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ORIGINAL ARTICLE

Deep, rapid, and durable prostate-specific antigen decline with apalutamide plus androgen deprivation therapy is associated with longer survival and improved clinical outcomes in TITAN patients with metastatic castration-sensitive prostate cancer☆

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Background: The first interim analysis of the phase III, randomized, double-blind, placebo-controlled, multinational TITAN study demonstrated improved overall survival (OS) and radiographic progression-free survival (rPFS) with apalutamide added to ongoing androgen deprivation therapy (ADT) in patients with metastatic castration-sensitive prostate cancer. The final analysis confirmed improvement in OS and other long-term outcomes. We evaluated prostate-specific antigen (PSA) kinetics and the association between PSA decline and outcomes in patients with metastatic castration-sensitive prostate cancer from TITAN.

Patients and methods: Patients received apalutamide (240 mg/day) or placebo plus ADT (1 : 1). This *post hoc* exploratory analysis evaluated PSA kinetics and decline in relation to rPFS (22.7 months' follow-up) and OS, time to PSA progression, and time to castration resistance (44.0 months' follow-up) in patients with or without confirmed PSA decline using a landmark analysis, the Kaplan–Meier method, and Cox proportional hazards model.

Results: One thousand and fifty-two patients (apalutamide, 525; placebo, 527) were enrolled. Best confirmed PSA declines ($\geq$50% or $\geq$90% from baseline or to $\leq$0.2 ng/ml) were achieved at any time during the study in 90%, 73%, and 68% of apalutamide-treated versus 55%, 29%, and 32% of placebo-treated patients, respectively. By 3 months of apalutamide treatment, best deep PSA decline of $\geq$90% or to $\leq$0.2 ng/ml occurred in 59% and 51% of apalutamide- and in 13% and 18% of placebo-treated patients, respectively. Achievement of deep PSA decline at landmark 3 months of apalutamide treatment was associated with longer OS [hazard ratio (HR) 0.35; 95% confidence interval (CI) 0.25-0.48), rPFS (HR 0.44; 95% CI 0.30-0.65), time to PSA progression (HR 0.31; 95% CI 0.22-0.44), and time to castration resistance (HR 0.38; 95% CI 0.27-0.52) compared with no decline ($P < 0.0001$ for all). Similar results were observed at landmark 6 and 12 months of apalutamide treatment.

Conclusions: Apalutamide plus ADT demonstrated a robust (rapid, deep, and durable) PSA decline that was associated with improved clinical outcomes, including long-term survival.

Key words: mCSPC, castration resistance, overall survival, PSA progression, radiographic progression-free survival

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INTRODUCTION

The treatment objectives for patients with metastatic castration-sensitive prostate cancer (mCSPC) are to delay disease progression to castration resistance and improve overall survival (OS). Androgen deprivation therapy (ADT) has been the main treatment of mCSPC for decades.[1] Although patients with mCSPC may initially respond to ADT, progression to castration resistance is inevitable for most.[2] Recent studies have demonstrated that the addition of other treatments/agents to ADT significantly improves outcomes; hence, ADT alone is no longer the recommended treatment of patients with mCSPC.[3-13]

Apalutamide is an oral androgen signalling inhibitor (ASI) that binds to the androgen receptor and prevents its translocation, DNA binding, and androgen receptor-mediated transcription, resulting in inhibited proliferation of prostate cancer cells.[14] TITAN, a phase III, randomized, placebo-controlled study, demonstrated improved radiographic progression-free survival (rPFS) at 22.7-month follow-up and OS at 22.7-month and long-term 44.0-month follow-ups with apalutamide added to ADT in a broad patient population with mCSPC versus ADT alone.[12,13] Additionally, prostate-specific antigen (PSA) progression and castration resistance were delayed at long-term follow-up. Based on the results of the TITAN study, apalutamide was approved in multiple locations, including the United States[15] and the European Union,[16] for the treatment of mCSPC.

The ability to accurately prognosticate outcomes of mCSPC treatment may help inform decisions for treatment selection (both intensification and de-escalation) and clinical management, especially frequency of visits and testing. In patients with prostate cancer, PSA may be an indicator of cancer activity.[17] Typically, an increase in serum PSA level is seen before radiological evidence of disease progression. A variety of PSA assessment endpoints have correlated with long-term therapeutic outcomes. Thus, a PSA decline by $\geq$50% at 4 weeks was reported as a predictor of improved OS in a study of enzalutamide and ADT.[18] Irrespective of treatment, PSA kinetics parameters, such as higher PSA nadir ($\geq$0.2 ng/ml versus $<$0.2 ng/ml) and more rapid time to PSA nadir ($<$6 months), were found to be associated with shorter survival (in univariate or multivariate analyses)[19] and a higher risk of progression.[20,21]

This *post hoc* exploratory analysis evaluated PSA kinetics, including the speed, depth, and duration of PSA decline in patients with mCSPC who were treated with apalutamide or placebo and continuous ADT. The association between achievement of deep PSA decline with rPFS and long-term outcomes, including OS, time to PSA progression, and time to castration resistance in apalutamide-treated patients, was also assessed.

PATIENTS AND METHODS

Study design and participants

This was a *post hoc* analysis of TITAN (ClinicalTrials.gov Identifier: NCT02489318), a phase III, randomized, double-blind, placebo-controlled, multinational study of apalutamide in patients with mCSPC who were receiving ADT. The study design has been described previously[12,13] and is presented in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2023.02.009. TITAN has been conducted in accordance with current International Conference on Harmonisation guidelines for Good Clinical Practice and according to the principles of the Declaration of Helsinki following approval by institutional review boards and written informed consent from patients. Additional details of the study design can be found in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2023.02.009.

Randomization

Randomization and stratification details have been published previously.[12] Briefly, patients were randomized 1 : 1 to receive ADT and either apalutamide (240 mg) or matched placebo given once daily.

Eligibility criteria

Key eligibility criteria for the TITAN study, as reported previously,[12] included age $\geq$18 years, documented adenocarcinoma of the prostate, and distant metastatic disease. Additional eligibility criteria are described in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2023.02.009.

Procedures and outcomes

Serum PSA was measured at screening, on day 1 of each treatment cycle until cycle 13, every other cycle until cycle 25, and every four cycles until the end-of-treatment visit. Samples were evaluated by a central laboratory. The results for cycles 1-4 were blinded to the investigator but those from cycle 5 to the end of treatment were available. Rates of PSA decline were determined by the proportion of patients who achieved $\geq$50% or $\geq$90% decline in PSA value from baseline, or undetectable PSA ($\leq$0.2 ng/ml), were reported at 3-, 6-, and 12-month landmark times. The PSA decline was confirmed by a central laboratory measurement obtained at least 4 weeks later.

OS was defined as time from randomization to date of death from any cause, and rPFS as time from randomization to first image-based documentation of radiographic progressive disease or death, whichever came first. If bone metastasis was detected, a confirmatory bone scan was required. Time to PSA progression was defined as the time from randomization to PSA progression based on Prostate Cancer Clinical Trials Working Group (PCWG2) criteria.[2] Time to castration resistance was defined as time from randomization to radiographic disease progression, PSA progression per PCWG2 criteria, or symptomatic skeletal event, whichever occurred first.

Statistical analysis

All patients randomized into the study were included in this *post hoc* analysis (intent-to-treat population). PSA kinetics

and rates of PSA decline were summarized descriptively by treatment group as the best PSA decline within 3, 6, and 12 months and overall (at any time) during the study. PSA decline was also assessed at 3-, 6-, and 12-month landmark times.

Associations between PSA decline and clinical outcomes were assessed in the apalutamide treatment group for four clinical outcomes: OS, rPFS, time to PSA progression, and time to castration resistance using landmark analysis. Outcomes were analyzed based on ≥90% PSA decline or PSA ≤0.2 ng/ml achieved at 3-, 6-, and 12-month landmark times of apalutamide treatment. Patients who had PSA measured at landmark months and had not experienced an event or those who were not censored for the respective endpoint were included in the landmark analysis and were separated into two categories according to the achievement of PSA decline. Survival probabilities were estimated using the Kaplan—Meier method in each PSA decline group, with PSA decline being a fixed covariate. Estimates were conditional on the group classification of patients at the landmark time. A Cox proportional hazards model with PSA decline as a fixed covariate at landmark times was used to estimate hazard ratios (HRs), associated 95% confidence intervals (CIs), and nominal *P* values. In addition, another Cox proportional hazards model with PSA decline as a time-varying covariate was also fitted. *P* values were reported without adjustment for multiplicity; two-sided *P* values of <0.05 were considered statistically significant. Data cut-off was at the first interim analysis for rPFS (22.7-month follow-up) and at the final analysis for OS, time to PSA progression, and time to castration resistance (44.0-month follow-up).

RESULTS

A total of 1052 TITAN patients were included, 525 apalutamide-treated and 527 placebo-treated, after initiation of ADT. The median time between initiation of ADT and randomization was 1.8 months. Results of the TITAN study have been reported previously.[12,13] A total of 144 (14%) patients had localized disease (M0) and 852 (81%) patients had *de novo* metastatic disease (M1). The patient flow and *post hoc* analyses are shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.02.009.

PSA kinetics

Table 1 summarizes PSA kinetics in TITAN patients. At the time of randomization (baseline), the median serum levels of PSA were comparable between treatment groups (apalutamide, 5.97 ng/ml; placebo, 4.02 ng/ml). The median PSA nadir in the apalutamide group was 0.02 ng/ml, and the median time to nadir was 5.6 months; in the placebo group, median PSA nadir was 0.75 ng/ml, and median time to nadir was 4.6 months.

We next assessed PSA kinetics using different metrics of the overall best PSA decline. Over the course of the study, more apalutamide-treated patients experienced deep PSA decline than placebo-treated patients. Thus, higher proportions of apalutamide-treated patients achieved best ≥50% PSA decline from baseline (90% versus 55%). Similarly, more apalutamide-treated patients achieved three categories of best deep PSA decline: ≥90% PSA decline from baseline, decline to undetectable levels of ≤0.2 ng/ml, and PSA decline ≥90% or PSA ≤0.2 ng/ml compared with placebo-treated patients: 73%, 68%, and 85% versus 29%, 32%, and 43%, respectively. Proportions of patients with best 50% to <90% or ≥90% PSA declines increased concurrently with progressive depth of PSA decline in the apalutamide group, whereas they remained similar the placebo group (Table 1).

When we assessed best PSA decline over time, we observed faster onset of deep PSA decline in the apalutamide versus placebo group. By 3 months of treatment, higher proportions of apalutamide-treated patients achieved ≥50% PSA decline, ≥90% PSA decline, undetectable PSA ≤0.2 ng/ml, and PSA decline ≥90% or PSA ≤0.2 ng/ml compared with placebo-treated patients (89%, 59%, 51%, and 75% versus 41%, 13%, 18%, and 28%, respectively)

Table 1. PSA kinetics and decline in TITAN patients

	Apalutamide + ADT (*n* = 525)	Placebo + ADT (*n* = 527)
Median (Q1-Q3) PSA at baseline, ng/ml	5.97 (1.10-26.03)	4.02 (0.80-25.46)
Median (Q1-Q3) PSA nadir, ng/ml	*n* = 521 0.02 (0.02-0.32)	*n* = 525 0.75 (0.06-4.49)
Median (Q1-Q3) time to PSA nadir, months	*n* = 521 5.6 (3.7-12.9)	*n* = 525 4.6 (1.8-10.2)
Confirmed PSA decline, *n* (%)		
Best overall decline		
PSA decline ≥50%	473 (90)	290 (55)
PSA decline ≥90%	385 (73)	150 (29)
PSA ≤0.2 ng/ml	356 (68)	166 (32)
PSA decline ≥90% or PSA ≤0.2 ng/ml	447 (85)	228 (43)
PSA decline ≥90% and PSA ≤0.2 ng/ml	294 (56)	88 (17)
Median (Q1-Q3) time to achieve confirmed best PSA decline, months		
PSA decline ≥50%	1.0 (1.0-1.0)	1.0 (1.0-3.7)
PSA decline ≥90%	1.9 (1.0-2.8)	3.7 (1.9-11.1)
PSA ≤0.2 ng/ml	1.9 (1.0-3.5)	1.9 (1.0-16.6)
Depth of best overall PSA decline, *n* (%)		
PSA decline <50%	52 (10)	237 (45)
PSA decline 50% to <90%	88 (17)	140 (27)
PSA decline ≥90%	385 (73)	150 (29)
Best PSA decline by 3 months, *n* (%)		
PSA decline ≥50%	469 (89)	216 (41)
PSA decline ≥90%	307 (59)	70 (13)
PSA ≤0.2 ng/ml	267 (51)	93 (18)
PSA decline ≥90% or PSA ≤0.2 ng/ml	392 (75)	147 (28)
PSA decline ≥90% and PSA ≤0.2 ng/ml	182 (35)	16 (3)
PSA decline at landmark 3 months, *n* (%)		
	n = 490[a]	*n* = 436[a]
PSA decline ≥50%	457 (93)	206 (47)
PSA decline ≥90%	298 (61)	69 (16)
PSA ≤0.2 ng/ml	263 (54)	89 (20)
PSA decline ≥90% or PSA ≤0.2 ng/ml	381 (78)	142 (33)
PSA decline ≥90% and PSA ≤0.2 ng/ml	179 (37)	16 (4)

ADT, androgen deprivation therapy; PSA, prostate-specific antigen.
[a]Patients with PSA measurement.

(Table 1). Similar differences in all types of best PSA decline between apalutamide- and placebo-treated patients were observed by 6 and 12 months of treatment (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.02.009). By 6 months of treatment, 90%, 68%, 61%, and 81% of apalutamide-treated and 49%, 18%, 21%, and 35% of placebo-treated patients achieved ≥50% PSA decline, ≥90% PSA decline, undetectable PSA ≤0.2 ng/ml, and PSA decline ≥90% or PSA ≤0.2 ng/ml, respectively. By 12 months of treatment, these proportions were 90%, 71%, 64%, and 83% and 51%, 22%, 23%, and 38% for apalutamide- and placebo-treated patients, respectively. The proportion of patients who achieved both ≥90% PSA decline and PSA ≤0.2 ng/ml with apalutamide increased from 35% by 3 months to 47% and 52% at 6 and 12 months, respectively, whereas these percentages were 3%, 5%, and 7% by 3, 6, and 12 months, respectively, with placebo (Table 1 and Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.02.009).

PSA decline at 3-, 6-, and 12-month landmark times showed similar trends to the best PSA decline (Table 1 and Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.02.009). Median PSA change from baseline reduced rapidly at 1 month of treatment and was sustained through 12 months in both treatment groups, with a greater change observed in the apalutamide group (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.02.009).

To confirm that baseline disease characteristics did not underlie differences in PSA decline between apalutamide- and placebo-treated patients, we assessed them by achievement of deep PSA decline (≥90% from baseline or to PSA ≤0.2 ng/ml) at 6 months. Whereas Gleason score at diagnosis, extent of disease, and Eastern Cooperative Oncology Group performance status at baseline were similar regardless of treatment group, they were generally worse in patients who did not achieve deep PSA decline (Table 2). Most patients (71%) had received prior ADT for mCSPC for ≤3 months before randomization. The median time from initiation of ADT for mCSPC to randomization was 1.8 months.

Treatment-emergent adverse events at 6 months of apalutamide treatment were assessed in patients with or without a deep PSA decline (Table 3). The overall safety profile was similar to that described previously for the overall intent-to-treat TITAN population.[12,13]

Association between PSA decline and outcomes in apalutamide-treated patients

Given the higher rate and rapid onset of deep PSA decline with apalutamide versus placebo, we examined the association of outcomes with the achievement of ≥90% PSA decline or PSA ≤0.2 ng/ml at 3 months landmark time of apalutamide treatment only. Achievement of deep PSA decline at 3-months landmark time was associated with improved OS (HR 0.35, 95% CI 0.25-0.48, $P < 0.0001$), rPFS (HR 0.44, 95% CI 0.30-0.65, $P < 0.0001$), time to PSA progression (HR 0.31, 95% CI 0.22-0.44, $P < 0.0001$), and time to castration resistance (HR 0.38, 95% CI 0.27-0.52, $P < 0.0001$) compared with lack of deep PSA decline (Figure 1).

Table 2. Baseline demographic and disease characteristics by achievement of deep PSA decline at 6 months during the TITAN study

Values	≥90% PSA decline or PSA ≤0.2 ng/ml achieved		≥90% PSA decline or PSA ≤0.2 ng/ml not achieved	
	Apalutamide ($n = 390$)	Placebo ($n = 152$)	Apalutamide ($n = 74$)	Placebo ($n = 228$)
Median (Q1-Q3) age, years	69 (64-75)	70 (63-75)	67 (61-73)	68 (62-73)
Median (Q1-Q3) time from initial diagnosis to randomization, months	3.6 (2.0-7.6)	3.6 (2.0-7.2)	5.5 (3.1-7.2)	3.9 (2.6-6.0)
Median (Q1-Q3) time from diagnosis of metastases to randomization, months	2.2 (1.4-4.3)	2.2 (1.3-4.8)	3.7 (2.5-5.7)	2.7 (1.7-4.6)
Gleason score at diagnosis, *n* (%)				
<8	135 (35)	56 (37)	24 (32)	75 (33)
≥8	255 (65)	96 (63)	50 (68)	153 (67)
ECOG performance status, *n* (%)				
0	255 (65)	113 (74)	40 (54)	152 (67)
1	135 (35)	39 (26)	34 (46)	76[a] (33)
Prior docetaxel use, *n* (%)	34 (9)	21 (14)	14 (19)	21 (9)
Metastatic disease, *n* (%)				
Localized disease at diagnosis (M0)	67 (17)	21 (14)	7 (10)	20 (9)
Metastatic disease at diagnosis (*de novo* metastatic; M1)	300 (77)	122 (80)	63 (85)	196 (86)
Metastatic disease cannot be measured (MX)	23 (6)	9 (6)	4 (5)	12 (5)
Extent of disease at study entry (non-exclusive), *n* (%)				
Bone metastases	390 (100)	152 (100)	74 (100)	228 (100)
Bone-only metastases	221 (57)	84 (55)	38 (51)	115 (50)
Lymph node metastases	142 (36)	59 (39)	32 (43)	95 (42)
Visceral metastases	39 (10)	12 (8)	6 (8)	34 (15)
Lung metastases	35 (9)	11 (7)	4 (5)	33 (15)
Liver metastases	5 (1)	1 (<1)	3 (4)	4 (2)
Soft tissue metastases	16 (4)	11 (7)	3 (4)	9 (4)
Median (Q1-Q3) PSA, ng/ml	5.9 (0.9-26.4)	2.6 (0.1-35.4)	6.1 (2.5-16.5)	3.1 (1.1-12.5)

ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.
[a]Includes one patient with ECOG performance status = 2.

Table 3. Treatment-emergent adverse events at 6 months of study treatment

Variable	≥90% PSA decline or PSA ≤0.2 ng/ml achieved		≥90% PSA decline or PSA ≤0.2 ng/ml not achieved	
	Apalutamide $n = 390$	Placebo $n = 152$	Apalutamide $n = 74$	Placebo $n = 228$
Median (Q1-Q3) treatment duration, months	41.2 (25.3-46.2)	23.5 (20.6-27.5)	25.4 (11.3-39.6)	21.8 (13.4-26.4)
Any TEAE, *n* (%)	383 (98)	146 (96)	73 (99)	223 (98)
Grade 3-4 TEAEs, *n* (%)	185 (47)	57 (38)	43 (58)	87 (38)
Serious AEs, *n* (%)	108 (28)	29 (19)	30 (41)	45 (20)
TEAEs leading to treatment discontinuation, *n* (%)	33 (9)	4 (3)	12 (16)	13 (6)
TEAEs leading to death, *n* (%)	10 (3)	3 (2)	8 (11)	6 (3)
COVID-19 AEs, *n* (%)	0	0	0	0
TEAEs of interest, *n* (%)				
Skin rash	122 (31)	15 (10)	16 (22)	29 (13)
Fracture	44 (11)	13 (9)	9 (12)	12 (5)
Falls	42 (11)	15 (10)	4 (5)	17 (8)
Ischemic heart disease	23 (6)	5 (3)	7 (10)	3 (1)
Ischemic cardiovascular disorder	9 (2)	1 (<1)	3 (4)	5 (2)
Seizure	0	1 (<1)	3 (4)	1 (<1)

AE, adverse event; COVID-19, coronavirus disease 2019; PSA, prostate-specific antigen; TEAE, treatment-emergent adverse event.

Similarly, achievement of deep PSA decline was associated with improved OS, rPFS, time to PSA progression, and time to castration resistance at 6 or 12 months' landmark time of apalutamide treatment (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.02.009). Time-varying analysis also showed a statistically significant association between achievement of deep PSA decline and improved OS, rPFS, time to PSA progression, and time to castration resistance (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2023.02.009).

Kaplan—Meier analyses showed that the time to death, radiographic or PSA progression, or castration resistance was longer in patients who achieved deep PSA decline (≥90% PSA or PSA ≤0.2 ng/ml) at 3 months of apalutamide treatment versus those who did not (Figure 2). Similar results were seen in patients who had deep PSA declines at 6 or 12 months of treatment with apalutamide (Supplementary Figures S2-S5, available at https://doi.org/10.1016/j.annonc.2023.02.009).

DISCUSSION

In the TITAN study, treatment with apalutamide plus ADT resulted in a more robust PSA decline than that achieved with ADT alone. PSA decline was rapid, deep, and achieved in a

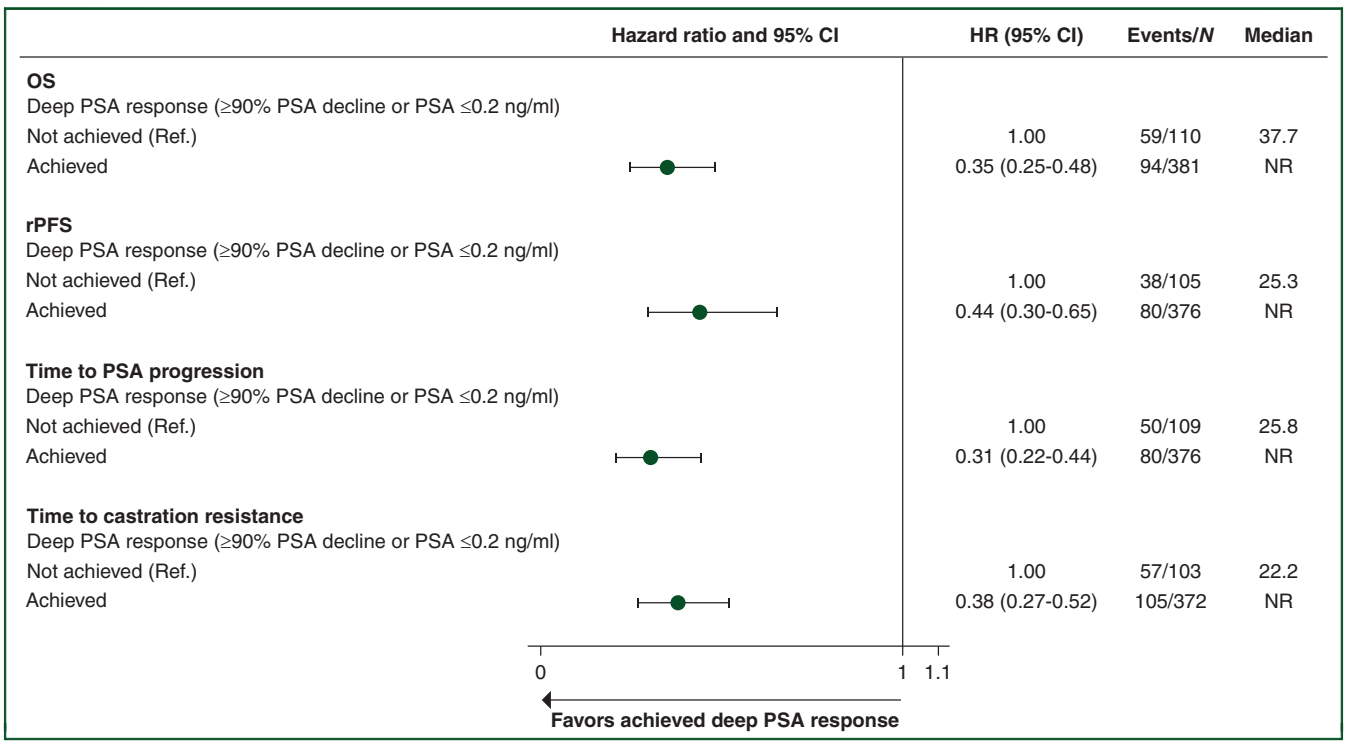

Figure 1. Improvement of survival, radiographic progression or death, time to PSA progression, and time to castration resistance by achievement of deep PSA decline (≥90% PSA decline or PSA ≤0.2 ng/ml) at 3 months landmark time of apalutamide treatment.

CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

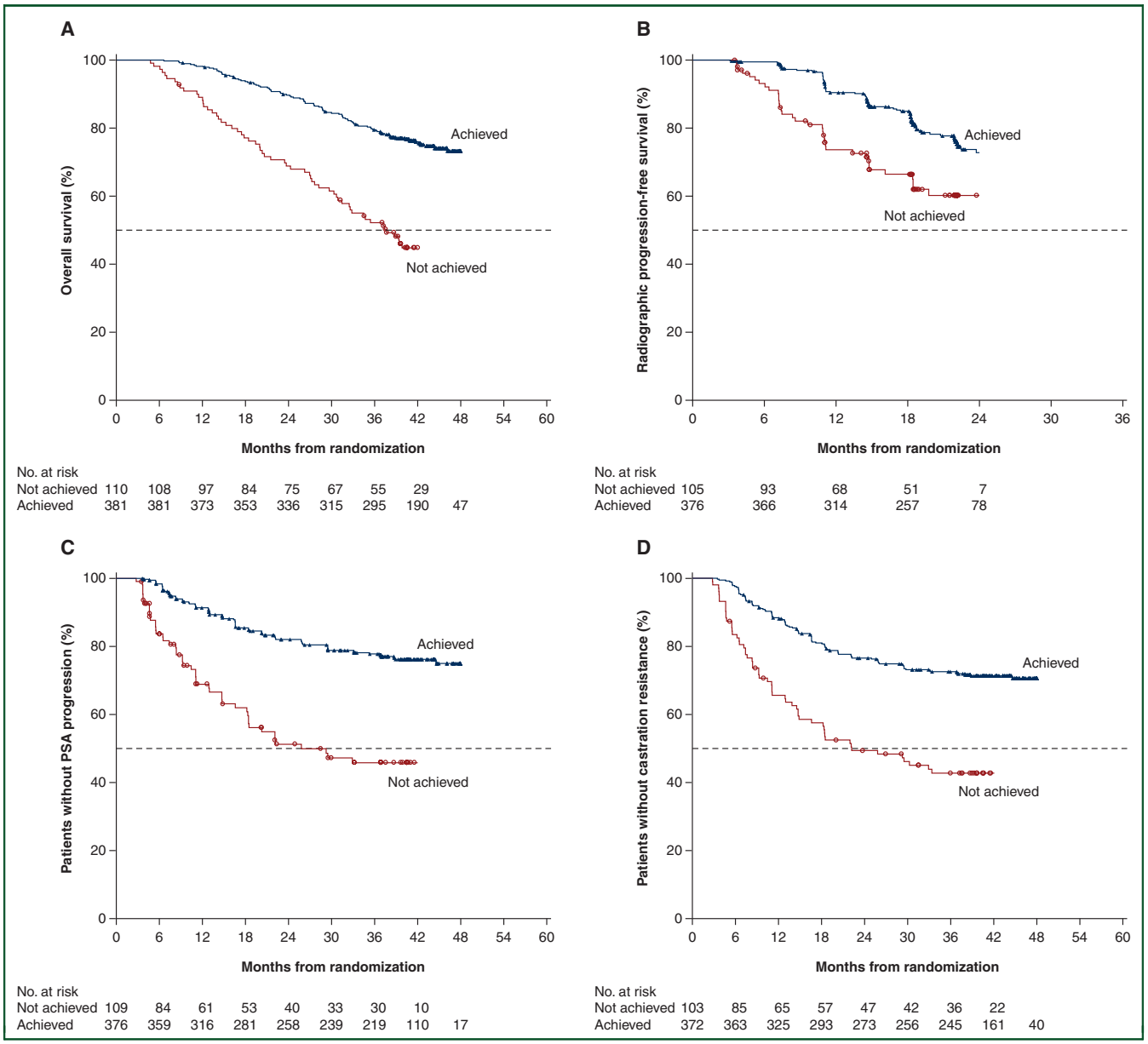

Figure 2. Outcomes by achievement of deep PSA decline (≥90% PSA decline or PSA ≤0.2 ng/ml) at 3 months of apalutamide treatment. (A) Overall survival. (B) Radiographic progression-free survival. (C) Time to PSA progression. (D) Time to castration resistance.
PSA, prostate-specific antigen.

greater proportion of apalutamide-treated than placebo-treated patients. Deep PSA decline (≥90% PSA decline, PSA ≤0.2 ng/ml, or both) was achieved as early as 3 months following apalutamide treatment and was observed at 6 and 12 months. The PSA decline was not only rapid and deep, but was also durable as indicated by prolonged time to PSA progression. Rapid and deep PSA decline was also associated with an improvement in rPFS and long-term survival and other long-term clinical endpoints. TITAN patients with mCSPC who had rapid and deep PSA decline had 65% less risk of death and 62% less risk of castration resistance. To our knowledge, this is the first demonstration of the association of PSA decline with progression to castration-resistant prostate cancer (CRPC). Our results highlight the prognostic importance of PSA measurement in mCSPC.

Other studies have reported the association of PSA levels with clinical outcomes in prostate cancer. Hussain et al.[20] have shown that PSA levels ≤4 ng/ml at 6 and 7 months of ADT were associated with improved survival in patients with metastatic prostate cancer ($P < 0.0001$ compared with PSA >4 ng/ml). A *post hoc* analysis of the CHAARTED clinical study has shown that patients whose PSA was ≤0.2 ng/ml at 7 months of treatment with ADT in combination with docetaxel had a longer median OS than patients with PSA >4 ng/ml at 7 months.[21] Finally, in the LATITUDE study, in high-risk patients with mCSPC, PSA levels ≤0.1 ng/ml after 6 months of treatment with abiraterone acetate plus prednisone were strongly predictive of improved OS and rPFS.[22] Our analysis of PSA decline in TITAN shows that patients who rapidly achieved

deep PSA decline following apalutamide treatment derived a long-term clinical benefit.

The speed of PSA decline is relevant to patients with mCSPC because it can be indicative of disease control. Relationships between speed and depth of PSA decline, however, are complex. Whereas a rapid PSA decline was associated with prolonged time to disease progression in patients treated with ADT alone,[23] a longer time to PSA nadir ($\geq$6 months) was also associated with reduced risk of death and progression.[19,24,25] After further examination, the latter association was apparent in patients with PSA nadir $\geq$0.2 ng/ml but not in those with PSA nadir $<$0.2 ng/ml.[19] In TITAN, median PSA nadir was 10 times lower than 0.2 ng/ml with apalutamide plus ADT, whereas it remained above 0.2 ng/ml with ADT alone (0.02 ng/ml versus 0.75 ng/ml). Median time to achieve PSA nadir was $\sim$1 month longer with addition of apalutamide to ADT ($\sim$6 versus $\sim$5 months). It is hypothesized that low PSA nadir following apalutamide treatment, rather than longer time to achieve it, translated into prolonged survival, delayed onset of castration resistance, and improved other outcomes.

When PSA nadir is very low following treatment, PSA decline at a defined time cut-off may be an appropriate measure of treatment efficacy and prognosis. A large proportion of patients ($\geq$50%) achieved $\geq$90% PSA decline from baseline or undetectable PSA (PSA $\leq$0.2 ng/ml) within 3 months of apalutamide treatment, and this proportion continued to increase through 12 months, possibly contributing to a lower PSA nadir. Although the percentage of placebo-treated patients with deep PSA decline also increased over time, it was lower than in the apalutamide group. Apalutamide has been shown to selectively inhibit androgen receptor translocation and subsequent signalling, thereby increasing cancer cell death *in vitro* and reducing tumor size *in vivo*.[14] This mechanism of action in combination with that of ADT may underlie superior PSA decline achieved with apalutamide plus ADT and its fast onset in a subset of patients, compared with ADT alone. Association between deep PSA decline at 3 months of apalutamide treatment and delayed death, metastases, PSA progression, and development of castration resistance suggest a good prognosis for long-term outcomes following apalutamide and ADT combination.

The real-world evidence study supported our clinical findings. In 351 patients with mCSPC receiving apalutamide (n = 186) or enzalutamide (n = 165) in United States urologic practices,[26] the attainment of $\geq$90% PSA decline from baseline/index in those who received apalutamide, with weighted baseline characteristics, occurred at a median of 3.1 months. A total of 49% of apalutamide-treated patients achieved $\geq$90% PSA decline at 3 months, 69% achieved it at 6 months, and 70% at 9 months. These real-world findings are very similar to the deep PSA decline with an early onset seen with apalutamide in TITAN.

To our knowledge, this analysis using well-established landmark analysis methodology is the first to assess the robustness of PSA decline with one of the ASIs in mCSPC using data from the large prospective phase III clinical study with clinical practice implications. We have previously reported that addition of apalutamide to ADT for 6 months produced rapid, deep, and durable PSA decline that was associated with clinical benefits in non-metastatic CRPC.[27] The speed, depth, and durability of PSA decline and its association with clinical outcomes in advanced cancer in the presence of other ASIs, such as enzalutamide and darolutamide, need to be evaluated in the future. Interestingly, the real-world study has shown that $\geq$90% PSA decline was attained much earlier in patients with mCSPC treated with apalutamide than in those treated with enzalutamide.[26] The median time to achieve $\geq$90% PSA decline among enzalutamide-treated patients was longer than among apalutamide-treated patients (5.2 versus 3.1 months). Thus, future assessments of differences or similarities in PSA decline following apalutamide and the other ASIs are intriguing. Although the merit of PSA as a biomarker for response to treatment in patients with CRPC has been challenged with a call for novel prostate cancer biomarkers,[28] this *post hoc* analysis of TITAN demonstrates the value of PSA in making informed patient management and counselling decisions, such as the close monitoring for disease progression of patients with mCSPC who have a less robust PSA decline, and for clinical trial designs.

Some limitations to these analyses may affect interpretation. These analyses were *post hoc* and were not part of the original study protocol. All *P* values were nominal; no multiplicity-adjusted *P* values were calculated. The TITAN inclusion criteria allowed patients to be enrolled with ADT treatment with or without docetaxel up to 6 months before randomization, and thus patients may have experienced a decline in PSA before the baseline measurement and administration of apalutamide, affecting the analyses of PSA decline; however, this limitation would not apply to analyses of absolute PSA levels ($\leq$0.2 ng/ml or $>$0.2 ng/ml). Our data should be validated in future studies.

Conclusions

This *post hoc* analysis of TITAN shows that addition of apalutamide to ADT results in a deep, rapid, and durable PSA decline in the majority of patients. This robust PSA decline seen with apalutamide plus ADT treatment is associated with improved outcomes in OS, rPFS, time to PSA progression, and time to castration resistance in patients with mCSPC. The data presented in this report may have prognostic implications for patients with mCSPC treated with apalutamide and ADT that we believe will help further improve the management of this lethal disease.

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DATA SHARING

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.

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