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Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer

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ABSTRACT

BACKGROUND

Apalutamide is an inhibitor of the ligand-binding domain of the androgen receptor. Whether the addition of apalutamide to androgen-deprivation therapy (ADT) would prolong radiographic progression–free survival and overall survival as compared with placebo plus ADT among patients with metastatic, castration-sensitive prostate cancer has not been determined.

METHODS

In this double-blind, phase 3 trial, we randomly assigned patients with metastatic, castration-sensitive prostate cancer to receive apalutamide (240 mg per day) or placebo, added to ADT. Previous treatment for localized disease and previous docetaxel therapy were allowed. The primary end points were radiographic progression–free survival and overall survival.

RESULTS

A total of 525 patients were assigned to receive apalutamide plus ADT and 527 to receive placebo plus ADT. The median age was 68 years. A total of 16.4% of the patients had undergone prostatectomy or received radiotherapy for localized disease, and 10.7% had received previous docetaxel therapy; 62.7% had high-volume disease, and 37.3% had low-volume disease. At the first interim analysis, with a median of 22.7 months of follow-up, the percentage of patients with radiographic progression–free survival at 24 months was 68.2% in the apalutamide group and 47.5% in the placebo group (hazard ratio for radiographic progression or death, 0.48; 95% confidence interval [CI], 0.39 to 0.60; P<0.001). Overall survival at 24 months was also greater with apalutamide than with placebo (82.4% in the apalutamide group vs. 73.5% in the placebo group; hazard ratio for death, 0.67; 95% CI, 0.51 to 0.89; P=0.005). The frequency of grade 3 or 4 adverse events was 42.2% in the apalutamide group and 40.8% in the placebo group; rash was more common in the apalutamide group.

CONCLUSIONS

In this trial involving patients with metastatic, castration-sensitive prostate cancer, overall survival and radiographic progression–free survival were significantly longer with the addition of apalutamide to ADT than with placebo plus ADT, and the side-effect profile did not differ substantially between the two groups. (Funded by Janssen Research and Development; TITAN ClinicalTrials.gov number, NCT02489318.)

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*A complete list of investigators in the TITAN trial is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

The initial treatment for metastatic prostate cancer is androgen-deprivation therapy (ADT) through medical or surgical castration. In the past few years, results from several large, randomized, phase 3 clinical trials have shown longer survival, particularly among patients with high-risk or high-volume disease, when ADT was combined with either abiraterone acetate plus prednisone or docetaxel for metastatic prostate cancer at the time of initial ADT administration when the disease is castration sensitive.[1-7] However, patient age, coexisting conditions, extent of disease, and preferences may affect decisions to initiate chemotherapy such as docetaxel.[8,9] Treatment with abiraterone acetate requires coadministration of prednisone to prevent increases in corticotropin and may cause adverse events related to mineralocorticoid excess and liver toxicity.

Direct inhibition of the androgen receptor in addition to ADT may provide more a complete blockade of androgen signaling than ADT alone, leading to improved patient outcomes. Apalutamide, an oral nonsteroidal antiandrogen agent that binds directly to the ligand-binding domain of the androgen receptor and prevents androgen-receptor translocation, DNA binding, and androgen receptor–mediated transcription,[10] has been approved in the United States and European Union for the treatment of patients with nonmetastatic, castration-resistant prostate cancer. The Targeted Investigational Treatment Analysis of Novel Anti-androgen (TITAN) trial was conducted to determine whether apalutamide would result in longer radiographic progression–free survival and overall survival than placebo with an acceptable safety profile and health-related quality of life among patients with metastatic, castration-sensitive prostate cancer who were receiving concomitant ADT.

METHODS

TRIAL DESIGN AND CONDUCT

The TITAN trial was a phase 3, randomized, double-blind, placebo-controlled, multinational trial involving patients with metastatic, castration-sensitive prostate cancer. The protocol and the statistical analysis plan are available with the full text of this article at NEJM.org. The trial was designed by the sponsor, Janssen Research and Development, with input from the first author and the protocol steering committee and was conducted at 260 sites in 23 countries. Review boards at all participating institutions approved the trial, which was conducted in accordance with current International Conference on Harmonisation guidelines for Good Clinical Practice and according to Declaration of Helsinki principles. All the patients provided written informed consent. Patients underwent randomization between December 15, 2015, and July 25, 2017. An independent data-monitoring committee was commissioned by the sponsor to monitor safety and efficacy before unblinding and to make recommendations regarding trial conduct. Data were transcribed by personnel at each site from source documents into sponsor-prepared electronic case-report forms.

All the authors assume responsibility for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol. The first author developed the first draft of the manuscript with editorial assistance funded by Janssen Research and Development. All the authors had full access to the data, participated in data interpretation, and reviewed and approved the manuscript before submission. The investigators, patients, trial-site personnel, and sponsor trial team were unaware of the randomization codes until trial completion, recommendation by the independent data-monitoring committee, or individual-patient medical need.

PATIENTS AND INTERVENTIONS

Eligible patients were required to have documented adenocarcinoma of the prostate and distant metastatic disease documented on the basis of at least one lesion on bone scanning, with or without visceral or lymph-node involvement. All the patients had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a scale of 0 to 5, with higher scores reflecting greater disability). Patients were castration sensitive (i.e., patients were not receiving ADT at the time of disease progression[11,12]). Previous treatment for prostate cancer was limited to previous docetaxel use (for a maximum of six cycles, with no evidence of progression during treatment or before randomization), ADT for no more than 6 months for metastatic, castration-sensitive prostate cancer or no more than 3 years for localized prostate cancer, one course of radiation or surgical therapy for symptoms associated with meta-

static disease, and other localized treatments (e.g., radiation therapy or prostatectomy) completed at least 1 year before randomization. Patients who had received a gonadotropin-releasing hormone agonist within 28 days before randomization were required to take a first-generation antiandrogen[13] (i.e., bicalutamide, flutamide, or nilutamide) for 14 or more days before randomization. Antiandrogen therapy must have been discontinued before randomization. Patients with severe angina, myocardial infarction, congestive heart failure, arterial or venous thromboembolic events, a history of or predisposition to seizure, or recent ventricular arrhythmias were excluded.

Patients were randomly assigned in a 1:1 ratio to receive apalutamide (240 mg) or matched placebo administered orally once daily, in addition to continuous ADT. Patients were stratified according to Gleason score at diagnosis (≤7 vs. >7, on a scale of 2 to 10, with higher scores indicating higher-grade cancer that may be more aggressive), geographic region (North America and European Union vs. all other countries), and previous treatment with docetaxel (yes vs. no).

END POINTS

The primary end points were radiographic progression–free survival and overall survival. Radiographic progression–free survival was defined as the time from randomization to first imaging-based documentation of progressive disease or death, whichever occurred first. A patient was considered to have radiographic progressive disease if he had either progression of soft-tissue lesions measured by means of computed tomography (CT) or magnetic resonance imaging (MRI) or new bone lesions on bone scanning. Overall survival was defined as the time from randomization to the date of death from any cause.

Secondary end points were the time to cytotoxic chemotherapy, time to pain progression as assessed by the Brief Pain Inventory–Short Form (BPI-SF; worst pain [item 3] was used for this end point; scores range from 0 to 10, with lower scores representing lower levels of pain intensity; a change of 2 was the minimally important difference[14]), time to chronic opioid use, and time to skeletal-related event. Definitions of secondary and exploratory end points are provided in the Methods section in the Supplementary Appendix, available at NEJM.org. A prespecified analysis of data from patients with low-volume or high-volume metastatic, castration-sensitive prostate cancer was planned, and evaluation of the efficacy of the intervention in these groups was a secondary objective. The definition of high-volume disease was adapted from the Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED)[7]: visceral metastases and at least one bone lesion, or at least four bone lesions with at least one outside the axial skeleton. Low-volume disease was defined as the presence of bone lesions not meeting the definition of high-volume disease.

Exploratory end points included the time to prostate-specific antigen (PSA) progression, second progression-free survival, and the time to symptomatic local progression. Second progression-free survival was defined as the time from randomization to the first occurrence of investigator-determined disease progression (PSA progression, progression on imaging, or clinical progression) while the patient was receiving first subsequent therapy for prostate cancer or death due to any cause, whichever occurred first. Patient-reported outcomes for health-related quality of life were assessed by means of the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire.[15-17] Raw FACT-P scores range from 0 to 156, with higher scores indicating more favorable health-related quality of life. A change of 6 to 10 points in the FACT-P total score is the minimally important difference.[15]

ASSESSMENTS

Patients were assessed for efficacy according to modified Response Evaluation Criteria in Solid Tumors, version 1.1, with the use of CT or MRI of the chest, abdomen, and pelvis during screening (≤6 weeks before randomization) and according to Prostate Cancer Working Group 2 criteria[18] (see the Methods section in the Supplementary Appendix) with the use of bone scanning during cycles 3 and 5 and every fourth cycle thereafter. Events of progression were assessed by the investigator. Scans from approximately 60% of the patients were randomly selected for independent central review. Adverse events were assessed monthly and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.3. FACT-P assessments were collected on day 1 of cycles 2 through 7, then every other cycle, at the end of the interven-

tion period, and every 4 months for up to 1 year after discontinuation. BPI-SF assessments were collected 6 days before cycle 1, then at each cycle, the end of the intervention period, and every 4 months for up to 1 year after discontinuation.

STATISTICAL ANALYSIS

The TITAN trial was designed to enroll approximately 1000 patients. Radiographic progression–free survival was tested first. If the difference between the apalutamide group and the placebo group was considered to be statistically significant, the alpha was recycled to overall survival on the basis of the fallback method.[19] An overall type I error of 5% was planned. A total of 368 events of radiographic progression were required to provide at least 85% power to detect a hazard ratio of 0.67 with a two-tailed significance level of 0.005. For the final overall survival analysis, 410 deaths were required to provide approximately 80% power to detect a hazard ratio of 0.75 with a two-tailed significance level of 0.045. Analyses of overall survival incorporated group-sequential design with an alpha-spending function that was calculated as Wang–Tsiatis power boundaries of shape parameter 0.2. Two interim analyses were planned for overall survival. It was estimated that the first interim analysis would include approximately 50% of the total required events for overall survival at the time of the primary analysis for radiographic progression–free survival. The alpha level for interim analysis for overall survival was 0.009, under the assumption of an overall two-tailed significance level of 0.045.

Subgroup analyses were prespecified to assess consistency of treatment effect. If the between-group differences in the primary end points were significant, evaluation of secondary end points was to be performed in the following hierarchical order, each with an overall two-sided significance level of 0.05: time to cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, and time to skeletal-related event. Demographic and clinical characteristics at baseline were summarized with the use of descriptive statistics. The primary statistical method of comparison for time-to-event end points was a stratified log-rank test, with stratification according to prespecified factors. The Kaplan–Meier product-limit method and Cox proportional-hazards model were used to estimate time-to-event variables and determine hazard ratios and associated confidence intervals.

RESULTS

PATIENTS

Between December 15, 2015, and July 25, 2017, a total of 525 patients were randomly assigned to the apalutamide group and 527 to the placebo group (Fig. S1 in the Supplementary Appendix). At the cutoff date (November 23, 2018) for the first prespecified interim analysis and after 83 deaths in the apalutamide group and 117 in the placebo group, the median follow-up time was 22.7 months. The median number of cycles received was 23 for apalutamide and 19 for placebo (range, 1 to 37 in each group). The median duration of the trial intervention was 20.5 months for apalutamide and 18.3 months for placebo. A total of 66.2% of the patients in the apalutamide group and 46.1% of those in the placebo group were receiving the trial intervention at the clinical cutoff date. A total of 45 patients across the two groups withdrew consent for the trial intervention (Fig. S1 in the Supplementary Appendix). These patients were followed for survival and secondary end points, so their data were not missing. A total of 39 patients were either lost to follow-up or withdrew from all further data collection; this information is not shown in Figure S1 in the Supplementary Appendix.

Demographic and clinical characteristics at baseline were well balanced (Table 1, and Table S1 in the Supplementary Appendix). The median age of the patients across both groups was 68 years. A total of 16.4% of the patients had undergone prostatectomy or received radiotherapy for localized disease, and 10.7% had received previous docetaxel therapy; 62.7% had high-volume disease, and 37.3% had low-volume disease. Patients had newly diagnosed metastatic, castration-sensitive prostate cancer or relapsed metastatic disease after an initial diagnosis of localized disease; most had newly diagnosed metastatic disease. Previous therapies for prostate cancer are listed in Table S2 in the Supplementary Appendix.

PRIMARY END POINTS

Radiographic Progression–free Survival

A total of 365 events of radiographic progression were observed (134 in the apalutamide group and

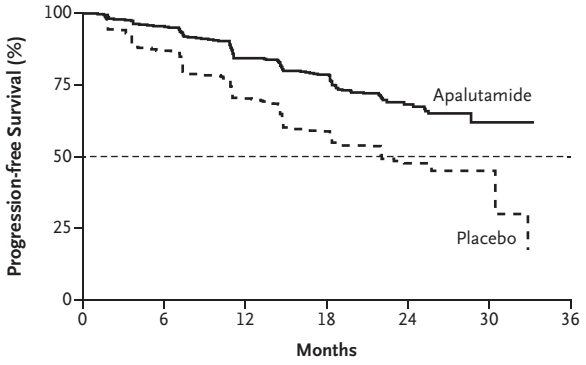
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Apalutamide (N = 525)	Placebo (N = 527)
Median age (range) — yr	69 (45–94)	68 (43–90)
ECOG performance-status score — no. (%)†		
0	328 (62.5)	348 (66.0)
1	197 (37.5)	178 (33.8)
2	0	1 (0.2)
Gleason score at initial diagnosis — no. (%)‡		
<7	41 (7.8)	39 (7.4)
7	133 (25.3)	130 (24.7)
>7	351 (66.9)	358 (67.9)
Metastatic stage at initial diagnosis — no. (%)		
M0	85 (16.2)	59 (11.2)
M1	411 (78.3)	441 (83.7)
MX	29 (5.5)	27 (5.1)
Disease volume — no. (%)		
Low	200 (38.1)	192 (36.4)
High	325 (61.9)	335 (63.6)
Previous treatment with docetaxel — no. (%)§	58 (11.0)	55 (10.4)
Previous therapy for localized prostate cancer — no. (%)¶	94 (17.9)	79 (15.0)
Median prostate-specific antigen level (range) — μg/liter	5.97 (0–2682)	4.02 (0–2229)
Mean baseline BPI-SF pain score — no. (%)		
0: no pain	198 (37.7)	200 (38.0)
1 to 3: mild pain	195 (37.1)	207 (39.3)
4 to 7: moderate pain	98 (18.7)	95 (18.0)
8 to 10: severe pain	12 (2.3)	11 (2.1)
Missing data	22 (4.2)	14 (2.7)

* Between-group differences were not evaluated statistically, but there were no substantial differences between the two groups. Percentages may not total 100 because of rounding. BPI-SF denotes Brief Pain Inventory–Short Form. Additional demographic and clinical characteristics are provided in Table S1 in the Supplementary Appendix.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores reflecting greater disability.
‡ Scores on the Gleason scale range from 2 to 10, with higher scores indicating higher-grade cancer that may be more aggressive.
§ Of the patients with previous docetaxel use, 27 patients (47%) in the apalutamide group and 22 patients (40%) in the placebo group had a node stage of N1 at diagnosis.
¶ Previous therapies for localized prostate cancer included prostatectomy and radiotherapy.

231 in the placebo group). The percentage of patients with radiographic progression–free survival at 24 months was 68.2% in the apalutamide group and 47.5% in the placebo group (hazard ratio for radiographic progression or death, 0.48; 95% confidence interval [CI], 0.39 to 0.60; P<0.001), for a 52% lower risk of radiographic progression or death in the apalutamide group (Fig. 1A). The effect of apalutamide on radiographic progression–free survival was consistently favorable across the subgroups analyzed (Fig. 1B), including previous docetaxel use and both high and low disease volume. Blinded independent central imaging review confirmed investigator assessment of radiographic progression (concordance, 84.5%).

A Radiographic Progression–free Survival



	No. of Patients	Median Radiographic Progression–free Survival (95% CI) *mo*	Patients with Radiographic Progression–free Survival at 24 Mo (95% CI) %
Apalutamide	525	NE	68.2 (62.9–72.9)
Placebo	527	22.1 (18.5–32.9)	47.5 (42.1–52.8)

Hazard ratio for radiographic progression or death, 0.48 (95% CI, 0.39–0.60)
P<0.001

No. at Risk

Apalutamide	525	469	389	315	89	2	0
Placebo	527	437	325	229	57	3	0

B Subgroup Analysis

Subgroup	Apalutamide *no. of events/no. of patients*	Placebo *no. of events/no. of patients*	Apalutamide *median radiographic progression–free survival (mo)*	Placebo *median radiographic progression–free survival (mo)*	Hazard Ratio for Radiographic Progression or Death (95% CI)
All patients	134/525	231/527	NE	22.1	0.49 (0.40–0.61)
Baseline ECOG performance status					
0	79/328	142/348	NE	30.5	0.52 (0.39–0.68)
1	55/197	89/178	28.7	15.0	0.42 (0.30–0.59)
Geographic region					
North America and European Union	32/173	67/173	NE	30.5	0.43 (0.28–0.66)
Other	102/352	164/354	NE	21.4	0.51 (0.40–0.65)
Bone metastasis only at baseline					
Yes	49/289	102/269	NE	32.9	0.38 (0.27–0.54)
No	85/236	129/258	NE	18.2	0.60 (0.46–0.80)
Visceral disease and bone metastasis at baseline					
Yes	25/56	38/72	23.7	14.9	0.71 (0.43–1.18)
No	109/469	193/455	NE	23.0	0.46 (0.37–0.59)
Gleason score at diagnosis					
≤7	41/174	65/169	NE	30.5	0.53 (0.36–0.78)
>7	93/351	166/358	NE	18.6	0.48 (0.37–0.61)
Previous docetaxel use					
Yes	10/58	19/55	NE	22.1	0.47 (0.22–1.01)
No	124/467	212/472	NE	22.0	0.49 (0.39–0.62)
Age					
<65 yr	40/149	85/182	NE	18.4	0.45 (0.31–0.66)
65–74 yr	61/243	105/232	NE	22.0	0.47 (0.34–0.64)
≥75 yr	33/133	41/113	NE	32.9	0.65 (0.41–1.03)
Baseline PSA above median					
Yes	92/285	119/241	NE	15.4	0.51 (0.39–0.67)
No	42/240	112/286	NE	30.5	0.39 (0.27–0.56)
Baseline LDH above ULN					
Yes	21/60	30/60	22.4	14.6	0.57 (0.33–1.00)
No	109/443	191/442	NE	23.0	0.48 (0.38–0.61)
Baseline ALP above ULN					
Yes	69/177	98/180	22.4	14.7	0.54 (0.40–0.74)
No	64/346	133/345	NE	30.5	0.42 (0.31–0.57)
Disease volume					
High	109/325	173/335	NE	14.9	0.53 (0.41–0.67)
Low	25/200	58/192	NE	30.5	0.36 (0.22–0.57)
Metastasis stage at initial diagnosis					
M0	17/85	23/59	NE	NE	0.41 (0.22–0.78)
M1	108/411	196/441	NE	22.0	0.49 (0.39–0.63)

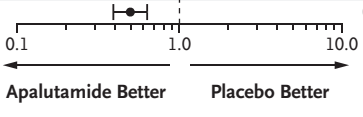


Figure 1 (facing page). Kaplan–Meier Estimate of Radiographic Progression–free Survival and Forest Plot of Radiographic Progression–free Survival According to Baseline Patient Characteristics.

In Panel A, analyses were performed with the use of a log-rank test with stratification according to Gleason score at diagnosis (≤7 vs. >7, on a scale of 2 to 10, with higher scores indicating higher-grade cancer that may be more aggressive), geographic region (North America and European Union vs. all other countries), and previous treatment with docetaxel (yes vs. no). In Panel B, the analyses were unstratified. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores reflecting greater disability. ALP denotes alkaline phosphatase, LDH lactic acid dehydrogenase, NE could not be estimated, PSA prostate-specific antigen, and ULN upper limit of the normal range.

Overall Survival

The first interim analysis for overall survival occurred after 200 deaths were observed (83 in the apalutamide group and 117 in the placebo group). The overall survival percentage at 24 months was 82.4% in the apalutamide group and 73.5% in the placebo group (hazard ratio for death, 0.67; 95% CI, 0.51 to 0.89; P=0.005), and there was a 33% lower risk of death in the apalutamide group (Fig. 2A). The treatment effect on overall survival consistently favored apalutamide over placebo, with no significant difference in the effect of apalutamide according to disease volume (Fig. 2B).

SECONDARY END POINTS

The time to cytotoxic chemotherapy was significantly longer with apalutamide than with placebo (Table 2, and Fig. S2 in the Supplementary Appendix). On the basis of the prespecified hierarchical testing sequence, the time to pain progression was tested next; because the between-group difference did not reach statistical significance, no formal testing for further secondary end points was conducted.

OTHER CLINICALLY RELEVANT END POINTS

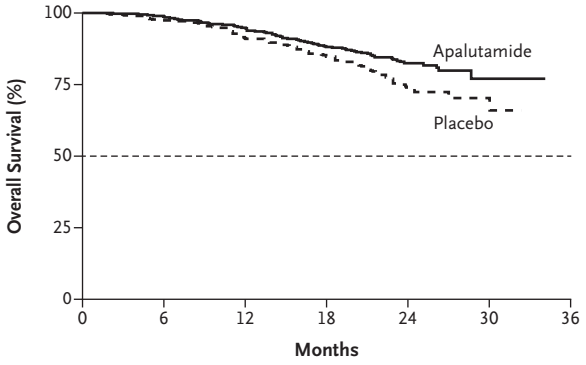
The median time to PSA progression was more favorable with apalutamide than with placebo (Table 2, and Fig. S3 in the Supplementary Appendix), and PSA reached undetectable levels (<0.2 ng per ml) in 68.4% of the patients in the apalutamide group and 28.7% of those in the placebo group. A total of 87 patients in the apalutamide group and 190 in the placebo group received subsequent treatment for prostate cancer (first subsequent therapies are shown in Table S3 in the Supplementary Appendix). The median second progression-free survival was longer with apalutamide than with placebo (Table 2, and Fig. S4 in the Supplementary Appendix). There were few events of symptomatic local progression and no substantial difference between the two groups in the time to symptomatic local progression (Table 2). Analysis of change from baseline in the FACT-P score with the use of a mixed-effect repeated-measures model showed that health-related quality of life was maintained with apalutamide, with no substantial between-group difference (Fig. S5 in the Supplementary Appendix).

SAFETY

Table 3 presents a summary of adverse events, and Table 4 shows the most common adverse events of any cause that occurred from the time of the first dose of the trial intervention through 30 days after the last dose. Frequencies of grade 3 or 4 events (42.2% in the apalutamide group and 40.8% in the placebo group) and of serious adverse events (19.8% in the apalutamide group and 20.3% in the placebo group) did not differ substantially between the two groups. Most discontinuations of the trial intervention were the result of progressive disease (in 99 patients [18.9%] in the apalutamide group and 227 [43.1%] in the placebo group) (Table S3 in the Supplementary Appendix). Adverse events led to discontinuation in 42 patients (8.0%) in the apalutamide group and 28 (5.3%) in the placebo group (Table S4 in the Supplementary Appendix). A total of 10 patients (1.9%) in the apalutamide group and 16 (3.0%) in the placebo group died as the result of an adverse event (Table S5 in the Supplementary Appendix).

Rash of any grade was more common among patients who received apalutamide than among those who received placebo (27.1% vs. 8.5%) (Table 4), and the most common adverse event of grade 3 or higher that was considered by the investigator to be related to apalutamide was rash of any type (6.3%). Hypothyroidism was reported by 6.5% of the patients in the apalutamide group and 1.1% of those in the placebo group (Table 4); all events were grade 1 or 2. Ischemic heart disease was reported in 4.4% of the patients in the apalutamide group and 1.5%

A Overall Survival



No. at Risk							
Apalutamide	525	513	490	410	165	14	0
Placebo	527	509	473	387	142	16	0

	No. of Patients	Median Overall Survival (95% CI)	Patients with Overall Survival at 24 Mo (95% CI)
		mo	%
Apalutamide	525	NE	82.4 (78.4–85.8)
Placebo	527	NE	73.5 (68.7–77.8)

Hazard ratio for death, 0.67 (95% CI, 0.51–0.89)
P=0.005

B Subgroup Analysis

Subgroup	Apalutamide *no. of events/no. of patients*	Placebo *no. of events/no. of patients*	Apalutamide *median overall survival (mo)*	Placebo *median overall survival (mo)*	Hazard Ratio for Death (95% CI)
All patients	83/525	117/527	NE	NE	0.68 (0.51–0.90)
Baseline ECOG performance status					
0	41/328	60/348	NE	NE	0.71 (0.47–1.05)
1	42/197	57/178	NE	NE	0.59 (0.40–0.89)
Geographic region					
North America and European Union	21/173	29/173	NE	NE	0.71 (0.40–1.25)
Other	62/352	88/354	NE	NE	0.66 (0.48–0.91)
Bone metastasis only at baseline					
Yes	28/289	53/269	NE	NE	0.47 (0.30–0.75)
No	55/236	64/258	NE	NE	0.88 (0.61–1.26)
Visceral disease and bone metastasis at baseline					
Yes	20/56	25/72	NE	26.6	0.99 (0.55–1.77)
No	63/469	92/455	NE	NE	0.63 (0.46–0.87)
Gleason score at diagnosis					
≤7	21/174	34/169	NE	NE	0.56 (0.33–0.97)
>7	62/351	83/358	NE	NE	0.73 (0.52–1.01)
Previous docetaxel use					
Yes	11/58	9/55	NE	NE	1.27 (0.52–3.09)
No	72/467	108/472	NE	NE	0.63 (0.47–0.85)
Age					
<65 yr	21/149	43/182	NE	NE	0.56 (0.33–0.94)
65–74 yr	42/243	51/232	NE	NE	0.73 (0.48–1.10)
≥75 yr	20/133	23/113	NE	NE	0.74 (0.41–1.35)
Baseline PSA above median					
Yes	58/285	66/241	NE	NE	0.68 (0.48–0.97)
No	25/240	51/286	NE	NE	0.56 (0.35–0.91)
Baseline LDH above ULN					
Yes	18/60	25/60	NE	NE	0.68 (0.37–1.24)
No	62/443	86/442	NE	NE	0.69 (0.49–0.95)
Baseline ALP above ULN					
Yes	40/177	61/180	NE	NE	0.63 (0.42–0.93)
No	43/346	56/345	NE	NE	0.73 (0.49–1.09)
Disease volume					
High	69/325	97/335	NE	NE	0.68 (0.50–0.92)
Low	14/200	20/192	NE	NE	0.67 (0.34–1.32)
Metastasis stage at initial diagnosis					
M0	7/85	11/59	NE	NE	0.40 (0.15–1.03)
M1	71/411	101/441	NE	NE	0.72 (0.53–0.98)

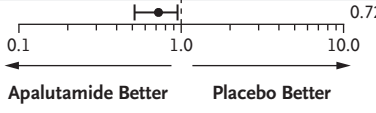


Figure 2 (facing page). Kaplan–Meier Estimate of Overall Survival and Forest Plot of Overall Survival According to Baseline Patient Characteristics.

In Panel A, analyses were performed with the use of a log-rank test with stratification according to Gleason score at diagnosis (≤7 vs. >7), geographic region (North America and European Union vs. all other countries), and previous treatment with docetaxel (yes vs. no). In Panel B, the analyses were unstratified.

of those in the placebo group; ischemic events led to death in two patients in each group.

DISCUSSION

In this phase 3 trial involving patients with metastatic, castration-sensitive prostate cancer, apalutamide plus ADT resulted in significantly longer overall survival and radiographic progression–free survival than placebo plus ADT. The lower risk of death with apalutamide than with placebo did not differ substantially according to disease volume, and benefits in radiographic progression–free survival were consistently observed across all subgroups analyzed, including patients with previous docetaxel exposure. Longer survival with apalutamide was observed even though a higher percentage of patients in the placebo group who discontinued the trial intervention received life-prolonging subsequent therapy for prostate cancer (64 of 170 patients [37.6%] in the apalutamide group and 165 of 271 patients [60.9%] in the placebo group) (Table S3 in the Supplementary Appendix). A post hoc analysis that accounted for the competing risk of death further supported the preplanned analyses presented in this article (Table S6 in the Supplementary Appendix). On the basis of the results from this final analysis for radiographic progression–free survival and first planned interim analysis for overall survival, the independent data-monitoring committee recommended unblinding to allow crossover of patients receiving placebo to receive apalutamide.

Secondary and exploratory end points also favored apalutamide treatment, including the time to cytotoxic chemotherapy and second progression-free survival. Apalutamide plus ADT also resulted in a higher percentage of patients in whom undetectable PSA levels were achieved

Table 2. Prespecified Secondary and Exploratory Efficacy End Points.*

End Point	Apalutamide (N = 525)	Placebo (N = 527)	Hazard Ratio (95% CI)	P Value by Stratified Log-Rank Test
	months			
Secondary end points				
Median time to cytotoxic chemotherapy	NE	NE	0.39 (0.27–0.56)	<0.001
Median time to pain progression†	NE	NE	0.83 (0.65–1.05)	0.12‡
Median time to chronic opioid use	NE	NE	0.77 (0.54–1.11)	—
Median time to skeletal-related event§	NE	NE	0.80 (0.56–1.15)	—
Other clinically relevant end points				
Median time to symptomatic local progression	NE	NE	1.20 (0.71–2.02)	—
Median time to PSA progression	NE	12.9	0.26 (0.21–0.32)	—
Median second progression-free survival¶	NE	NE	0.66 (0.50–0.87)	—

* NE denotes could not be estimated, and PSA prostate-specific antigen.
† Pain progression was reported by patients according to worst pain on the BPI-SF (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.[14]
‡ Secondary end points were tested in a preplanned hierarchical sequence. When the between-group difference in the time to pain progression was determined not to be significant, further secondary end points were not formally tested.
§ Skeletal-related events were defined as the occurrence of symptomatic pathologic fracture, spinal cord compression, radiation to bone, or surgery to bone.
¶ Second progression-free survival was defined as the time from randomization to the first occurrence of investigator-determined disease progression (PSA progression, progression on imaging, or clinical progression) while the patient was receiving first subsequent therapy for prostate cancer or death due to any cause, whichever occurred first.

Table 3. Summary of Adverse Events.*

Event	Apalutamide (N=524)	Placebo (N=527)
	number of patients (percent)	
Any adverse event	507 (96.8)	509 (96.6)
Grade 3 or 4 adverse event	221 (42.2)	215 (40.8)
Any serious adverse event	104 (19.8)	107 (20.3)
Any adverse event leading to discontinuation of the trial intervention	42 (8.0)	28 (5.3)
Adverse event leading to death	10 (1.9)	16 (3.0)

* Shown are adverse events of any cause that occurred from the time of the first dose of the trial intervention through 30 days after the last dose. Adverse events 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.

Table 4. Individual Adverse Events.*

Event	Apalutamide (N=524)		Placebo (N=527)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Events reported in ≥10% of patients in either group or events of grade ≥3 reported in ≥10 patients in either group				
Hot flush	119 (22.7)	0	86 (16.3)	0
Fatigue	103 (19.7)	8 (1.5)	88 (16.7)	6 (1.1)
Hypertension	93 (17.7)	44 (8.4)	82 (15.6)	48 (9.1)
Back pain	91 (17.4)	12 (2.3)	102 (19.4)	14 (2.7)
Arthralgia	91 (17.4)	2 (0.4)	78 (14.8)	5 (0.9)
Pain in an arm or leg	64 (12.2)	3 (0.6)	67 (12.7)	5 (0.9)
Pruritus	56 (10.7)	1 (0.2)	24 (4.6)	1 (0.2)
Weight increased	54 (10.3)	6 (1.1)	89 (16.9)	10 (1.9)
Anemia	48 (9.2)	9 (1.7)	71 (13.5)	17 (3.2)
Constipation	47 (9.0)	0	57 (10.8)	0
Asthenia	37 (7.1)	10 (1.9)	44 (8.3)	3 (0.6)
Bone pain	34 (6.5)	6 (1.1)	53 (10.1)	9 (1.7)
Rash, generalized	34 (6.5)	14 (2.7)	5 (0.9)	2 (0.4)
Blood alkaline phosphatase increased	16 (3.1)	2 (0.4)	28 (5.3)	13 (2.5)
Urinary retention	13 (2.5)	4 (0.8)	19 (3.6)	10 (1.9)
Adverse events of special interest				
Rash†	142 (27.1)	33 (6.3)	45 (8.5)	3 (0.6)
Fall	39 (7.4)	4 (0.8)	37 (7.0)	4 (0.8)
Fracture‡	33 (6.3)	7 (1.3)	24 (4.6)	4 (0.8)
Hypothyroidism§	34 (6.5)	0	6 (1.1)	0
Seizure¶	3 (0.6)	1 (0.2)	2 (0.4)	0

* Shown are adverse events of any cause that occurred from the time of the first dose of the trial intervention through 30 days after the last dose. Adverse events 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.
† Rash was a grouped term including rash, butterfly rash, erythematous rash, exfoliative rash, follicular rash, generalized rash, macular rash, maculopapular rash, papules, papular rash, pruritic rash, pustular rash, genital rash, blister, skin exfoliation, exfoliative dermatitis, skin reaction, systemic lupus erythematosus rash, toxic skin eruption, mouth ulceration, drug eruption, conjunctivitis, erythema multiforme, stomatitis, and urticaria.
‡ Fracture was a grouped term including acetabulum fracture, ankle fracture, clavicle fracture, femoral neck fracture, femur fracture, fibula fracture, foot fracture, forearm fracture, fracture, fractured ischium, fracture pain, hand fracture, hip fracture, lower limb fracture, patella fracture, radius fracture, rib fracture, skull fracture, spinal compression fracture, spinal fracture, sternal fracture, thoracic vertebral fracture, tibia fracture, traumatic fracture, ulna fracture, upper limb fracture, and wrist fracture.
§ Hypothyroidism was a grouped term including autoimmune thyroiditis, blood thyrotropin increased, and hypothyroidism.
¶ Seizure was a grouped term including seizure and tongue biting.

and a longer time to PSA progression than placebo plus ADT. In our trial, initial therapy with apalutamide in patients with metastatic, castration-sensitive prostate cancer led to improved clinical outcomes.

The intent of the trial was to enroll a broad group of patients with metastatic, castration-sensitive prostate cancer, resulting in the limitation that certain patient subgroups were relatively small. For example, although all the patients acknowledged the survival benefit of docetaxel during informed consent, only 10.7% had received previous docetaxel therapy before trial enrollment. This probably reflects perceived patient fitness for docetaxel and differences in patient choice or care approaches. However, the consistency of clinical benefit of apalutamide across all subgroups is reassuring.

The incidence of high-grade and serious adverse events did not differ substantially between the apalutamide group and the placebo group; discontinuation because of adverse events was low in both groups. Adverse events were generally consistent with the known safety profile of apalutamide. Rash that was related to treatment with apalutamide was common and was typically managed with antihistamines and topical glucocorticoids, dose interruption, and dose reduction (see the Results section in the Supplementary Appendix). Hypothyroidism was mild to moderate; the condition was monitored according to thyrotropin level and managed with levothyroxine. The incidence of hypertension was lower and of ischemic heart disease was higher in the apalutamide group in the TITAN trial than in the Selective Prostate Androgen Receptor Targeting with ARN-509 (SPARTAN) trial, which showed efficacy of apalutamide in patients with nonmetastatic, castration-resistant prostate cancer.[20] The differences in the incidence of falls and fractures between the apalutamide group and the placebo group were smaller in the TITAN trial than in the SPARTAN trial.[20] Health-related quality of life in the TITAN trial was also preserved, with no substantial difference between the two groups, a finding that supports the feasibility of treatment with apalutamide plus ADT.

In conclusion, in the TITAN trial involving patients with metastatic, castration-sensitive prostate cancer, including those with high-volume or low-volume disease, previous docetaxel use, previous treatment for localized disease, and previously or newly diagnosed disease, apalutamide plus ADT resulted in significantly longer overall survival and radiographic progression–free survival than placebo plus ADT. The safety profile did not differ notably between the two groups, and health-related quality of life was preserved during apalutamide treatment.

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