
No	472 (89.6)	467 (89.0)
Yes	55 (10.4)	58 (11.0)
Metastatic classification at initial diagnosis		
M0	59 (11.8)	85 (17.1)
M1	441 (88.2)	411 (82.9)
Missing	27	29
Evidence of visceral disease		
No	455 (86.3)	469 (89.3)
Yes	72 (13.7)	56 (10.7)
Mean BPI-SF pain score		
<4	407 (79.3)	392 (78.1)
≥4	106 (20.7)	110 (21.9)
Missing	14	23
Hemoglobin concentration: Median [IQR], g/dL	137.0 [125.0–146.0]	137.0 [125.0–147.0]
No. missing	6	3
Baseline LDH: Median [IQR], U/L	179 [158–211]	178 [157–205]
No. missing	25	22
Baseline PSA: Median [IQR], ng/mL	4.0 [0.8–25.4]	6.0 [1.1–26.0]

Abbreviations: ADT, androgen-deprivation therapy; BPI-SF, Brief Pain Inventory Short Form; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; LDH, lactate dehydrogenase; PSA, prostate-specific antigen.

[a]Percentages have been rounded and may not total 100%.

First, our findings suggest that the benefit of apalutamide varied based on the baseline bone metastasis count; however, we did not observe an association between the presence of visceral metastasis and the benefit of apalutamide. In addition to the CHAARTED criteria, several criteria have been proposed to categorize disease volume by combining the extent of bone metastasis and the presence of visceral metastasis based on data from the pre-ARPI era.[23,24] However, our findings suggest that bone metastasis counts alone were associated with the benefit of apalutamide in patients with mCSPC.

Second, we observed that the benefit of apalutamide for PFS2 and OS were low in patients who had fewer bone metastases, especially in those with two or less, suggesting that the cutoff values of the current disease volume criteria, such as the

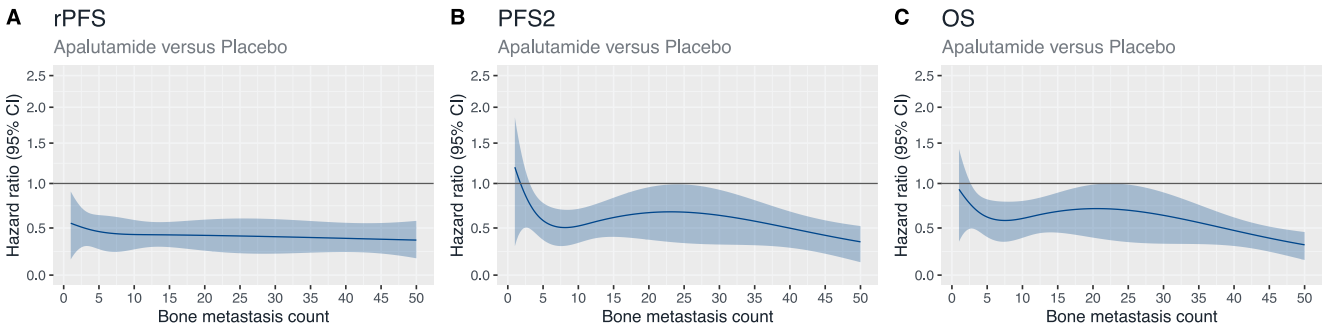

FIGURE 1 Associations between effect of apalutamide and bone metastasis count. Splines with 95% CIs for HRs for (A) rPFS, (B) PFS2, and (C) OS. Solid lines represent point estimates, and shaded areas represent 95% CIs. HRs <1.0 favor apalutamide, whereas HRs >1.0 indicate favorable outcomes with placebo. CI indicates confidence interval; HRs, hazard ratios; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; rPFS, radiographic progression-free survival.

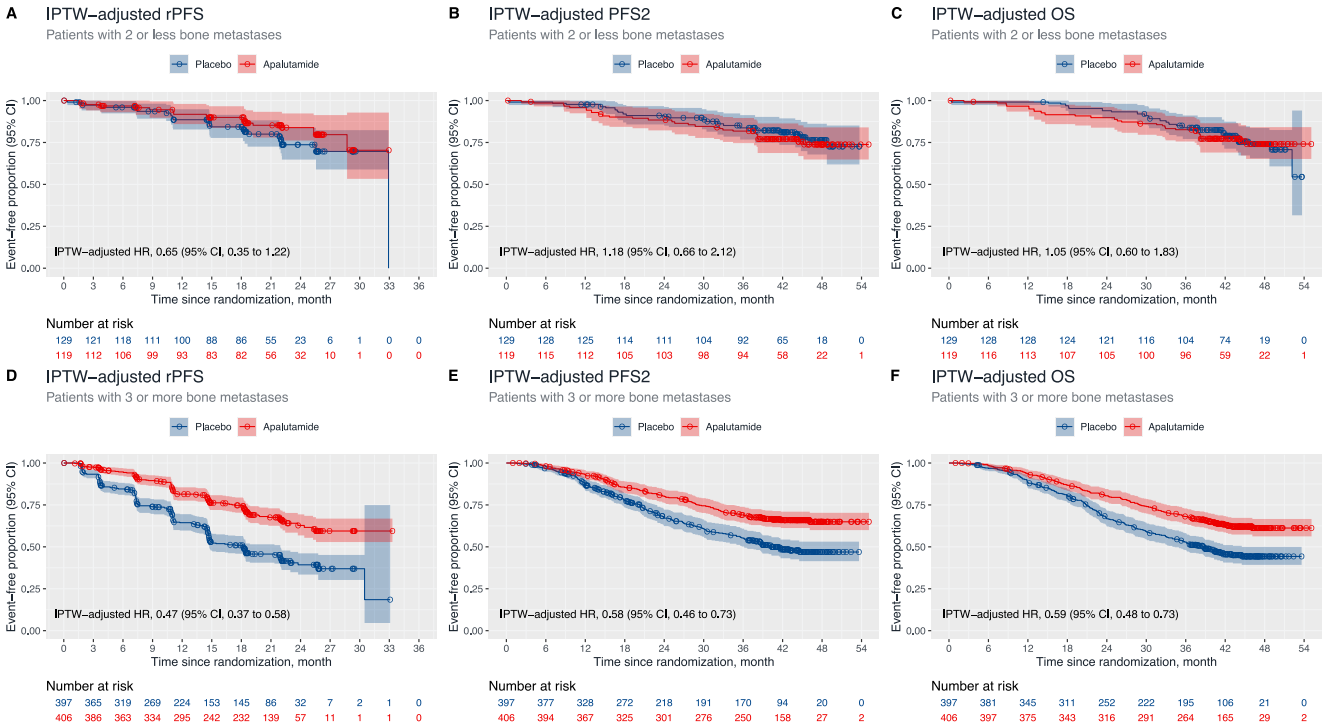

FIGURE 2 Inverse probability of treatment weighting-adjusted Kaplan–Meier plots based on bone metastasis count. (A–F) Inverse probability of treatment weighting-adjusted Kaplan–Meier plots by treatment, with subgroups based on bone metastasis count (one or two vs. three or more). Solid lines represent point estimates, and shaded areas represent 95% CIs. HRs were estimated based on inverse probability of treatment weighting-adjusted Cox proportional hazards regression models. HRs <1.0 favor apalutamide. CI indicates confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; rPFS, radiographic progression-free survival.

CHAARTED criteria, need to be reconsidered to develop the disease volume criteria that guide treatment decisions. Contrary to our findings, the previous studies demonstrated a consistent effect of ARPIs irrespective of disease volume.[10,11,25,26] Importantly, our findings suggested that the benefit of apalutamide became lower but marginal in patients who had from three to five bone metastases. Categorizing a portion of such a population into a group with low-volume disease might lead to the conclusion of the previous studies.

Third, a previous, protocol-defined, post hoc analysis from the TITAN trial suggested that patients who had five or less bone-only metastases and received apalutamide had favorable OS.[25] Our findings collectively suggested that, although patients with less bone metastases had a favorable prognosis, a clear benefit of the addition of apalutamide to ADT was not observed in a part of this population.

Contrary to our findings, the individual participant-level data meta-analysis from the STAMPEDE trial (ClinicalTrials.gov identifier NCT00268476) demonstrated an OS benefit of adding abiraterone

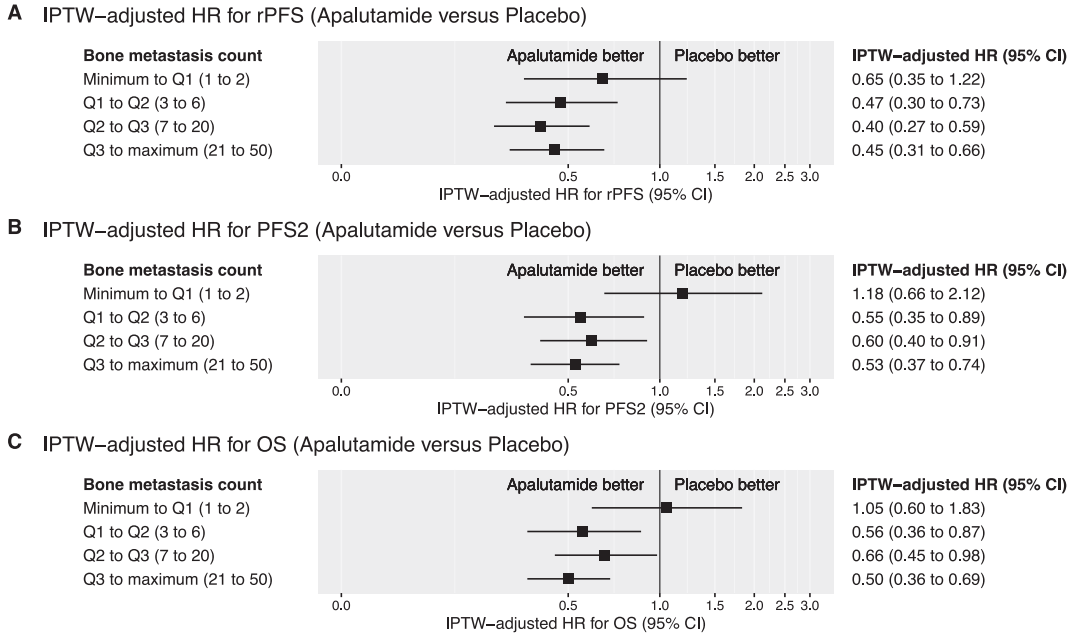

FIGURE 3 Inverse probability of treatment weighting-adjusted hazard ratios by bone metastasis count. (A–C) Forest plots showing HRs estimated from IPFW-adjusted Cox proportional hazards regression model plus ADT based on bone metastasis count. Bone metastasis counts were categorized based on the quartiles: from the minimum to the first quartile (Q1; one or two bone metastases), from the first to the second quartile (Q2; from three to six bone metastases), from the second to the third quartile (Q3; (from seven to 20 bone metastases), and from the third quartile to the maximum (from 21 to 50 bone metastases). HRs <1.0 indicates favorable outcomes for patients who received apalutamide plus ADT compared with those who received placebo plus ADT. ADT indicates androgen-deprivation therapy; CI, confidence interval; HRs, hazard ratios; IPTW, inverse probability of treatment weighting; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; Q, quartile; rPFS, radiographic progression-free survival.

acetate to ADT in patients with high-risk, nonmetastatic prostate cancer.[27] The published Kaplan–Meier OS curve suggested that the benefit of abiraterone acetate was apparent between 24 and 36 months from randomization; however, over a 53.6-month follow-up in patients who had from one to two bone metastases, such benefit was not observed in the current study. The following factors may explain the differences in the results: (1) The open-label design of the study, (2) differences in follow-up periods, and (3) differences in trial periods (STAMPEDE recruitment period, from November 15, 2011, to March 31, 2016; TITAN recruitment period, from December 15, 2015, to July 25, 2017), which may have led to differences in subsequent therapy and treatment sequences.

Importantly, we observed a heterogeneous effect of apalutamide on PFS2 and OS based on the bone metastasis count, but not on rPFS, especially in patients with fewer bone metastases. This aligns with findings from a recent individual participant data meta-analysis of 6390 patients with mCSPC from nine RCTs, which demonstrated a weak association between rPFS and OS in patients with CHAARTED-defined low-volume disease (R^2 [coefficient of determination] between 5-year OS and 3-year rPFS, 0.43; 95% CI, 0.04–0.98), despite of the strong correlation in the overall population.[28] The concordance between PFS2 and OS in the current study suggested that disease progression on first-line therapy might be effectively managed with subsequent therapy, especially in patients with a low metastatic burden.

The primary strengths of this study include its use of individual participant data from the TITAN trial. The TITAN trial included patients from 260 centers across 23 countries, and the data were prospectively collected at regular, protocol-defined intervals. The trial recorded baseline bone metastasis counts on a continuous scale, enabling a detailed evaluation of the association between the bone metastasis count and the effect of apalutamide. However, the findings of the current study have some limitations because of the exploratory nature and the study design of the TITAN trial. The results of this study are based on data from a median follow-up of 44.0 months, so data from longer follow-up might affect our findings. Baseline bone metastasis counts were evaluated manually and not reviewed centrally, which may not accurately represent bone metastatic volume. Assessing the volume of bone metastasis using an automated bone scan index might help to quantify this more accurately.[29] Because we used clinical trial data, it is debatable whether our findings can be applied to those outside the clinical trial setting because such patients are likely to be more fragile and less selected.[30] Although our study did not establish evidence of a benefit of the addition of apalutamide to ADT in patients with two or less bone metastases, these results should be validated in further, non-inferiority designed RCTs. We used PFS2 to negate the effect of subsequent lines of therapy on our findings. However, our findings on PFS2 warrant careful interpretation because this end

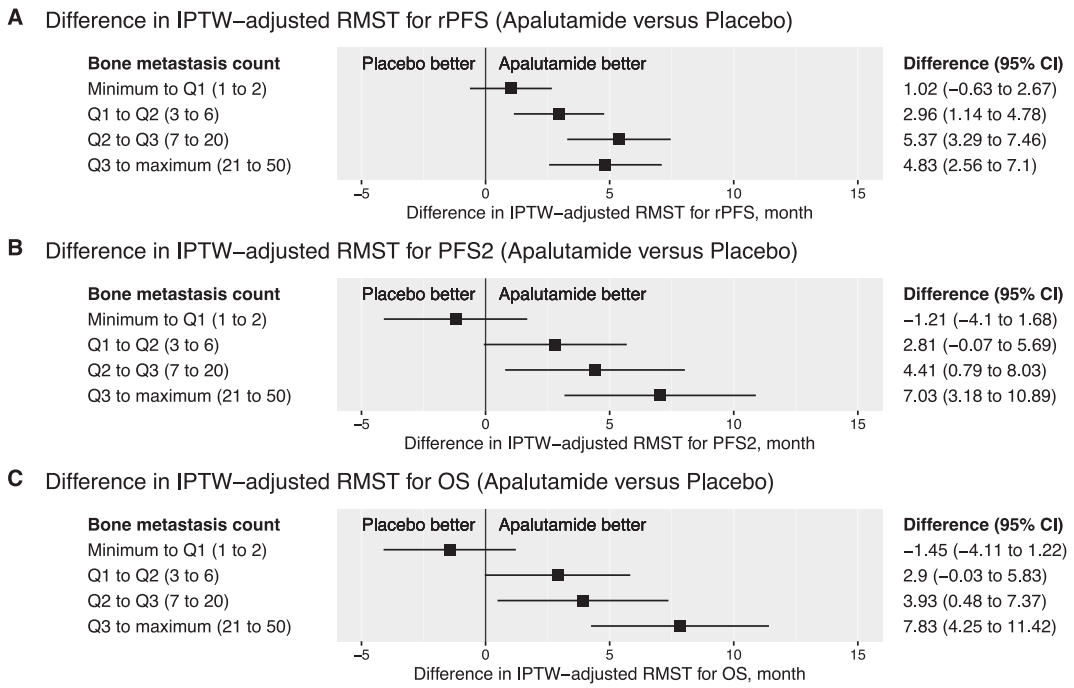

FIGURE 4 Difference in inverse probability of treatment weighting-adjusted restricted mean survival time by bone metastasis count. (A–C) Forest plots showing differences in inverse probability of treatment weighting-adjusted restricted mean survival times for rPFS and OS between patients who received apalutamide plus ADT and those who received placebo plus ADT based on bone metastasis count. Bone metastasis counts were categorized based on the quartiles: from the minimum to the first quartile (Q1; one or two bone metastases), from the first to the second quartile (Q2; from three to six bone metastases), from the second to the third quartile (Q3; from seven to 20 bone metastases), and from the third quartile to the maximum (from 21 to 50 bone metastases). Differences greater than zero indicate favorable outcomes for patients who received apalutamide plus ADT compared with those who received placebo plus ADT. The truncation times were set at the minimum of the longest observation times among the subgroups (25.9 months for rPFS, 46.9 months for PFS2, and 47.6 months for OS). ADT indicates androgen-deprivation therapy; CI, confidence interval; HRs, hazard ratios; IPTW, inverse probability of treatment weighting; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; Q, quartile; RMST, restricted mean survival time; rPFS, radiographic progression-free survival.

point defined disease progression on subsequent lines of therapy based on investigator judgment rather than objective findings. Generalizing our findings to patients who receive other ARPIs or triplet therapy in combination with ADT, ARPIs, and docetaxel should be validated with further studies. Our analysis did not consider the effects of later lines of treatment. Also, we did not assess the biologic mechanism behind the heterogeneity in treatment effects of apalutamide. Finally, the difference in baseline characteristics between the apalutamide and placebo group and losing the randomization assumption in the subgroup analysis might bias the results of rank-preserving failure-time analysis.

CONCLUSIONS

Our findings suggested a lesser benefit from the addition of apalutamide to ADT in patients with mCSPC whose bone metastasis counts were relatively low at baseline. We did not observe an association between visceral metastasis and the benefit of adding apalutamide. Encouraging a bone metastasis count at baseline may help guide treatment optimization in this population.

AUTHOR CONTRIBUTIONS

Wataru Fukuokaya: Conceptualization, methodology, writing–original draft, formal analysis and data curation. **Keiichiro Mori**: Conceptualization, supervision, writing–review and editing, validation, formal analysis, writing–original draft, and data curation. **Takafumi Yanagisawa**: Validation, writing–review and editing, supervision, writing–original draft and data curation. **Fumihiko Urabe**: Validation, writing–review and editing. supervision. writing–original draft, and data curation. **Pawel Rajwa**: Validation, writing–review and editing, supervision, and writing–original draft. **Alberto Briganti**: Writing–review and editing. **Shahrokh F. Shariat**: Writing–review and editing. **Nobuaki Matsubara**: Writing–review and editing. **Takahiro Kimura**: Writing–review and editing and supervision. **Akihiro Hirakawa**: Methodology; writing–review and editing, and supervision.

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CONFLICT OF INTEREST STATEMENT

Pawel Rajwa reports personal/consulting fees from Astellas Pharma and Janssen Pharmaceuticals outside the submitted work. Alberto Briganti reports grants/contracts from Sandoz; personal/consulting or advisory fees/honoraria from Astellas Pharma, Bayer, Janssen Pharmaceuticals, MDx Health, and OPKO Health Inc.; and support for other professional activities from Ferring outside the submitted work. Shahrokh F. Shariat owns or co-owns the following patents: "Methods to determine prognosis after therapy for prostate cancer" (granted September 6, 2002), "Methods to determine prognosis after therapy for bladder cancer" (granted June 19, 2003), "Prognostic methods for patients with prostatic disease" (granted August 5, 2004), and "Soluble Fas: urinary marker for the detection of bladder transitional cell carcinoma" (granted July 20, 2010); reports personal/consulting fees from Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Cepheid, Ferring, Eli Lilly & Company, Ipsen Biopharm, Janssen Biotech, Merck, Merck Sharp and Dohme, Olympus, Pfizer, Pierre Fabre, Roche, Sanochemia, Sanofi, Takeda Oncology, Urogen, and Wolff; and reports travel support from Astellas Pharma outside the submitted work. Nobuaki Matsubara reports grants/contracts from Amgen, Astellas Pharma, AstraZeneca, Bayer, Chugai Pharmaceutical, Eisai, Eli Lilly and Company, Exelis, Janssen Pharmaceuticals, Merck Sharp and Dohme, Pfizer, PRA Health Science, Roche, Sanofi, Seagen, Taiho Pharmaceutical, and Takeda Oncology; and support for other professional activities from Eli Lilly and Company outside the submitted work. Takahiro Kimura reports personal/consulting fees from Astellas Pharma, AstraZeneca, Bayer, Janssen Pharmaceuticals, Sanofi, and Takeda Pharmaceutical Company Ltd. outside the submitted work. Akihiro Hirakawa reports personal/consulting or advisory fees/honoraria from AbbVie, Astellas Pharma, Chugai Pharmaceutical Company Ltd., Janssen Pharmaceuticals, Kissei Pharmaceutical Company, Kyowa Kirin Company Ltd., Mochida Pharmaceutical Company, Ono Pharmaceuticals, Sanofi, and Taiho Pharmaceuticals; service on a Data and Safety Monitoring Board for Novartis Pharma; and support for other professional activities from Pfizer outside the submitted work. The remaining authors disclosed no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available at https://yoda.yale.edu/.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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