ORIGINAL ARTICLE

Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Fred Saad, M.D., Simon Chowdhury, M.B., B.S., Ph.D., Stéphane Oudard, M.D., Ph.D., Boris A. Hadaschik, M.D., Julie N. Graff, M.D., David Olmos, M.D., Ph.D., Paul N. Mainwaring, M.B., B.S., M.D., Ji Youl Lee, M.D., Hiroji Uemura, M.D., Ph.D., Angela Lopez-Gitlitz, M.D., Géralyn C. Trudel, Ph.D., Byron M. Espina, B.S., Youyi Shu, Ph.D., Youn C. Park, Ph.D., Wayne R. Rackoff, M.D., Margaret K. Yu, M.D., and Eric J. Small, M.D., for the SPARTAN Investigators*

ABSTRACT

BACKGROUND

Apalutamide, a competitive inhibitor of the androgen receptor, is under development for the treatment of prostate cancer. We evaluated the efficacy of apalutamide in men with nonmetastatic castration-resistant prostate cancer who were at high risk for the development of metastasis.

METHODS

We conducted a double-blind, placebo-controlled, phase 3 trial involving men with nonmetastatic castration-resistant prostate cancer and a prostate-specific antigen doubling time of 10 months or less. Patients were randomly assigned, in a 2:1 ratio, to receive apalutamide (240 mg per day) or placebo. All the patients continued to receive androgen-deprivation therapy. The primary end point was metastasis-free survival, which was defined as the time from randomization to the first detection of distant metastasis on imaging or death.

RESULTS

A total of 1207 men underwent randomization (806 to the apalutamide group and 401 to the placebo group). In the planned primary analysis, which was performed after 378 events had occurred, median metastasis-free survival was 40.5 months in the apalutamide group as compared with 16.2 months in the placebo group (hazard ratio for metastasis or death, 0.28; 95% confidence interval [CI], 0.23 to 0.35; P<0.001). Time to symptomatic progression was significantly longer with apalutamide than with placebo (hazard ratio, 0.45; 95% CI, 0.32 to 0.63; P<0.001). The rate of adverse events leading to discontinuation of the trial regimen was 10.6% in the apalutamide group and 7.0% in the placebo group. The following adverse events occurred at a higher rate with apalutamide than with placebo: rash (23.8% vs. 5.5%), hypothyroidism (8.1% vs. 2.0%), and fracture (11.7% vs. 6.5%).

CONCLUSIONS

Among men with nonmetastatic castration-resistant prostate cancer, metastasis-free survival and time to symptomatic progression were significantly longer with apalutamide than with placebo. (Funded by Janssen Research and Development; SPARTAN ClinicalTrials.gov number, NCT01946204.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Smith at Massachusetts General Hospital Cancer Center, Yawkey 7030, 55 Fruit St., Boston, MA 02114, or at smith.matthew@mgh.harvard.edu.

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

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Metastases are a major cause of complications and death among men with prostate cancer. Nearly all men who die from prostate cancer have antecedent metastases to bone or other sites, including the lymph nodes, lung, and liver.[1] Bone metastases are associated with pain, pathologic fractures, and spinal cord compression.[2] Prevention of metastases to bone and other sites represents an important treatment goal.

Androgen-deprivation therapy — either bilateral orchiectomy or treatment with a gonadotropin-releasing hormone analogue agonist or antagonist — is the mainstay of treatment for metastatic prostate cancer.[3] Androgen-deprivation therapy is also an important part of care for many men with nonmetastatic prostate cancer. Although androgen-deprivation therapy is initially effective, castration-resistant disease eventually develops in almost all men with prostate cancer.[4] Among men with nonmetastatic castration-resistant prostate cancer, a shorter prostate-specific antigen (PSA) doubling time (the estimated time required for the PSA level to double) is associated with a shorter time to metastasis or death.[5,6]

Apalutamide is a nonsteroidal antiandrogen agent that is under development for the treatment of prostate cancer. Apalutamide binds directly to the ligand-binding domain of the androgen receptor and prevents androgen-receptor translocation, DNA binding, and androgen-receptor–mediated transcription.[7] In a phase 2 study involving men with nonmetastatic castration-resistant prostate cancer who were at high risk for disease progression (with a PSA level of ≥8 ng per milliliter or a PSA doubling time of ≤10 months), apalutamide resulted in durable PSA responses.[8] We conducted the international, randomized, placebo-controlled, phase 3 SPARTAN (Selective Prostate Androgen Receptor Targeting with ARN-509) trial to evaluate the effect of apalutamide on metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer and a PSA doubling time of 10 months or less.

Methods

Trial Design and Conduct

The trial was designed by two of the academic authors (the first and last authors) and representatives of the sponsor, Aragon Pharmaceuticals. The trial was conducted at 332 sites in 26 countries in North America, Europe, and the Asia–Pacific region. The review board at each participating institution approved the trial, which was conducted in accordance with the current International Conference on Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. All the patients provided written informed consent. The sponsor commissioned an independent data and safety monitoring committee to review safety data on an ongoing basis and to review the results of the primary efficacy analysis before unblinding. Data were transcribed, by trial personnel at each clinical site, from source documents into electronic case-report forms prepared by the sponsor. 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, available with the full text of this article at NEJM.org. All the authors had full access to the data, drafted the manuscript with input from the sponsor, reviewed and approved the manuscript before submission, and made the decision to submit the manuscript for publication. The sponsor provided funding for editorial assistance. All the authors and participating institutions have agreements with the sponsor regarding data confidentiality.



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Patients and Trial Regimen

Eligible patients were 18 years of age or older, had histologically or cytologically confirmed adenocarcinoma of the prostate that was castration-resistant, and were at high risk for the development of metastasis, which was defined as a PSA doubling time of 10 months or less during continuous androgen-deprivation therapy (bilateral orchiectomy or treatment with gonadotropin-releasing hormone analogue agonists or antagonists). At screening, all the patients underwent a technetium-99m bone scan and computed tomography (CT) of the pelvis, abdomen, chest, and head. Patients in whom distant metastasis was detected, either on these imaging studies or with the use of other information sources, were excluded. Patients were required to have no local or regional nodal disease (classified as N0 on the tumor–node–metastasis staging system) or to have malignant pelvic lymph nodes that measured less than 2 cm in the short axis (classified as N1) and were located below the aortic bifurcation.

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Androgen-deprivation therapy was continued throughout the trial.

Patients were stratified according to PSA doubling time (>6 months vs. ≤6 months), use of bone-sparing agents (yes vs. no), and classification of local or regional nodal disease (N0 vs. N1) at the time of trial entry. Patients were randomly assigned, in a 2:1 ratio, to receive apalutamide (240 mg per day) or matched placebo, which was administered orally according to a continuous daily dosing regimen until protocol-defined progression, adverse events, or withdrawal of consent occurred. Interventions for the management of local or regional symptoms were allowed. After the first detection of distant metastasis, patients were eligible to receive treatment with sponsor-provided abiraterone acetate plus prednisone. After the trial regimen was discontinued, the administration of abiraterone acetate plus prednisone or any treatment for metastatic castration-resistant prostate cancer was at the discretion of the treating physician.

ASSESSMENTS

At screening, the patients' demographic characteristics, relevant medical history, and other pertinent clinical conditions were recorded, and a physical examination was performed. Vital signs and Eastern Cooperative Oncology Group performance-status scores (which range from 0 to 5, with higher scores indicating greater disability) were obtained at screening and at every scheduled visit during the double-blind period. The PSA level was measured at a central laboratory. The patients, trial staff, and sponsor representatives were unaware of the patients' PSA values and group assignments until unblinding occurred. Data on adverse events, including type, incidence, severity (according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0), timing, seriousness, and whether they were related to the trial regimen according to the assessment of the investigator, were recorded at each visit. Disease assessments, including technetium-99m bone scans and CT of the pelvis, abdomen, and chest, were performed every 16 weeks and at additional time points if distant metastasis was suspected. Evidence of distant metastasis on imaging was determined on the basis of Response Evaluation Criteria in Solid Tumors, version 1.1.[9] All imaging studies were assessed prospectively by means of blinded independent central review. When a new bone lesion was detected on a bone scan, a second imaging study (CT or magnetic resonance imaging) was required in order to confirm metastasis.

END POINTS

The primary end point was metastasis-free survival, which was defined as the time from randomization to the first detection of distant metastasis on imaging (as assessed by means of blinded independent central review) or death from any cause, whichever occurred first. Secondary end points were time to metastasis (defined as the time from randomization to the first detection of distant metastasis involving the bone or soft tissue on imaging, as assessed by means of blinded independent central review), progression-free survival (defined as the time from randomization to the first detection of local or distant metastatic disease on imaging, as assessed by means of blinded independent central review, or death from any cause, whichever occurred first), time to symptomatic progression (defined as the time from randomization to a skeletal-related event, pain progression, or worsening of disease-related symptoms leading to the initiation of a new systemic anticancer therapy or the time to the development of clinically significant symptoms due to local or regional tumor progression leading to surgery or radiation therapy), overall survival, and time to the initiation of cytotoxic chemotherapy.

Exploratory end points included time to PSA progression, PSA response rate, patient-reported outcomes, and second-progression–free survival. Time to PSA progression was defined as the time from randomization to PSA progression, according to Prostate Cancer Working Group 2 (PCWG2) criteria (Table S1 in the Supplementary Appendix, available at NEJM.org).[10] PSA response rate was defined as the percentage of patients who had a decline from baseline in the PSA level of at least 50%, according to PCWG2 criteria.[10] Patient-reported outcomes were assessed with the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire and the three-level version of the European Quality of Life–5 Dimensions (EQ-5D-3L) questionnaire. The FACT-P consists of 39 items that assess physical, functional, emotional, and social or family well-being, including concerns specific to prostate cancer; scores range from 0 to 156, with higher scores indicating more favorable health-related quality of life. The EQ-5D-3L

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consists of the EQ-5D descriptive system and the EQ visual-analogue scale; scores on the EQ visual-analogue scale range from 0 to 100, with 0 indicating the worst health imaginable and 100 the best health imaginable. Second-progression–free survival was defined as the time from randomization to investigator-assessed disease progression (PSA progression, detection of metastatic disease on imaging, symptomatic progression, or any combination thereof) during the first subsequent treatment for metastatic castration-resistant disease or death from any cause.

STATISTICAL ANALYSIS

We calculated that a sample of 1200 patients with 372 primary end-point events would provide the trial with 90% power to detect a hazard ratio for metastasis or death in the apalutamide group versus the placebo group of 0.70, at a two-sided significance level of 0.05. A single, final analysis was planned for the primary end point of metastasis-free survival and for the secondary end points of time to metastasis and progression-free survival. The secondary end points of time to symptomatic progression, overall survival, and time to the initiation of cytotoxic chemotherapy were assessed with the use of a hierarchical, adaptive, group-sequential procedure, according to the prespecified Lan–DeMets alpha spending function with the O'Brien–Fleming efficacy boundary. The first interim analysis of overall survival and time to the initiation of cytotoxic chemotherapy occurred at the time of the final analysis of metastasis-free survival. Final analyses for overall survival and time to the initiation of cytotoxic chemotherapy are planned to occur after 427 events have been observed for each outcome. The Kaplan–Meier method was used to estimate medians for each trial group. The primary statistical method of comparison for time-to-event end points was a log-rank test with stratification according to the prespecified factors. Cox proportional-hazards models were used to estimate the hazard ratios and 95% confidence intervals.

RESULTS

PATIENTS

From October 14, 2013, to December 15, 2016, a total of 1207 patients underwent randomization: 806 were assigned to the apalutamide group and 401 to the placebo group (Fig. S1 in the Supplementary Appendix). Six patients (3 per group) underwent randomization but never received apalutamide or placebo. The clinical cutoff date for the primary analysis was May 19, 2017. At that time, the median follow-up was 20.3 months; 60.9% of the patients in the apalutamide group and 29.9% in the placebo group were still receiving the assigned regimen. Demographic and disease characteristics were well balanced between the two groups (Table 1, and Table S2 in the Supplementary Appendix). The median PSA doubling time at baseline was less than 5 months in each group.

PRIMARY END POINT

The final analysis for metastasis-free survival was performed after distant metastasis or death had been observed in 378 patients: 184 (22.8%) in the apalutamide group and 194 (48.4%) in the placebo group. The median metastasis-free survival was 40.5 months in the apalutamide group as compared with 16.2 months in the placebo group (hazard ratio for metastasis or death, 0.28; 95% confidence interval [CI], 0.23 to 0.35; P<0.001) (Fig. 1A). Of the patients who had metastases, 60.5% in the apalutamide group and 54.4% in the placebo group had bone metastases. The treatment effect of apalutamide was consistently favorable across prespecified subgroups (Fig. 1B). In July 2017, the independent data and safety monitoring committee concluded that the efficacy and safety data constituted compelling evidence of a clinical benefit in the apalutamide group, and the committee unanimously recommended that the trial be unblinded and that the patients in the placebo group be given the option to receive apalutamide.

SECONDARY END POINTS

Apalutamide was associated with better results than placebo for all secondary end points (Table 2 and Fig. 2, and Fig. S2 in the Supplementary Appendix). Time to metastasis, progression-free survival, and time to symptomatic progression were significantly longer with apalutamide than with placebo (P<0.001 for all comparisons).

EXPLORATORY END POINTS

The median time to PSA progression was not reached in the apalutamide group as compared with 3.7 months in the placebo group (hazard ratio, 0.06; 95% CI, 0.05 to 0.08) (Fig. 2). At 12 weeks after randomization, the median PSA level had

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Table 1. Demographic and Disease Characteristics at Baseline.*

Characteristic	Apalutamide (N=806)	Placebo (N=401)
Age — yr		
Median	74	74
Range	48–94	52–97
Median time from initial diagnosis to randomization — yr	7.95	7.85
Prostate-specific antigen doubling time		
Median — mo	4.40	4.50
≤6 Mo — no. (%)	576 (71.5)	284 (70.8)
>6 Mo — no. (%)	230 (28.5)	117 (29.2)
Use of bone-sparing agent — no. (%)		
Yes	82 (10.2)	39 (9.7)
No	724 (89.8)	362 (90.3)
Classification of local or regional nodal disease — no. (%)		
N0	673 (83.5)	336 (83.8)
N1	133 (16.5)	65 (16.2)
Previous prostate-cancer treatment — no. (%)		
Prostatectomy or radiation therapy	617 (76.6)	307 (76.6)
Gonadotropin-releasing hormone analogue agonist	780 (96.8)	387 (96.5)
First-generation antiandrogen agent†	592 (73.4)	290 (72.3)

* There were no significant differences between groups in the demographic and disease characteristics at baseline.
† First-generation antiandrogen agents are flutamide, bicalutamide, and nilutamide.

decreased by 89.7% in the apalutamide group and had increased by 40.2% in the placebo group. Patient-reported outcomes (FACT-P and EQ-5D-3L results) indicated that patients who received apalutamide in addition to androgen-deprivation therapy maintained stable overall health-related quality of life over time, as did patients in the placebo group (Table 2).

Of the patients who discontinued the trial regimen, 52.5% in the apalutamide group and 77.8% in the placebo group received subsequent approved treatment for metastatic castration-resistant prostate cancer (Table S3 in the Supplementary Appendix). The most common subsequent treatment was abiraterone acetate plus prednisone, which was administered in 75.8% of the patients in the apalutamide group and in 74.2% of those in the placebo group. The median time from the detection of distant metastasis to the initiation of subsequent therapy was 56 days in the apalutamide group and 44 days in the placebo group. Second-progression–free survival was significantly longer in the apalutamide group than the placebo group (hazard ratio for progression or death, 0.49; 95% CI, 0.36 to 0.66) (Fig. 2).

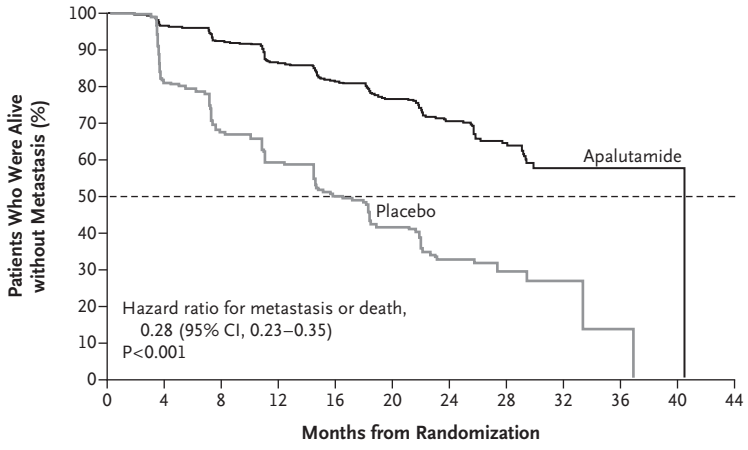
SAFETY

The trial regimen was discontinued owing to progressive disease in 155 patients (19.3%) in the

Figure 1 (facing page). Metastasis-free Survival.
Panel A shows Kaplan–Meier estimates of metastasis-free survival in the apalutamide group and the placebo group. The dashed line indicates the median. The analysis was performed with the use of a log-rank test with stratification according to prostate-specific antigen (PSA) doubling time (>6 months vs. ≤6 months), use of bone-sparing agents (yes vs. no), and classification of local or regional nodal disease (N0 vs. N1) at the time of trial entry. Panel B shows subgroup analyses of metastasis-free survival. In the forest plot, the size of the circle reflects the number of patients affected. The analysis of all patients and all subgroup analyses were unstratified. An Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 indicates asymptomatic, and a score of 1 indicates restricted in strenuous activity but ambulatory. Race was reported by the patient. NR denotes not reached.

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A Kaplan–Meier Estimates of Metastasis-free Survival

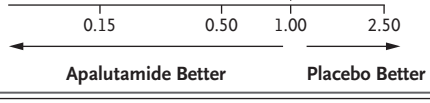


No. at Risk

Apalutamide	806	713	652	514	398	282	180	96	36	16	3	0
Placebo	401	291	220	153	91	58	34	13	5	1	0	0

B Subgroup Analyses

Subgroup	Apalutamide	Placebo	Hazard Ratio (95% CI)
	median metastasis-free survival (mo)		
All patients	40.5	16.2	0.30 (0.24–0.36)
Age			
<65 yr	NR	7.3	0.14 (0.08–0.27)
65 to <75 yr	NR	14.6	0.25 (0.18–0.34)
≥75 yr	40.5	18.5	0.42 (0.31–0.56)
Race			
White	40.5	14.6	0.26 (0.21–0.34)
Black	25.8	36.8	0.63 (0.23–1.72)
Asian	NR	18.5	0.33 (0.16–0.67)
Other	30.0	18.4	0.40 (0.24–0.65)
Region			
North America	40.5	15.7	0.30 (0.21–0.42)
Europe	NR	14.8	0.29 (0.22–0.39)
Asia–Pacific	NR	18.5	0.30 (0.17–0.54)
No. of previous hormonal therapies			
1	NR	16.6	0.34 (0.21–0.53)
≥2	40.5	16.2	0.29 (0.23–0.36)
Baseline ECOG performance status			
0	40.5	15.7	0.27 (0.21–0.34)
1	27.8	18.4	0.40 (0.27–0.60)
Baseline PSA level			
At or below median	NR	18.4	0.28 (0.20–0.39)
Above median	30.0	14.5	0.29 (0.23–0.38)
PSA doubling time			
≤6 mo	40.5	14.6	0.29 (0.23–0.36)
>6 mo	NR	22.8	0.30 (0.20–0.47)
Use of bone-sparing agent			
Yes	NR	22.0	0.38 (0.19–0.76)
No	40.5	14.8	0.29 (0.23–0.36)
Classification of local or regional nodal disease			
N0	40.5	18.3	0.33 (0.26–0.41)
N1	NR	10.8	0.15 (0.09–0.25)



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Table 2. Prespecified Secondary and Exploratory End Points.*

End Point	Apalutamide (N=806)	Placebo (N=401)	Hazard Ratio (95% CI)	P Value
Secondary end points (mo)†				
Median time to metastasis	40.5	16.6	0.27 (0.22–0.34)	<0.001
Median progression-free survival	40.5	14.7	0.29 (0.24–0.36)	<0.001
Median time to symptomatic progression	NR	NR	0.45 (0.32–0.63)	<0.001
Median overall survival	NR	39.0	0.70 (0.47–1.04)	0.07
Median time to the initiation of cytotoxic chemotherapy	NR	NR	0.44 (0.29–0.66)	—
Exploratory end points				
Median second-progression–free survival (mo)	NR	39.0	0.49 (0.36–0.66)	
Median time to PSA progression (mo)	NR	3.7	0.06 (0.05–0.08)	
Patients with a PSA response (%)	89.7	2.2	40 (21–77)‡	
Patient-reported outcomes§				
Change in total FACT-P score from baseline to 29 months¶	−0.99±0.98	−3.29±1.97	—	
Change in total EQ VAS score from baseline to 29 months‖	1.44±0.87	0.26±1.75	—	

* Plus–minus values are means ±SE. NR denotes not reached, and PSA prostate-specific antigen.
† The P value for time to symptomatic progression crossed the O'Brien–Fleming efficacy boundary of 0.00008; the P value for overall survival did not. The P value for time to the initiation of cytotoxic chemotherapy was not calculated because the P value for overall survival did not cross the O'Brien–Fleming efficacy boundary.
‡ The comparison for this exploratory end point was calculated as a relative risk rather than a hazard ratio.
§ Patient-reported outcomes were calculated with the use of mixed models for repeated measures.
¶ Scores on the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire range from 0 to 156, with higher scores indicating more favorable health-related quality of life.
‖ Scores on the European Quality of Life (EQ) visual-analogue scale (VAS) range from 0 to 100, with 0 indicating the worst health imaginable and 100 the best health imaginable.

apalutamide group and in 210 (52.8%) in the placebo group. Adverse events led to discontinuation of the trial regimen in 85 patients (10.6%) in the apalutamide group and in 28 (7.0%) in the placebo group (Table 3, and Table S4 in the Supplementary Appendix). Grade 3 or 4 adverse events were observed in 45.1% of the patients in the apalutamide group and in 34.2% of those in the placebo group. The rate of serious adverse events was similar in the apalutamide group and the placebo group (24.8% and 23.1%, respectively). A total of 7.0% of the patients in the apalutamide group and 10.6% of those in the placebo group withdrew consent from the trial. Adverse events were associated with death in 10 patients in the apalutamide group (with acute myocardial infarction, cardiorespiratory arrest, cerebral hemorrhage, myocardial infarction, multiple organ dysfunction, and pneumonia as the cause in 1 patient each and with prostate cancer and sepsis as the cause in 2 patients each) and in 1 patient in the placebo group (with cardiorespiratory arrest as the cause) (Table S5 in the Supplementary Appendix). The following adverse events that were considered by the investigators to be related to the trial regimen occurred at a higher rate in the apalutamide group than in the placebo group: fatigue (30.4% vs. 21.1%), rash (23.8% vs. 5.5%), falls (15.6% vs. 9.0%), fracture (11.7% vs. 6.5%), hypothyroidism (8.1% vs. 2.0%), and seizure (0.2% vs. 0%). Management strategies for rash, hypothyroidism, and fracture are described in the Supplemental Results section in the Supplementary Appendix.

DISCUSSION

In this international, placebo-controlled, randomized trial involving men with castration-resistant prostate cancer, the risk of metastasis or death was more than 70% lower with apalutamide than with placebo, and the median metastasis-free survival was more than 2 years longer (40.5 months vs. 16.2 months). The effect was observed across all subgroups, including patients in all age groups,

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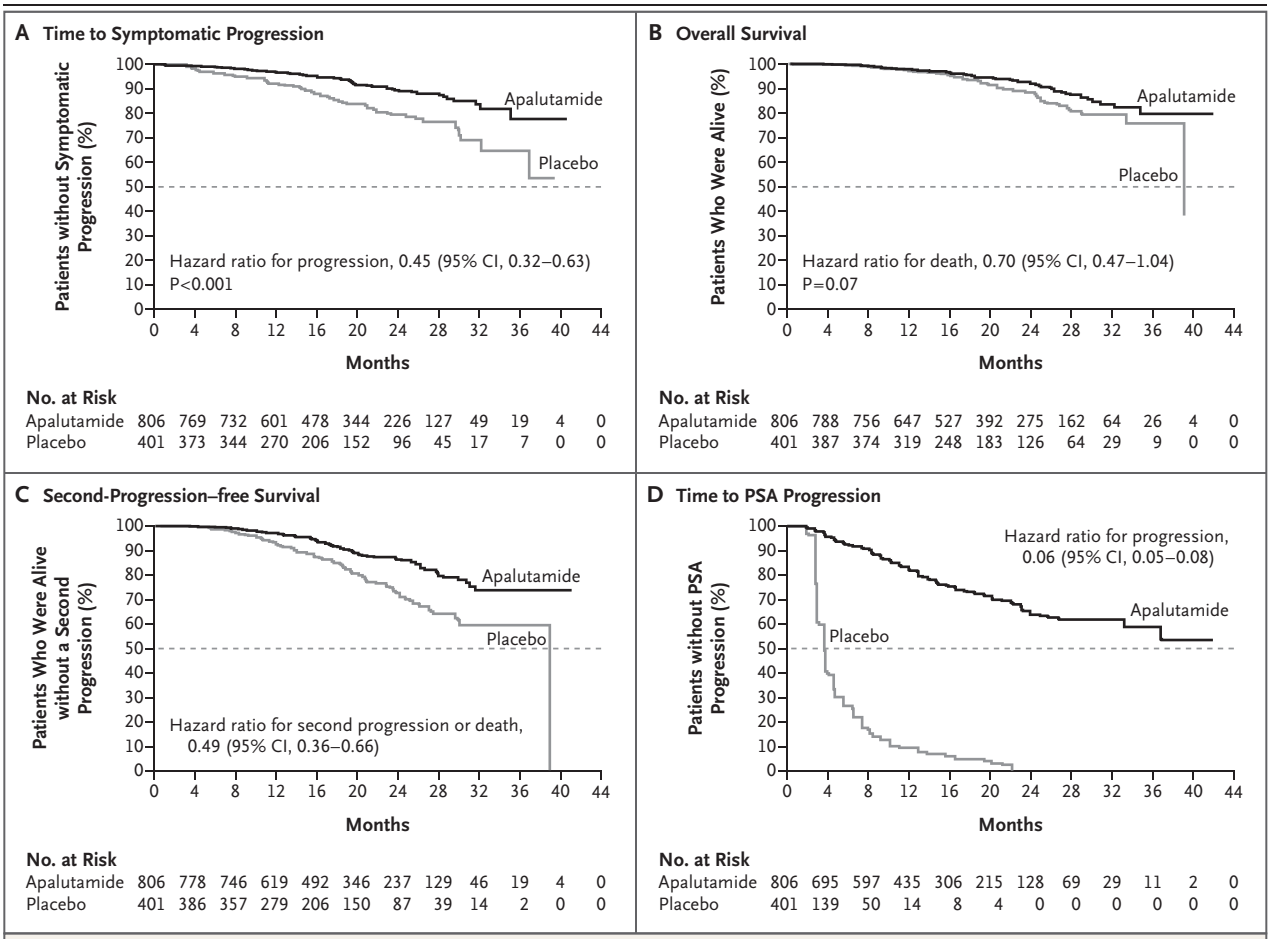


Figure 2. Prespecified Secondary and Exploratory Efficacy End Points.

Shown are Kaplan–Meier estimates of the time to symptomatic progression (Panel A), overall survival (Panel B), second-progression–free survival (Panel C), and time to PSA progression (Panel D) in the apalutamide group and the placebo group. The dashed lines indicate the medians. All analyses were performed with the use of a log-rank test with stratification according to PSA doubling time (>6 months vs. ≤6 months), use of bone-sparing agents (yes vs. no), and classification of local or regional nodal disease (N0 vs. N1) at the time of trial entry. The analysis of second-progression–free survival included patients who received any subsequent therapy (approved or nonapproved).

those with short PSA doubling times, and those with local or regional nodal disease at trial entry. Time to metastasis, progression-free survival, and time to symptomatic progression were significantly longer with apalutamide than with placebo. In addition, overall survival, time to the initiation of cytotoxic chemotherapy, and second-progression–free survival were longer with apalutamide than with placebo; these findings support the clinical benefit of apalutamide.

This trial has several strengths. Imaging studies were performed every 16 weeks for the detection of metastatic disease. If bone metastasis was detected, confirmation on a second imaging study was required. All imaging studies were assessed by means of blinded independent central review. The trial design allowed patients who had metastatic disease to receive standard treatment for metastatic castration-resistant prostate cancer. To improve access to subsequent approved treatment, the trial provided abiraterone acetate plus prednisone as a treatment option after the diagnosis of metastatic disease. Moreover, the trial included scheduled assessments after the diagnosis of metastatic disease to reliably determine other important clinical outcomes that might occur many months after the detection of metastatic disease on imaging.

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Table 3. Adverse Events.

Adverse Event*	Apalutamide (N=803)		Placebo (N=398)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	no. of patients (%)			
Any adverse event	775 (96.5)	362 (45.1)	371 (93.2)	136 (34.2)
Serious adverse event	199 (24.8)	—	92 (23.1)	—
Adverse event leading to discontinuation of the trial regimen	85 (10.6)	—	28 (7.0)	—
Adverse event associated with death	10 (1.2)	—	1 (0.3)	—
Adverse events that occurred in ≥15% of patients in either group†				
Fatigue‡	244 (30.4)	7 (0.9)	84 (21.1)	1 (0.3)
Hypertension	199 (24.8)	115 (14.3)	79 (19.8)	47 (11.8)
Rash‡	191 (23.8)	42 (5.2)	22 (5.5)	1 (0.3)
Diarrhea	163 (20.3)	8 (1.0)	60 (15.1)	2 (0.5)
Nausea	145 (18.1)	0	63 (15.8)	0
Weight loss	129 (16.1)	9 (1.1)	25 (6.3)	1 (0.3)
Arthralgia	128 (15.9)	0	30 (7.5)	0
Falls‡	125 (15.6)	14 (1.7)	36 (9.0)	3 (0.8)
Other adverse events of interest				
Fracture‡	94 (11.7)	22 (2.7)	26 (6.5)	3 (0.8)
Dizziness	75 (9.3)	5 (0.6)	25 (6.3)	0
Hypothyroidism‡	65 (8.1)	0	8 (2.0)	0
Mental-impairment disorder§	41 (5.1)	0	12 (3.0)	0
Seizure‡	2 (0.2)	0	0	0

* The incidences of the following adverse events in the apalutamide group versus the placebo group were adjusted for exposure (events per 100 patient-years): fatigue (incidence, 32.3 vs. 27.2), hypertension (36.3 vs. 38.7), rash (29.6 vs. 8.3), diarrhea (21.6 vs. 22.6), nausea (15.8 vs. 20.4), weight loss (18.3 vs. 10.5), arthralgia (14.7 vs. 8.0), falls (13.6 vs. 10.0), fracture (10.5 vs. 7.8), dizziness (7.7 vs. 6.6), hypothyroidism (7.6 vs. 2.2), mental-impairment disorder (3.9 vs. 3.4), and seizure (0.2 vs. 0).
† This category includes adverse events that occurred up to 28 days after the last dose of the trial regimen was administered.
‡ These adverse events were considered by the investigators to be related to the trial regimen.
§ Mental-impairment disorders included the following adverse events: disturbance in attention, memory impairment, cognitive disorder, and amnesia.

Approximately 80% of the patients in the placebo group received subsequent treatment for metastatic castration-resistant prostate cancer. Although subsequent approved treatment was administered at a high rate in the control group, apalutamide was associated with better results than placebo for secondary end points analyzed late during the trial, including time to symptomatic progression, time to the initiation of cytotoxic chemotherapy, and overall survival. Apalutamide was also associated with longer second-progression–free survival than placebo.

Apalutamide was associated with higher rates of rash, fatigue, arthralgia, weight loss, falls, and fracture than placebo. The majority of adverse events were grade 1 or 2. The median duration of the trial regimen was substantially longer in the apalutamide group than in the placebo group. Disease progression was the most common reason for discontinuation of the trial regimen in both groups. The rate of adverse events leading to discontinuation was less than 11% in both the apalutamide group and the placebo group. The benefits of apalutamide treatment for men with

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nonmetastatic castration-resistant prostate cancer should be weighed against the potential harms.

Treatment with apalutamide increased metastasis-free survival and improved other clinical outcomes in patients with castration-resistant prostate cancer who did not have evidence of metastasis on conventional imaging. Newer and more sensitive imaging studies (e.g., prostate-specific membrane antigen positron-emission tomography) have identified metastases in some patients with no evidence of metastases on conventional imaging.[11-13] The regulatory approvals of currently marketed treatments for metastatic castration-resistant prostate cancer were based on the results of clinical trials involving men with metastases that were detected on conventional imaging, such as a bone scan or CT. It is possible that more sensitive imaging tests could have identified metastases at baseline in many of the patients in our trial, particularly because of the requirement for a short PSA doubling time at trial entry. The consistent increase in metastasis-free survival associated with apalutamide across all patient subgroups (including those with a high PSA level, a short PSA doubling time, or local or regional nodal disease at trial entry), however, suggests that the clinical benefits of apalutamide extend to patients with a high disease burden.

In conclusion, among men with nonmetastatic castration-resistant prostate cancer, metastasis-free survival was significantly longer with apalutamide than with placebo. Consistent improvements in secondary and exploratory end points provide support for the veracity of our primary finding.

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APPENDIX

The authors' affiliations are as follows: the Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston (M.R.S.); Centre Hospitalier de l'Université de Montréal, Université de Montréal, Montreal (F.S.); Guy's, King's and St. Thomas' Hospitals, Great Maze Pond, London (S.C.); Georges Pompidou Hospital, Paris (S.O.); University of Duisburg–Essen and German Cancer Consortium (DKTK)–University Hospital Essen, Essen, and Ruprecht-Karls-University Heidelberg, Heidelberg — both in Germany (B.A.H.); Veterans Affairs Portland Health Care System, Portland, and Knight Cancer Institute, Oregon Health and Science University, Portland (J.N.G.); Spanish National Cancer Research Center, Madrid, and Hospitales Universitarios Virgen de la Victoria y Regional, Institute of Biomedical Research in Malaga, Malaga — both in Spain (D.O.); Centre for Personalised Nanomedicine, University of Queensland, Brisbane, Australia (P.N.M.); St. Mary's Hospital of Catholic University, Seoul, South Korea (J.Y.L.); Yokohama City University Medical Center, Yokohama, Japan (H.U.); Janssen Research and Development, Los Angeles (A.L.-G., G.C.T., B.M.E., Y.S., Y.C.P., W.R.R., M.K.Y.); and Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco (E.J.S.).

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REFERENCES

1. Scher HI, Solo K, Valant J, Todd MB, Mehra M. Prevalence of prostate cancer clinical states and mortality in the United States: estimates using a dynamic progression model. PLoS One 2015;10(10):e0139440.
2. Gartrell BA, Saad F. Managing bone metastases and reducing skeletal related events in prostate cancer. Nat Rev Clin Oncol 2014;11:335-45.
3. Sharifi N, Gulley JL, Dahut WL. An update on androgen deprivation therapy for prostate cancer. Endocr Relat Cancer 2010;17:R305-R315.
4. Dai C, Heemers H, Sharifi N. Androgen signaling in prostate cancer. Cold Spring Harb Perspect Med 2017;7(9):a030452.
5. Smith MR, Kabbinavar F, Saad F, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol 2005;23:2918-25.
6. Smith MR, Saad F, Oudard S, et al. Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol 2013;31:3800-6.
7. Clegg NJ, Wongvipat J, Joseph JD, et al. ARN-509: a novel antiandrogen for prostate cancer treatment. Cancer Res 2012;72:1494-503.
8. Smith MR, Antonarakis ES, Ryan CJ, et al. Phase 2 study of the safety and antitumor activity of apalutamide (ARN-509), a potent androgen receptor antagonist, in the high-risk nonmetastatic castration-resistant prostate cancer cohort. Eur Urol 2016;70:963-70.
9. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
10. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148-59.
11. Beheshti M, Rezaee A, Geinitz H, Loidl W, Pirich C, Langsteger W. Evaluation of prostate cancer bone metastases with 18F-NaF and 18F-fluorocholine PET/CT. J Nucl Med 2016;57:Suppl 3:55S-60S.
12. Eiber M, Fendler WP, Rowe SP, et al. Prostate-specific membrane antigen ligands for imaging and therapy. J Nucl Med 2017;58:Suppl 2:67S-76S.
13. Schwarzenboeck SM, Rauscher I, Bluemel C, et al. PSMA ligands for PET imaging of prostate cancer. J Nucl Med 2017;58:1545-52.

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