original reports

Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study

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abstract

PURPOSE The first interim analysis of the phase III, randomized, placebo-controlled TITAN study showed that apalutamide significantly improved overall survival (OS) and radiographic progression-free survival in patients with metastatic castration-sensitive prostate cancer (mCSPC) receiving ongoing androgen deprivation therapy (ADT). Herein, we report final efficacy and safety results after unblinding and placebo-to-apalutamide crossover.

METHODS Patients with mCSPC (N = 1,052) were randomly assigned 1:1 to receive apalutamide (240 mg QD) or placebo plus ADT. After unblinding in January 2019, placebo-treated patients were allowed to receive apalutamide. Efficacy end points were updated using the Kaplan-Meier method and Cox proportional-hazards model without formal statistical retesting and adjustment for multiplicity. Change from baseline in Functional Assessment of Cancer Therapy-Prostate total score was assessed.

RESULTS With a median follow-up of 44.0 months, 405 OS events had occurred and 208 placebo-treated patients (39.5%) had crossed over to apalutamide. The median treatment duration was 39.3 (apalutamide), 20.2 (placebo), and 15.4 months (crossover). Compared with placebo, apalutamide plus ADT significantly reduced the risk of death by 35% (median OS not reached *v* 52.2 months; hazard ratio, 0.65; 95% CI, 0.53 to 0.79; $P < .0001$) and by 48% after adjustment for crossover (hazard ratio, 0.52; 95% CI, 0.42 to 0.64; $P < .0001$). Apalutamide plus ADT delayed second progression-free survival and castration resistance ($P < .0001$ for both). Health-related quality of life, per total Functional Assessment of Cancer Therapy-Prostate, in both groups was maintained through the study. Safety was consistent with previous reports.

CONCLUSION The final analysis of TITAN confirmed that, despite crossover, apalutamide plus ADT improved OS, delayed castration resistance, maintained health-related quality of life, and had a consistent safety profile in a broad population of patients with mCSPC.

ASSOCIATED CONTENT

Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Multiple phase III studies have demonstrated that outcomes for patients with metastatic castration-sensitive prostate cancer (mCSPC) are improved with the addition of an androgen signaling inhibitor or docetaxel to standard androgen deprivation therapy (ADT).[1-4] These treatments are now considered standard of care and included in prostate cancer treatment guidelines.[5-7] Despite this, new combination treatments with ADT may still be used relatively infrequently, compared with ADT alone,[8,9] owing to concerns about side effects of chemotherapy, prolonged exposure to steroids, the need for patient monitoring, and a lack of long-term follow-up from recently reported studies. Thus, long-term safety data are of interest.

The efficacy and safety of the androgen signaling inhibitor apalutamide in a broad population of patients with mCSPC were assessed in TITAN.[2] At the first interim analysis, apalutamide in combination with ADT significantly improved overall survival (OS; hazard ratio [HR] for death, 0.67; 95% CI, 0.51 to 0.89; $P = .005$) and radiographic progression-free survival (rPFS; HR, 0.48; 95% CI, 0.39 to 0.60; $P < .001$) compared with placebo plus ADT in a broad population of patients with mCSPC. The treatment effect on OS consistently

CONTEXT

Key Objective

Does treatment intensification with the addition of apalutamide to androgen deprivation therapy (ADT) provide long-term survival benefit and an acceptable safety profile in patients with metastatic castration-sensitive prostate cancer?

Knowledge Generated

The final analysis of TITAN demonstrated that the long-term use of apalutamide plus ADT provided significant improvement in overall survival and delayed onset of progression despite almost 40% crossover from placebo to apalutamide after the study was unblinded. With substantially longer follow-up and exposure than at the primary analysis, apalutamide treatment had a safety profile consistent with previous reports and patients maintained health-related quality of life under treatment with apalutamide.

Relevance

Patients with metastatic castration-sensitive prostate cancer can benefit from early treatment intensification with the addition of apalutamide to ADT.

favored apalutamide over placebo across patient subgroups, including those with low-volume disease, regardless of whether patients had metastases at primary diagnosis or had previous treatment of localized disease. All secondary end points favored apalutamide plus ADT, with time to cytotoxic chemotherapy being significantly longer for patients treated with apalutamide than with placebo plus ADT (HR, 0.39; 95% CI, 0.27 to 0.56; $P < .001$). The other clinically relevant end points of time to prostate-specific antigen (PSA) progression and second progression-free survival (PFS2) also favored apalutamide treatment. The safety of apalutamide was manageable, and health-related quality of life (HRQoL) was preserved during apalutamide treatment.[2] On the basis of these results, the independent data-monitoring committee recommended unblinding TITAN to allow patients receiving placebo to receive apalutamide (crossover).

In this prespecified, event-driven final analysis of TITAN, with matured data and long-term follow-up, we report updated results for OS and for the secondary and other clinically relevant end points, patient-reported HRQoL, and safety data with longer follow-up.

METHODS

Study Design and Conduct

TITAN was a phase III, randomized, double-blind, placebo-controlled multinational study in patients with mCSPC; the full study design has been reported previously.[2] Briefly, a broad population of patients with mCSPC was randomly assigned 1:1 to receive apalutamide (240 mg daily) or matched placebo orally once daily in addition to continuous ADT. Patients received treatment until disease progression or unacceptable toxicity. Prior treatment for mCSPC was limited to previous docetaxel (up to six cycles, with the last dose ≤ 2 months before random assignment and with no evidence of progression during treatment or before random assignment), ADT for ≤ 6 months, and one course of radiation or surgical intervention completed before random assignment (Data Supplement, online only).

End Points

The dual primary end points were OS and rPFS. rPFS was estimated as the time from random assignment to first imaging-based documentation of disease progression or death, whichever occurred first; rPFS was prespecified to be final coinciding with the first interim analysis of OS and is not updated in this analysis. OS was defined as the time from random assignment to date of death from any cause. Secondary end points were time to initiation of cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, and time to skeletal-related event. Other clinically relevant end points were time to symptomatic local progression, time to PSA progression based on Prostate Cancer Clinical Trials Working Group 2 (PCWG2),[10] and PFS2. Time to castration resistance was assessed in an ad hoc analysis. Definitions of secondary, other clinically relevant, and ad hoc end points can be found in the Data Supplement. Patient-reported HRQoL was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire. Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.3.

Statistical Analysis

At the first interim analysis of TITAN, reported previously,[2] OS and rPFS met statistical significance. Based on these results, the independent data and safety monitoring committee unanimously recommended unblinding the study and allowing placebo-treated patients without progression to cross over to receive open-label apalutamide. After unblinding, all patients were followed for survival, with crossover patients analyzed as a part of the intent-to-treat population in the placebo group.

Two interim analyses and the updated final analysis for OS were planned (additional details on the sample size required for interim and final analyses are provided in the Data Supplement). At the first interim analysis,[11] the statistical significance of OS had been formally achieved. The final analysis provided mature OS results without formal statistical inference.

In this final report, updated analyses were performed for secondary end points of time to cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, and time to skeletal-related event without formal statistical retesting. Because the time to pain progression end point did not reach statistical significance at the first interim analysis (additional details are provided in the Data Supplement), no formal testing for time to pain progression, time to chronic opioid use, and time to skeletal-related event was conducted. Nominal *P* values are reported without adjustment for multiplicity. Prespecified subgroup analyses assessed consistency of treatment effect; additional subgroup analysis on patients with low- or high-volume disease (adapted from the definition used in the CHAARTED study)[12] at the time of OS analysis was performed without assigned alpha spending.

A prespecified sensitivity analysis for OS, using the inverse probability censoring weighted (IPCW) log-rank test[13] (additional details are provided in the Data Supplement), was conducted to estimate the effect of treatment on OS with the adjustment for the potential confounding effect in the presence of crossover. The Kaplan-Meier method and Cox proportional-hazards model were used to estimate time-to-event variables and determine HRs and associated CIs. Details on censoring rules are provided in the Data

TABLE 1. First Subsequent and Life-Prolonging Subsequent Therapy After Study Treatment Discontinuation

	Safety Population (N = 1,051)[a]		
Category	**Apalutamide Plus ADT (n = 524)**	**Placebo Plus ADT (n = 319)**	**Placebo to Apalutamide (n = 208)**
Patients ongoing	267 (51.0)	0	169 (81.3)
Discontinued study treatment	257 (49.0)	319 (100.0)	39 (18.8)
Reason for discontinuation			
PD	138 (26.3)	245 (76.8)	16 (7.7)
AE	62 (11.8)	19 (6.0)	16 (7.7)
Withdrawal by patient	36 (6.9)	37 (11.6)	7 (3.4)
Death	11 (2.1)	13 (4.1)	0
Physician decision	6 (1.1)	4 (1.3)	0
Protocol violations	2 (0.4)	1 (0.3)	0
Others	2 (0.4)	0	0

	ITT Population (N = 1,052)	
Category	**Apalutamide Plus ADT (n = 525)**	**Placebo Plus ADT (n = 527)**
Patients who discontinued treatment and remained alive, No. (%)	247[b]	345
Patients with first life-prolonging subsequent therapy for prostate cancer,[c] No. (%)	89 (36.0)	173 (50.1)
Patients who discontinued treatment for progressive disease and remained alive (denominator for first subsequent therapy and first life-prolonging subsequent therapies), No.	138	261
Patients with first subsequent therapy for prostate cancer,[c] No. (%)	94 (68.1)	193 (73.9)
Patients with first life-prolonging subsequent therapy for prostate cancer,[c,d] No. (%)	75 (54.3)	151 (57.9)
Abiraterone acetate plus prednisone	20 (14.5)	56 (21.5)
Enzalutamide	9 (6.5)	20 (7.7)
Docetaxel	37 (26.8)	71 (27.2)
Cabazitaxel	2 (1.4)	4 (1.5)
Radium-223	5 (3.6)	5 (1.9)
Sipuleucel-T	2 (1.4)	2 (0.8)

Abbreviations: ADT, androgen deprivation therapy; AE, adverse event; ITT, intent-to-treat; PD, progressive disease.

[a]Excludes one patient who did not receive apalutamide.

[b]Includes one patient who did not receive apalutamide.

[c]Continuing ADT was not considered a subsequent therapy.

[d]Patients could receive ≥ 1 therapy.

Supplement. A mixed-effects repeated measures model was used to assess mean change from baseline in FACT-P total score.

RESULTS

Study Population

Patient disposition from the intent-to-treat population (N = 1,052 [apalutamide plus ADT, n = 525; placebo plus ADT, n = 527]) is summarized in the Data Supplement. One patient in the apalutamide plus ADT group did not receive apalutamide. Patient demographics and disease characteristics have been described previously[2] and are included in the Data Supplement.

The first prespecified interim analysis for OS and final analysis for rPFS occurred after 200 deaths (83, apalutamide; 117, placebo) at the cutoff on November 23, 2018, with a median follow-up of 22.7 months. After unblinding,

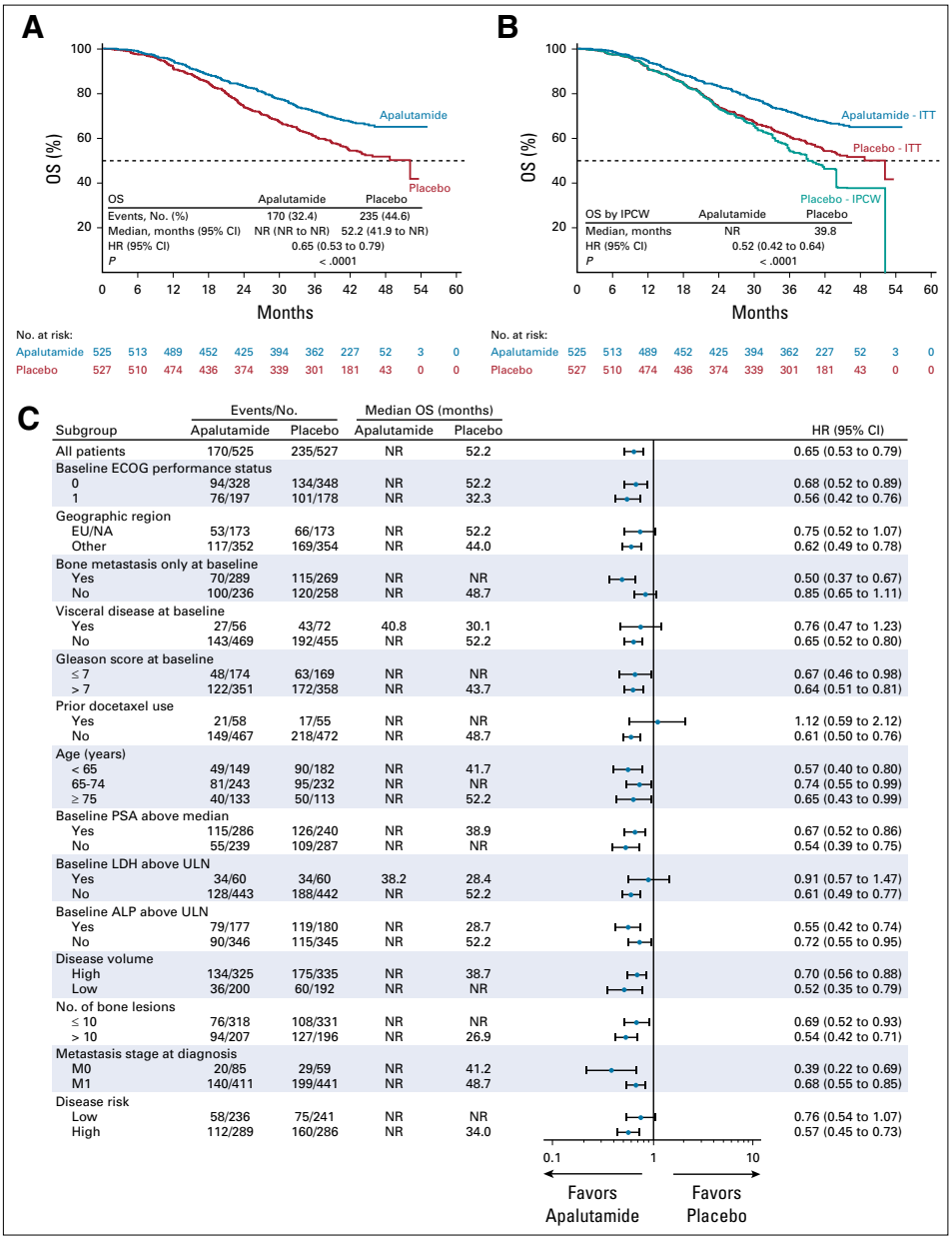

FIG 1. Survival analysis in TITAN. Kaplan-Meier estimates of (A) OS and (B) OS adjusted for patient crossover from placebo to apalutamide using the IPCW sensitivity analysis. (C) Forest plot of OS according to baseline patient characteristics. ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; EU, European Union; HR, hazard ratio; IPCW, inverse probability censoring weighted; ITT, intent-to-treat; LDH, lactate dehydrogenase; NA, North America; NR, not reached; OS, overall survival; PSA, prostate-specific antigen; ULN, upper limit of normal.

208 (39.5%) patients in the placebo group without disease progression crossed over to receive open-label apalutamide. At the prespecified final analysis clinical cutoff on September 7, 2020, 405 deaths (170, apalutamide; 235, placebo) of the required ≈410 had occurred; the median follow-up time was 44.0 months. A total of 267 (51.0%) of 524 patients originally randomly assigned to and treated with apalutamide and 169 (81.3%) of 208 who crossed over continued treatment with apalutamide (Data Supplement).

Of apalutamide- and placebo-treated patients, 257 of 525 (49.0%) and 358 of 527 (67.9%) discontinued study treatment, respectively. The most common reason for discontinuation was progressive disease. At treatment discontinuation, 247 (47.0%) apalutamide- and 345 (65.5%) placebo-treated patients were alive (Table 1, Data Supplement), of whom 36.0% (n = 89) and 50.1% (n = 173) received a first subsequent life-prolonging therapy (life-prolonging defined as a treatment shown to improve OS in a randomized study; Table 1). A complete list of first subsequent systemic therapies is shown in the Data Supplement.

Of 138 apalutamide- and 261 placebo-treated patients who were alive and discontinued because of progressive disease, 54.3% and 57.9%, respectively, received first subsequent life-prolonging therapy, most commonly docetaxel and abiraterone acetate plus prednisone (Table 1). On the other hand, among 109 apalutamide- and 84 placebo-treated patients who were alive and discontinued for other reasons, 12.8% and 26.2%, respectively, also received first subsequent life-prolonging therapy.

Overall, of 527 placebo-treated patients, 173 (32.8%) received first subsequent life-prolonging therapy. Together with 208 (39.5%) placebo-treated patients who crossed

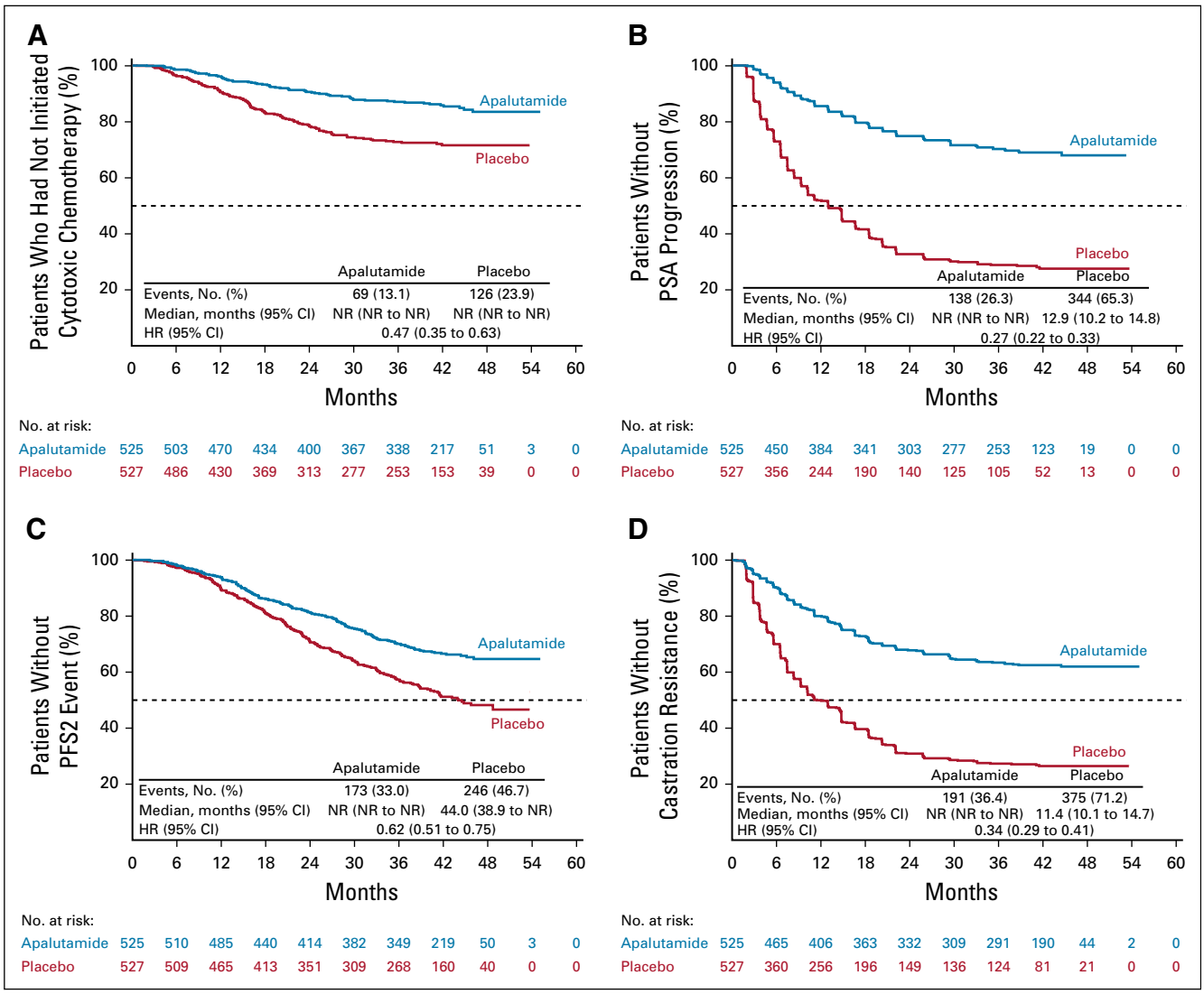

FIG 2. Kaplan-Meier estimates of (A) time to initiation of cytotoxic chemotherapy, (B) time to PSA progression, (C) PFS2, and (D) time to castration resistance. HR, hazard ratio; NR, not reached; PFS2, second progression-free survival; PSA, prostate-specific antigen.

TABLE 2. Secondary and Other Efficacy End Points

End Point	Median (95% CI), months		Apalutamide *v* Placebo	
	Apalutamide Plus ADT (n = 525)	Placebo Plus ADT (n = 527)	HR (95% CI)	*P*[a]
Secondary end points				
Time to initiation of cytotoxic chemotherapy[b]	NR (NR to NR)	NR (NR to NR)	0.47 (0.35 to 0.63)	< .0001
Time to pain progression[c]	NR (NR to NR)	NR (51.3 to NR)	0.87 (0.70 to 1.08)	.197
Time to chronic opioid use[d]	NR (NR to NR)	NR (51.3 to NR)	0.79 (0.58 to 1.09)	.156
Time to skeletal-related event[e]	NR (NR to NR)	NR (51.8 to NR)	0.86 (0.62 to 1.19)	.361
Other clinically relevant end points				
Time to PSA progression[f]	NR (NR to NR)	12.9 (10.2 to 14.8)	0.27 (0.22 to 0.33)	< .0001
PFS2[g]	NR (NR to NR)	44 (38.9 to NR)	0.62 (0.51 to 0.75)	< .0001
Ad hoc end point				
Time to castration resistance[h]	NR (NR to NR)	11.4 (10.1 to 14.7)	0.34 (0.29 to 0.41)	< .0001

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; NR, not reached; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PFS2, second progression-free survival; PSA, prostate-specific antigen.

[a]*P* values for secondary and other clinically relevant end points are nominal.

[b]Time to initiation of cytotoxic chemotherapy was defined as time from random assignment to initiation of cytotoxic chemotherapy.

[c]Pain progression was reported by patients according to worst pain on the Brief Pain Inventory-Short Form (item 3). Scores range from 0 to 10, with lower scores representing lower levels of pain intensity; a change of 2 was the minimally important difference.

[d]Time to chronic opioid use was defined as time from random assignment to chronic opioid use.

[e]Time to skeletal-related events was defined as time from random assignment to date of the occurrence of symptomatic skeletal event (ie, pathologic fracture, spinal cord compression, radiation to bone, or surgery to bone).

[f]Time to PSA progression was defined as date of random assignment to date of PSA progression based on PCWG2 criteria.

[g]PFS2 was defined as time from random assignment to the first occurrence of investigator-determined disease progression (PSA progression, progression on imaging, or clinical progression) on first subsequent therapy or death.

[h]Time to castration resistance was defined as time from random assignment to radiographic disease progression, PSA progression per PCWG2, or symptomatic skeletal event, whichever occurred first.

over to receive apalutamide, the number of patients in the placebo group who received active subsequent life-prolonging treatment after study treatment discontinuation was 381 (72.3%).

OS

The final analysis of OS occurred after 405 death events, 170 in apalutamide and 235 in placebo plus ADT groups. Compared with placebo, apalutamide significantly decreased the risk of death by 35% (HR, 0.65; 95% CI, 0.53 to 0.79; $P < .0001$; Fig 1A). The median OS for apalutamide-treated patients was not reached (NR) versus 52.2 months for placebo-treated patients, with 39.5% of crossover patients analyzed as a part of the intent-to-treat population in the placebo plus ADT group. The OS rates at 48 months were 65.1% and 51.8% for apalutamide- and placebo-treated patients, respectively.

To account for a crossover effect, we performed an IPCW sensitivity analysis of OS that showed reduction of the risk of death with apalutamide by 48% compared with placebo (Fig 1B). The median OS in the placebo plus ADT group in the IPCW analysis (39.8 months) was 12.4 months shorter than that in the original analysis without accounting for crossover (52.2 months), whereas it remained NR in the apalutamide plus ADT group. The survival rates at 48 months by IPCW analysis were 65.2% (apalutamide) and 37.9% (placebo).

The treatment effect of apalutamide plus ADT on OS was favorable across prespecified subgroups, including high-risk patients (modified definition of high risk per LATITUDE[14]) and with both high-volume and low-volume disease (definition of disease volume per CHAARTED[12]). In the subgroup of patients with prior docetaxel treatment, the HR point estimate was > 1 with the lower boundary of CI crossing 1. However, the number of OS events and of patients with prior docetaxe use were low in both apalutamide (21 events from 58 patients) and placebo (17 events from 55 patients) plus ADT groups (Fig 1C). Relatively small numbers of patients and events were also observed in patients with visceral metastases. The interaction effect between treatment and any of the subgroups was not statistically significant for OS, except for the subgroup with bone metastases only at baseline ($P = .0108$).

Secondary and Other Clinically Relevant End Points

The final formal statistical testing for all secondary end points was performed at the time of the first interim analysis. For this report, we performed an updated analysis of secondary end points based on the final data cutoff. The hierarchical testing or inferential statistics are not applicable for

any of the secondary end points; therefore, this analysis is for descriptive purposes only.

At final analysis, cytotoxic chemotherapy had been initiated in 195 patients, including 69 (13.1%) apalutamide- and 126 (23.9%) placebo-treated patients. Treatment with apalutamide significantly reduced the risk of initiating cytotoxic chemotherapy by 53% versus placebo (Fig 2A). The updated analyses of the secondary end points of time to pain progression, time to chronic opioid use, and time to skeletal-related event also favored apalutamide over placebo, although their nominal *P* values did not cross a level of statistical significance (Table 2, Data Supplement).

The exploratory end points of median time to PSA progression and PFS2 also favored apalutamide versus placebo at the time of final analysis. PSA progression occurred in 138 (26.3%) and 344 (65.3%) apalutamide- and placebo-treated patients, respectively. Compared with placebo, apalutamide significantly reduced the risk of PSA progression by 73% (Table 2) and prolonged median time to PSA progression (Fig 2B). PFS2 events occurred in 173 (33.0%) and 246 (46.7%) apalutamide- and placebo-treated patients. Apalutamide prolonged PFS2 and significantly reduced the risk of second progression or death by 38% compared with placebo (Fig 2C, Table 2). The risk of symptomatic local progression was similar between treatment groups; however, the number of events was low (38 [7.2%], apalutamide and 30 [5.7%], placebo; Data Supplement).

In the post hoc analysis, 191 (36.4%) apalutamide-treated and 375 (71.2%) placebo-treated patients developed castration-resistant prostate cancer. Apalutamide significantly reduced the risk of castration resistance by 66% (Table 2) and delayed the onset of castration resistance (Fig 2D).

Patient-Reported Outcomes

Analysis of change from baseline in the total FACT-P score showed that favorable baseline HRQoL per total FACT-P was maintained with the addition of apalutamide to ADT, with no substantial between-group differences (Fig 3). Specific HRQoL domains, as measured by FACT-P subscales, were also maintained with apalutamide (Data Supplement).

Safety

The median treatment duration was 19.1 months longer in the apalutamide plus ADT group than in the placebo plus ADT group (apalutamide, 39.3 months; placebo, 20.2 months). The median treatment duration with apalutamide in the crossover group was 15.4 months (Table 3). Overall incidence of any treatment-emergent AEs (TEAEs) was similar between treatment groups (Data Supplement) and to those reported previously.[2] Exposure-adjusted rates of TEAEs of interest per 100 patient-years were 40.0, 22.4, and 41.9 in apalutamide plus ADT, placebo plus ADT, and crossover groups (Table 3). Cumulative incidence of first grade 3-4 TEAEs, serious AEs, and any-grade treatment-emergent falls, fracture, and fatigue was also similar between groups (Data Supplement). Consistent with previous reports,[11] incidence of first any-grade skin rash event was higher in apalutamide-treated than in placebo-treated patients, reaching

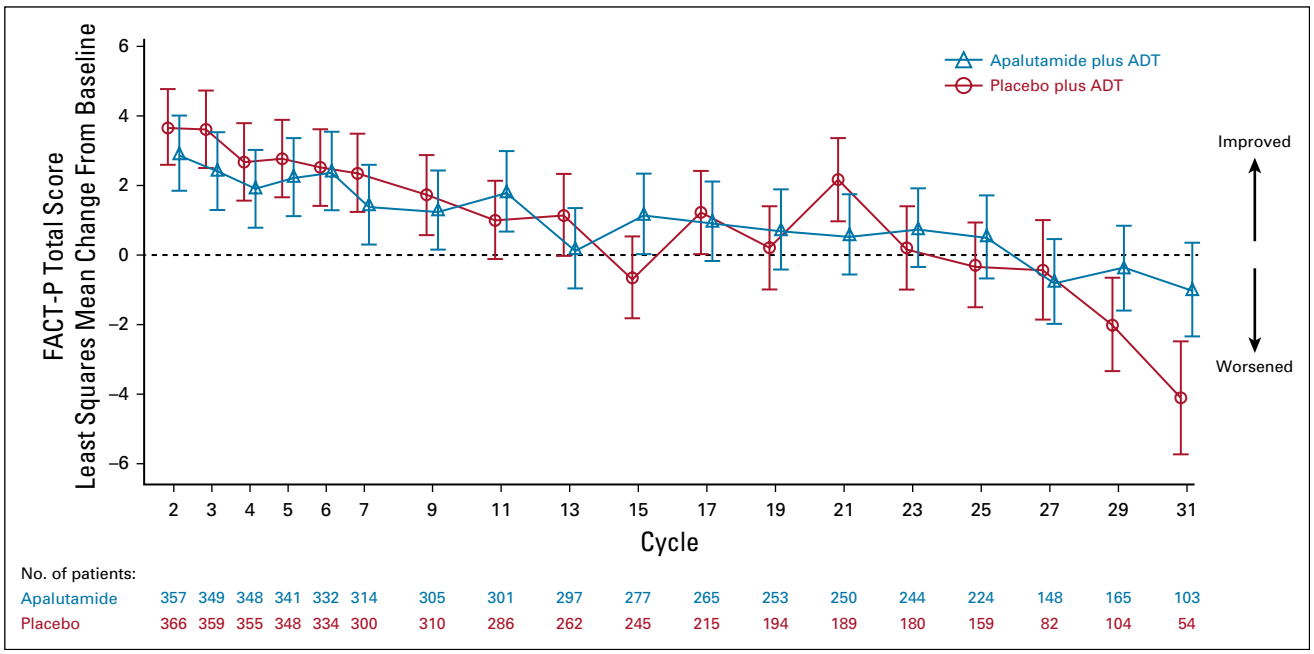

FIG 3. Mixed-effects repeated measures analyses for least squares mean change from baseline in FACT-P total score. Error bars are standard errors of the mean. Raw FACT-P scores range from 0 to 156, with higher scores indicating more favorable HRQoL; a 6- to 10-point change in FACT-P total score would be the minimally important difference. ADT, androgen deprivation therapy; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HRQoL, health-related quality of life.

TABLE 3. Exposure-Adjusted Rates of TEAEs of Interest in the Safety Population (N = 1,051)

Category	Apalutamide Plus ADT (n = 524)		Placebo Plus ADT (n = 527)		Placebo to Apalutamide (n = 208)	
Median treatment duration, months (range)[a]	39.3 (0-55.7)		20.2 (0.1-37.0)		15.4 (0.6-18.2)	
Total exposure, patient-years	1,358.9		793.3		243.6	
TEAEs by group term, event (event rate/100 patient-years of exposure)[b]	All grades[c]	Grade 3-4[c]	All grades	Grade 3-4	All grades	Grade 3-4
Any TEAE of interest	543 (40.0)	103 (7.6)	178 (22.4)	21 (2.7)	102 (41.9)	16 (6.5)
Skin rash[d]	331 (24.4)	40 (2.9)	66 (8.3)	5 (0.6)	44 (18.1)	8 (3.3)
Fracture[e]	83 (6.1)	21 (1.5)	33 (4.2)	4 (0.5)	5 (2.1)	0
Fall	63 (4.6)	9 (0.7)	54 (6.8)	5 (0.6)	14 (5.7)	0
Ischemic heart disease[f]	45 (3.3)	21 (1.5)	13 (1.6)	5 (0.7)	1 (0.4)	1 (0.4)
Ischemic cerebrovascular disorders[g]	18 (1.3)	11 (0.8)	10 (1.3)	2 (0.3)	7 (2.9)	7 (2.8)
Seizure[h]	3 (0.2)	1 (0.1)	2 (0.3)	0	0	0

Abbreviations: ADT, androgen deprivation therapy; AE, adverse event; TEAE, treatment-emergent AE.

[a]Patients received treatment until disease progression or unacceptable toxicity.

[b]Event rate per 100 patient-years of exposure is calculated as 100 times the number of distinct events with the group term/total patient-years of exposure (total days of exposure/365.25) for the treatment group. AEs occurred from the time of the first dose of the study intervention through 30 days after the last dose. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.3. One patient who was assigned to the apalutamide group withdrew consent before treatment.

[c]The worst toxicity grade is included. Patients with missing toxicity grades were counted in the all-grade column.

[d]Skin rash was a grouped term including rash, maculopapular rash, conjunctivitis, dermatitis, stomatitis, pruritic rash, urticaria, papular rash, skin exfoliation, blister, mouth ulceration, drug eruption, erythema multiforme, exfoliative rash, toxic skin eruption, papule, skin reaction, butterfly rash, generalized exfoliative dermatitis, genital rash, erythematous rash, macular rash, systemic lupus erythematosus rash, oral mucosal blistering, follicular rash, pustular rash, and vesicular rash.

[e]Fracture was a grouped term including rib fracture, spinal compression fracture, hand fracture, femoral neck fracture, foot fracture, femur fracture, thoracic vertebral fracture, traumatic fracture, upper limb fracture, wrist fracture, ankle fracture, fracture, hip fracture, spinal fracture, radius fracture, acetabulum fracture, fracture pain, clavicle fracture, comminuted fracture, compression fracture, forearm fracture, humerus fracture, patella fracture, pelvic fracture, sternal fracture, stress fracture, ulna fracture, fibula fracture, lower limb fracture, skull fracture, and tibia fracture.

[f]Ischemic heart disease was a group term including angina pectoris, myocardial infarction, acute myocardial infarction, coronary artery stenosis, coronary artery arteriosclerosis, myocardial ischemia, coronary artery disease, coronary artery occlusion, acute coronary syndrome, abnormal cardiac stress test, ischemic cardiomyopathy, unstable angina, and increased troponin.

[g]Ischemic cardiovascular disorder was a group term including cerebrovascular accident, transient ischemic attack, ischemic stroke, cerebrovascular disorder, lacunar infarction, cerebral ischemia, hemiplegia, vascular encephalopathy, carotid artery stenosis, and carotid arteriosclerosis.

[h]Seizure was a group term including seizure and tongue biting.

a plateau after about 6 months (Data Supplement). The most common treatment-related AEs related to treatment with apalutamide were rash and fatigue (Data Supplement). There were no treatment-related deaths. Three patients, only from the crossover group, reported COVID-19 TEAEs, which resolved and did not lead to treatment discontinuation or death. Additional safety details are provided in the Data Supplement.

DISCUSSION

In the final analysis of TITAN, after a median follow-up of almost 4 years, apalutamide consistently improved survival compared with placebo in a broad population of patients with mCSPC receiving ADT, reducing the risk of death by 35%. The survival benefit of apalutamide was observed despite almost 40% of placebo-treated patients without progression crossing over to apalutamide after study unblinding followed by a median 15.4-month exposure to apalutamide. After adjusting for crossover, the risk of death was reduced by 48%. The long-term survival benefit of apalutamide plus ADT remained consistent with the results of the first interim analysis, with follow-up that was twice as long.[2] Notably, the majority of placebo-treated patients (> 72%) received active subsequent life-prolonging therapy after study treatment discontinuation. This includes almost 40% of patients who received apalutamide after crossover and almost 33% of those who received first subsequent life-prolonging therapy. Together with the superior PFS2 results for patients receiving apalutamide plus ADT versus placebo plus ADT, these data emphasize the benefit of early institution of potent androgen signaling inhibition with apalutamide at the time of initial ADT for mCSPC and before progression to castration-resistant prostate cancer.

The reduced risk of death with apalutamide versus placebo was observed consistently across the prespecified subgroups, including patients with high- and low-volume disease, with no evidence for heterogeneity of treatment effect, except in patients with bone metastases only at

baseline. The benefit in OS with apalutamide in patients who received prior docetaxel or those with visceral disease remains to be established in future studies because of the relatively low number of patients (from 55 to 72 patients) and events (from 17 to 43 events) per treatment group. The robust clinical efficacy associated with apalutamide treatment was further supported by significantly delayed time to PSA progression, castration resistance, and initiation of cytotoxic chemotherapy compared with placebo. FACT-P total scores indicate that HRQoL was preserved with the addition of apalutamide to ADT. This is consistent with our findings from the first interim analysis, confirming HRQoL maintenance in a broad population of patients who were mostly asymptomatic at baseline.[2]

Over the past 5 years, a series of studies have demonstrated benefits of intensifying ADT with additional treatment for patients with mCSPC. Reports on the long-term follow-up of the CHAARTED,[12] STAMPEDE,[15] and LATITUDE[4] studies showed continuous and consistent OS improvements with docetaxel or abiraterone acetate added to ADT for the initial treatment of a broad spectrum of patients with mCSPC. Despite this compelling evidence, the use of ADT intensification strategies with docetaxel or abiraterone is still rather infrequent in the real world.[8,9] The risk of AEs associated with chemotherapy and long-term exposure to steroids and monitoring requirements for abiraterone may contribute to this. At a median follow-up of almost 4 years in the TITAN final analysis, the safety profile of apalutamide remained consistent with that reported previously, with rash continuing to be notably prevalent over placebo. No new safety signals were detected, and no treatment-related deaths occurred. Apalutamide, approved for a broad mCSPC population by US Food and Drug Administration, requires little laboratory monitoring. The TITAN final analysis, confirming long-term benefits of apalutamide, provides a greater opportunity for the majority of patients with mCSPC to derive benefit from the intensified ADT treatment strategy using apalutamide.

Our analysis has the methodological limitation that the inference statistics are not applicable for the analysis of secondary end points. *P* values are nominal and are provided for descriptive purposes only. Therefore, any conclusions of statistical significance related to secondary end points should be made cautiously. The definition of PFS2 as time from random assignment to progression on first subsequent therapy or death may have bias because of censoring, as it consists of first progression-free survival and time between initiation of first subsequent therapy and progression on first subsequent therapy. However, PFS2 reflects the advantage of early treatment with a study drug after random assignment.

In conclusion, the final analysis of TITAN and its long-term results demonstrate that apalutamide plus ADT consistently provides significant improvements in OS and delays onset of progression despite a large number of placebo-treated patients crossing over to active treatment with apalutamide during the study. Apalutamide benefit was robustly supported by other efficacy end points, including delayed castration resistance and prolonged PFS2. Apalutamide maintained HRQoL and had an acceptable safety profile confirmed with substantially longer follow-up and exposure. These results support the early addition of apalutamide to ADT for optimal therapeutic outcomes in patients with mCSPC.

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DATA SHARING STATEMENT

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 https://yoda.yale.edu.

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