ORIGINAL ARTICLE

# Perioperative Apalutamide in High-Risk Localized Prostate Cancer

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## ABSTRACT

### BACKGROUND

Radical prostatectomy is potentially curative in patients with high-risk localized or locally advanced prostate cancer; however, relapse occurs within 5 years in up to 50% of patients.

### METHODS

We conducted a phase 3, double-blind, placebo-controlled trial in which patients with newly diagnosed high-risk localized or locally advanced prostate cancer were randomly assigned in a 1:1 ratio to receive androgen-deprivation therapy (ADT) plus apalutamide (240 mg per day) or ADT plus placebo for 6 cycles (28 days each) before and after radical prostatectomy with pelvic lymph-node dissection. The dual primary end points were a composite of pathological complete response or minimal residual disease (defined as a pathological stage of ypT2 or lower, with a tumor size of ≤5 mm in the greatest dimension) and metastasis-free survival, as assessed with conventional imaging or prostate-specific membrane antigen positron-emission tomography. Secondary end points included event-free survival, first subsequent treatment, and distant metastasis (assessed in time-to-event analyses), as well as safety.

### RESULTS

A total of 2109 patients underwent randomization: 1057 were assigned to receive ADT plus apalutamide, and 1052 to receive ADT plus placebo. The median follow-up was 61.7 months. The percentage of patients with a pathological complete response or minimal residual disease was significantly higher in the apalutamide group than in the placebo group (8.9% vs. 1.0%; odds ratio, 10.17; 95% confidence interval [CI], 5.27 to 19.64; P<0.001), as was the percentage of patients with metastasis-free survival (probability of metastasis-free survival at 5 years, 78.2% vs. 73.5%; hazard ratio for distant metastasis or death, 0.80; 95% CI, 0.67 to 0.96; P=0.02). Event-free survival, time to the first subsequent treatment, and time to distant metastasis significantly favored ADT plus apalutamide over ADT plus placebo (P<0.001 for all between-group comparisons). Grade 3 or 4 adverse events occurred in 39.6% of the patients in the apalutamide group and in 31.0% of those in the placebo group, with the difference between the groups driven primarily by a higher incidence of rash in the apalutamide group.

### CONCLUSIONS

Perioperative treatment with ADT plus apalutamide was associated with better oncologic outcomes of radical prostatectomy in patients with high-risk localized or locally advanced prostate cancer than treatment with ADT plus placebo. Adverse events were more common in the apalutamide group than in the placebo group. (Funded by Johnson & Johnson; PROTEUS ClinicalTrials.gov number, NCT03767244.)

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This article was published on May 31, 2026, at NEJM.org.

N Engl J Med 2026;395:546-60.
DOI: 10.1056/NEJMoa2603878

Patients with high-risk localized or locally advanced prostate cancer have a greater risk of recurrence and death than patients with low-risk disease, despite curative-intent treatment with radical prostatectomy or radiotherapy with androgen-deprivation therapy (ADT).[1,2] Despite over a century of clinical progress in treatment with prostatectomy,[3] relapse occurs within 5 years in up to 50% of patients who undergo radical prostatectomy, and up to 20% die within 10 years.[4-8] The definition of high risk in patients with localized or locally advanced prostate cancer varies[1,2,9]; the National Comprehensive Cancer Network (NCCN) defines high risk as having a Gleason score of 8 or higher (scores range from 6 to 10, with higher scores indicating more aggressive disease), a prostate-specific antigen (PSA) level of 20 ng per milliliter or higher, or a clinical disease stage of T3.[10] A better regimen that prevents recurrence is needed to improve the prognosis for patients with high-risk disease who undergo radical prostatectomy with pelvic lymph-node dissection.

Although neoadjuvant systemic therapy and surgical resection are a well-established standard for many cancers, this approach has not shown benefit in prostate cancer thus far.[11] Previous trials involving neoadjuvant therapy for prostate cancer were hampered by the inclusion of patients with low-risk disease and the use of primary end points such as PSA response, and the results were not practice-changing.[12,13] During the past decade, a series of phase 2, randomized trials of neoadjuvant androgen-receptor pathway inhibitors have shown a favorable safety profile and prostate tumor response, as indicated by pathological complete response and minimal residual disease.[14-18]

Apalutamide is an oral nonsteroidal androgen-receptor inhibitor[19] approved for the treatment of nonmetastatic, castration-resistant prostate cancer (i.e., progressive cancer in the context of very low serum testosterone levels) and metastatic, castration-sensitive prostate cancer on the basis of results from the phase 3 SPARTAN (Selective Prostate Androgen Receptor Targeting with ARN-509) and TITAN (Targeted Investigational Treatment Analysis of Novel Anti-androgen) trials, respectively.[20-22] In metastatic, castration-sensitive prostate cancer, treatment with ADT plus apalutamide led to rapid, deep, and durable decline in PSA levels and better overall survival than ADT plus placebo.[21,23] We conducted the PROTEUS (Perioperative Treatment with Erleada United with Surgery) trial to assess the efficacy and safety of 12 cycles of perioperative treatment with ADT plus apalutamide as compared with ADT plus placebo in patients with high-risk localized or locally advanced prostate cancer undergoing radical prostatectomy.

*A Quick Take is available at NEJM.org*

## Methods

### Trial Design and Oversight

We conducted this phase 3, double-blind, randomized, placebo-controlled trial at 184 sites in 18 countries (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was designed by the sponsor, Johnson & Johnson, with input from the protocol steering committee and health authorities. The review board at each participating institution and national health authorities (where applicable) approved the trial, which was conducted in accordance with the International Council for 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-monitoring committee to monitor safety and review efficacy. The sponsor collected and analyzed the data. All the authors had full access to the data, participated in data interpretation, assisted in drafting the manuscript with input from the sponsor, and reviewed and approved the manuscript before submission. Writing assistance was funded by the sponsor. The authors worked under confidentiality agreements with the sponsor. All the authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol (available at NEJM.org).

### Patients

Eligible patients had histologically confirmed adenocarcinoma, were candidates for radical prostatectomy as assessed by investigators, and had high-risk localized or locally advanced prostate cancer as defined according to a combination of NCCN criteria[10] and additional trial-specific criteria involving the number of positive biopsy cores (see the Supplementary Appendix).[24] Patients had no evidence of metastatic disease on conventional imaging, as confirmed by blinded independent central review; patients with clinical stage N1 (indicating disease spread within the

pelvis) could be included. Patients had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (scores range from 0 to 5, with higher numbers indicating greater disability and a score of 5 indicating death) and were deemed to be able to receive ADT for at least 13 months on the basis of cardiovascular risk and investigator assessment.

### TREATMENT

Patients were randomly assigned in a 1:1 ratio to receive apalutamide (240 mg) or matched placebo orally once daily, in addition to ADT (gonadotropin-releasing hormone analogue [agonist or antagonist]). Patients received six cycles (28 days each) of neoadjuvant treatment (ADT plus apalutamide or ADT plus placebo), with cessation of apalutamide or placebo during the period from 2 weeks before radical prostatectomy to 4 weeks after prostatectomy, followed by six cycles (28 days each) of adjuvant treatment (ADT plus apalutamide or ADT plus placebo) after prostatectomy. ADT was continuous throughout the treatment phase. Patients were stratified according to region (Europe, North America, or the rest of the world), the involvement of locoregional lymph nodes (N0 vs. N1), and Gleason score (7 vs. 8 to 10). At the investigator's discretion, postoperative radiotherapy (adjuvant or salvage) and metastasis-directed therapy could be administered according to local standard practice.

### END POINTS AND ASSESSMENTS

The dual primary end points were pathological complete response or minimal residual disease (a composite end point) and metastasis-free survival. Pathological complete response or minimal residual disease, as assessed by blinded independent central review, was defined by the presence of a minimal residual tumor of no more than 5 mm (in the greatest dimension of the largest tumor lesion) in prostate-confined disease (stage ypT2 or lower) or no identifiable tumor (stage ypT0), as determined by hematoxylin and eosin staining with immunohistochemical analysis (with NKX3.1, CAM5.2, and PIN4 cocktail staining) as needed.

Metastasis-free survival was assessed by blinded independent central review and was defined as the time from randomization to the first occurrence of distant metastasis detected on conventional imaging (computed tomography, magnetic resonance imaging, or bone scan) or on prostate-specific membrane antigen positron-emission tomography (PSMA PET), a pathological finding of distant metastasis, or death from any cause. The use of PSMA PET to detect distant metastases was allowed in protocol amendment 7 (adopted on April 14, 2022).

Secondary end points, listed in hierarchical testing order, were event-free survival (the time from randomization to biochemical failure [defined by two consecutive increases in the PSA level, measured at least 1 week apart, with the second PSA level ≥0.2 ng per milliliter], local or regional recurrence, distant metastasis, or death, whichever occurred first); first subsequent local or systemic treatment; distant metastasis detected on conventional imaging or PSMA PET; freedom from disease (defined as having no evidence of disease) at 4 years; metastasis-free survival, as assessed with conventional imaging alone; and PSA-free survival with recovery of the testosterone level to at least 200 ng per deciliter. With the exception of freedom from disease at 4 years, all the secondary end points were assessed in time-to-event analyses. Exploratory end points included low residual cancer burden (≤0.25 $cm^3$ of residual disease in the prostate in organ-confined tumors [stages ypT0 to ypT2] without lymph-node involvement [ypN0] and negative surgical margins of radical prostatectomy), as well as castration-resistant prostate cancer, testosterone recovery to a level of at least 200 ng per deciliter, and overall survival, the last three of which were assessed in time-to-event analyses. Post hoc end points included metastasis-free survival after radical prostatectomy, as assessed according to residual cancer burden. Additional details on the end points and end-point assessments are provided in the Supplementary Appendix.

Biochemical failure triggered consideration of subsequent therapy, including adjuvant or salvage radiation therapy, at the discretion of the treating physician (such therapy was not defined in the protocol). Adverse events were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Adverse events that occurred during the treatment period were prespecified to include those

events that occurred on or after the first dose of apalutamide or placebo and before the start of subsequent therapy or no more than 30 days after the last dose of apalutamide or placebo, whichever occurred first, as well as events that were considered to be related to treatment, regardless of the start date of the event. Cardiovascular risk was assessed during screening and before surgery. Thromboprophylaxis was administered on the basis of risk factors and local guidelines according to protocol amendment 4. Additional details on the safety assessments are provided in the Supplementary Appendix.

### STATISTICAL ANALYSIS

A sample size of 2000 was estimated to provide the trial with 94% power to detect a between-group difference of 5 percentage points in the percentage of patients with a pathological complete response or minimal residual disease at the two-sided significance level of 0.01 under the assumption that the percentages would be 10% in the apalutamide group and 5% in the placebo group. For the final analysis of metastasis-free survival, 477 end-point events were estimated to provide the trial with 85% power to detect a between-group difference of 25% in the risk of distant metastasis or death (i.e., a hazard ratio of 0.75 with a two-sided significance level of 0.04) in the apalutamide group as compared with the placebo group (details are provided in the Supplementary Appendix).

Baseline demographic and clinical characteristics were summarized descriptively. Binary end points were analyzed by means of logistic regression, and the odds ratios were adjusted according to the prespecified stratification factors (region, locoregional lymph-node involvement, and Gleason score). An odds ratio overestimates the magnitude of effect as compared with relative risk and should be interpreted with caution; therefore, unadjusted relative risks are provided to illustrate the difference. A log-rank test stratified according to the prespecified stratification factors, the Kaplan–Meier method with 95% simultaneous confidence-interval bands to account for inference over multiple time points on the survival curves, and the Cox proportional-hazards model were used to assess time-to-event end points and obtain the hazard ratios and the 95% confidence intervals. Primary and secondary end points were assessed with adjustment for multiplicity (see the Supplementary Appendix for details on the handling of missing data and censoring). Analyses were performed according to an intention-to-treat approach; however, safety end points were assessed in the population of patients who received at least one dose of apalutamide or placebo.

To strongly control an overall family-wise type I error rate at the two-sided 0.05 level, a multiple-comparison testing procedure in a group-sequential setting[25] was applied (Fig. S2). The graphical procedure accounts for multiplicity of multiple hypotheses, and the Kim–DeMets alpha-spending function — $\alpha(\gamma,t)=\gamma t^{\rho}$, with $\rho=3$, where $\gamma$ represents the allocated significance level and t represents the proportion of event information for which the spending function is computed — accounts for multiplicity of repeated hypothesis testing. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

## RESULTS

### PATIENTS

A total of 2109 patients underwent randomization in a 1:1 ratio between July 15, 2019, and June 30, 2022, with 1057 assigned to receive ADT plus apalutamide and 1052 to receive ADT plus placebo (Fig. S3). At the clinical cutoff date (February 2, 2026), the median follow-up was 61.7 months; 899 patients (85.1%) in the apalutamide group and 922 (87.6%) in the placebo group remained in the trial as of the cutoff date. Demographic and disease characteristics were well balanced between the two groups (Table 1). The representativeness of the trial population is summarized in Table S1. Black patients accounted for 44 of the 431 patients (10.2%) from North America. The median age of the patients was 66 years (interquartile range, 61 to 71). Most patients (95.8%) had a Gleason score of 8 or higher, 35.5% had a clinical tumor stage of T3 or T4, 12.3% had clinical lymph-node metastases, and the median PSA level was 14.8 ng per milliliter (interquartile range, 8.1 to 31.5). All the patients who underwent randomization were included in the intention-to-treat population, and all those who received at least one dose of apalutamide or placebo

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

| Characteristic | ADT plus Apalutamide (N=1057) | ADT plus Placebo (N=1052) | Overall (N=2109) |
|---|---|---|---|
| Age | | | |
| Median (IQR) — yr | 66.0 (62–71) | 66.0 (61–70) | 66.0 (61–71) |
| Distribution — no. (%) | | | |
| <65 yr | 406 (38.4) | 442 (42.0) | 848 (40.2) |
| 65 to 69 yr | 289 (27.3) | 300 (28.5) | 589 (27.9) |
| 70 to 74 yr | 256 (24.2) | 216 (20.5) | 472 (22.4) |
| ≥75 yr | 106 (10.0) | 94 (8.9) | 200 (9.5) |
| Race or ethnic group — no. (%)† | | | |
| American Indian or Alaska Native | 5 (0.5) | 1 (0.1) | 6 (0.3) |
| Asian | 197 (18.6) | 211 (20.1) | 408 (19.3) |
| Black | 35 (3.3) | 44 (4.2) | 79 (3.7) |
| Native Hawaiian or other Pacific Islander | 4 (0.4) | 5 (0.5) | 9 (0.4) |
| White | 746 (70.6) | 717 (68.2) | 1463 (69.4) |
| Multiple | 3 (0.3) | 3 (0.3) | 6 (0.3) |
| Not reported | 67 (6.3) | 71 (6.7) | 138 (6.5) |
| Median time from initial diagnosis to randomization (range) — mo‡ | 2.4 (0.5–192.5) | 2.3 (0.5–245.5) | 2.3 (0.5–245.5) |
| PSA level§ | | | |
| Median (IQR) — ng/ml | 14.4 (8.3– 29.2) | 15.1 (8.1–33.7) | 14.8 (8.1–31.5) |
| Range — ng/ml | 1.2–1753.0 | 0.0–2798.0 | 0.0–2798.0 |
| Distribution — no./total no. (%) | | | |
| <20 ng/ml | 630/1025 (61.5) | 604/1033 (58.5) | 1234/2058 (60.0) |
| <10 ng/ml | 352/1025 (34.3) | 344/1033 (33.3) | 696/2058 (33.8) |
| 10 to <20 ng/ml | 278/1025 (27.1) | 260/1033 (25.2) | 538/2058 (26.1) |
| ≥20 ng/ml | 395/1025 (38.5) | 429/1033 (41.5) | 824/2058 (40.0) |
| 20 to <40 ng/ml | 216/1025 (21.1) | 223/1033 (21.6) | 439/2058 (21.3) |
| ≥40 ng/ml | 179/1025 (17.5) | 206/1033 (19.9) | 385/2058 (18.7) |
| Tumor stage at diagnosis — no. (%) | | | |
| T1 | 219 (20.7) | 197 (18.7) | 416 (19.7) |
| T2 | 465 (44.0) | 470 (44.7) | 935 (44.3) |
| T3 | 338 (32.0) | 344 (32.7) | 682 (32.3) |
| T4 | 33 (3.1) | 33 (3.1) | 66 (3.1) |
| TX | 2 (0.2) | 8 (0.8) | 10 (0.5) |
| Regional lymph-node stage at diagnosis — no. (%) | | | |
| N0 | 928 (87.8) | 922 (87.6) | 1850 (87.7) |
| N1 | 129 (12.2) | 130 (12.4) | 259 (12.3) |
| Gleason score at diagnosis — no. (%)¶ | | | |
| 7 | 45 (4.3) | 44 (4.2) | 89 (4.2) |
| ≥8 | 1012 (95.7) | 1008 (95.8) | 2020 (95.8) |
| 8 | 350 (33.1) | 360 (34.2) | 710 (33.7) |
| 9 | 623 (58.9) | 596 (56.7) | 1219 (57.8) |
| 10 | 39 (3.7) | 52 (4.9) | 91 (4.3) |

**Table 1. (Continued.)**

| Characteristic | ADT plus Apalutamide (N=1057) | ADT plus Placebo (N=1052) | Overall (N=2109) |
|---|---|---|---|
| ECOG performance-status score — no./total no. (%)‖ | | | |
| 0 | 1019/1057 (96.4) | 1017/1051 (96.8) | 2036/2108 (96.6) |
| 1 | 38/1057 (3.6) | 34/1051 (3.2) | 72/2108 (3.4) |
| Geographic region — no. (%) | | | |
| Europe | 557 (52.7) | 559 (53.1) | 1116 (52.9) |
| North America | 217 (20.5) | 214 (20.3) | 431 (20.4) |
| Rest of the world | 283 (26.8) | 279 (26.5) | 562 (26.6) |

* Data are shown for the intention-to-treat population, which included all the patients who underwent randomization. Numbers may not total 100 because of rounding. IQR denotes interquartile range.
† Race and ethnic group were reported by the patients. Missing data are categorized as not reported.
‡ The time in months from initial diagnosis was determined by adding one to the number of days from the date of initial diagnosis to the date of randomization and dividing by 30.4375.
§ The prostate-specific antigen (PSA) level at baseline was defined as the last level assessed before the first dose of androgen-deprivation therapy or apalutamide. Data were available for a total of 2058 patients: 1025 in the apalutamide group and 1033 in the placebo group.
¶ Gleason scores range from 6 to 10, with higher scores indicating more aggressive disease.
‖ Scores on the Eastern Cooperative Oncology Group (ECOG) performance-status scale range from 0 to 5, with higher scores indicating greater disability and a score of 5 indicating death.

(1050 patients in each group) were included in the safety population.

### DUAL PRIMARY END POINTS

The percentage of patients with a pathological complete response or minimal residual disease was significantly higher in the apalutamide group than in the placebo group (8.9% vs. 1.0%; odds ratio, 10.17; 95% confidence interval [CI], 5.27 to 19.64; relative risk, 9.36; 95% CI, 4.90 to 17.86; P<0.001) (Fig. 1A and Table 2). A disease stage of ypT0 was reached in 54 of 1057 patients (5.1%) in the apalutamide group and in 4 of 1052 (0.4%) in the placebo group. At surgery, positive surgical margins were present in 20.9% of the patients in the apalutamide group and in 42.7% of those in the placebo group; 53.1% and 70.6%, respectively, had a disease stage higher than ypT2; and 23.3% and 24.4% had pathological lymph-node involvement (Table S2). Subgroup analyses of pathological complete response or minimal residual disease are shown in Figure S4A.

The final analysis for metastasis-free survival was performed after 472 end-point events had occurred (99.0% of the expected 477 events): an end-point event occurred in 215 patients (20.3%) in the apalutamide group and in 257 (24.4%) in the placebo group (Table S3). Among end-point events, most distant metastases were identified by PSMA PET (53.0% of those in the apalutamide group and 60.7% in the placebo group). Post hoc analysis showed that 686 patients (64.9%) in the apalutamide group and 755 patients (71.8%) in the placebo group underwent PSMA PET at least once. The probability of metastasis-free survival at 5 years was 78.2% (95% CI, 75.3 to 80.8) in the apalutamide group, as compared with 73.5% (95% CI, 70.4 to 76.3) in the placebo group. Metastasis-free survival was significantly higher with apalutamide than with placebo (hazard ratio for distant metastasis or death, 0.80; 95% CI, 0.67 to 0.96; P=0.02) (Fig. 1B). The effect of ADT plus apalutamide on metastasis-free survival across subgroups is shown in Figure S4B.

### SECONDARY END POINTS

The better outcomes with apalutamide than with placebo for the primary end points were supported by the results for the secondary end points, which showed significantly better outcomes with apalutamide than with placebo for event-free survival (median, 57.1 months vs. 38.4 months; hazard ratio, 0.71; 95% CI, 0.63 to 0.80; P<0.001), time to the first subsequent local or systemic therapy (median, 74.2 months vs. 41.5 months; hazard ratio, 0.65; 95% CI, 0.57 to 0.73; P<0.001),

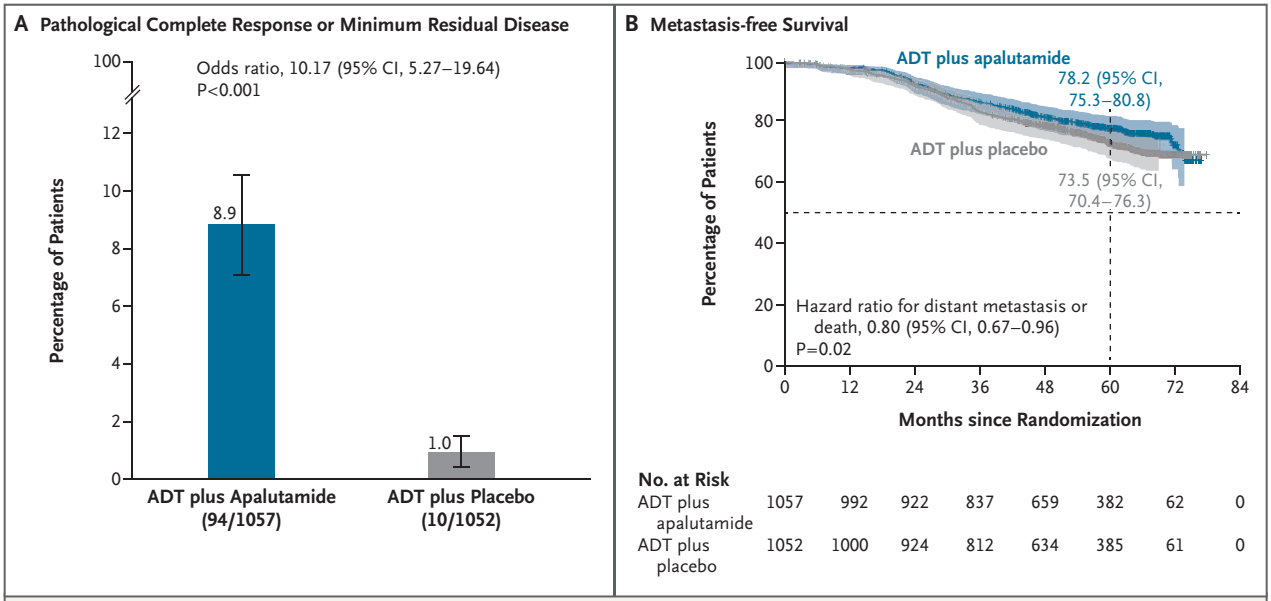


**Figure 1. Pathological Complete Response or Minimal Residual Disease and Metastasis-free Survival (Dual Primary End Points).**

Shown are the percentage of patients with a pathological complete response or minimal residual disease (defined as having no identifiable tumor [disease stage ypT0] or a minimal residual tumor of no more than 5 mm in the greatest dimension of the largest tumor lesion in prostate-confined disease [stage ypT2 or lower]) (Panel A) and Kaplan–Meier estimates of metastasis-free survival (Panel B) in the intention-to-treat population. Patients were not considered to have a pathological complete response or minimal residual disease if they had a tumor inside the prostate that was larger than 5 mm in the greatest dimension of the largest tumor lesion or a tumor of any size at stage ypT3 or T4, N1, or M1; if they were not tested for a pathological complete response or minimal residual disease (4 patients); or if they had not undergone radical prostatectomy (112 patients). The odds ratio is from a logistic-regression analysis adjusted for the prespecified stratification factors: geographic region (Europe, North America, or the rest of the world), nodal status (N0 or N1), and Gleason score (7 or ≥8; scores range from 6 to 10, with higher scores indicating more aggressive disease). The P value for pathological complete response or minimal residual disease is based on a Cochran–Mantel–Haenszel test stratified according to the prespecified stratification factors. The hazard ratio for distant metastasis or death is from a proportional-hazards model, and the P value is from a log-rank test, both stratified according to the prespecified stratification factors. An odds ratio of greater than 1 and a hazard ratio of less than 1 favor apalutamide over placebo. I bars in Panel A and shading in Panel B indicate 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

and time to distant metastasis detected on conventional imaging or PSMA PET (hazard ratio, 0.68; 95% CI, 0.55 to 0.83; P<0.001), as well as a significantly higher percentage of patients in the apalutamide group than in the placebo group with no evidence of disease at 4 years (21.9% vs. 18.3%; odds ratio, 1.25; 95% CI, 1.01 to 1.55; relative risk, 1.20; 95% CI, 1.01 to 1.42; P=0.04) (Fig. 2 and Table 2). No significant between-group difference was observed in metastasis-free survival assessed with conventional imaging alone (hazard ratio, 0.84; 95% CI, 0.67 to 1.07) (Table 2 and Fig. S5). For the final end point in the hierarchy, PSA-free survival with testosterone recovery, the median was 35.4 months in the apalutamide group, as compared with 30.3 months in the placebo group (hazard ratio, 0.83; 95% CI, 0.73 to 0.94). The effects of ADT plus apalutamide on event-free survival across the evaluated subgroups are shown in Figure S4C, and subgroup analyses of the time to the first subsequent local or systemic therapy are shown in Figure S4D.

### EXPLORATORY END POINTS

Analyses of exploratory efficacy end points support the results for the primary and secondary end points (Table 2 and Fig. S6). Testosterone recovery to a level of at least 200 ng per deciliter was reached in 81.6% of the patients in the apalutamide group and in 83.0% of those in the placebo group. The time to the development of castration-resistant prostate cancer and the time to testosterone recovery from baseline, as well as results for other exploratory end points, are shown

**Table 2. Primary, Secondary, Exploratory, and Post Hoc End Points.***

| End Point | ADT plus Apalutamide (N=1057) | ADT plus Placebo (N=1052) | Hazard Ratio or Odds Ratio (95% CI)† | P Value |
|---|---|---|---|---|
| **Primary end points** | | | | |
| Pathological complete response or MRD‡ | | | | |
| No. of patients (%) | 94 (8.9) | 10 (1.0) | 10.17 (5.27–19.64)§ | <0.001¶ |
| 95% CI — % | 7.2–10.6 | 0.4–1.5 | | |
| Metastasis-free survival — mo‖ | NR | NR | 0.80 (0.67–0.96) | 0.02** |
| **Secondary end points** | | | | |
| Event-free survival (95% CI) — mo | 57.1 (50.9–67.7) | 38.4 (35.5–44.3) | 0.71 (0.63–0.80) | <0.001** |
| Time to first subsequent local or systemic therapy (95% CI) — mo†† | 74.2 (63.8–NE) | 41.5 (36.6–47.3) | 0.65 (0.57–0.73) | <0.001** |
| Time to distant metastasis detected on conventional imaging or PSMA PET — mo | NR | NR | 0.68 (0.55–0.83) | <0.001** |
| Freedom from disease (no evidence of disease) at 4 yr | | | | |
| No. of patients (%) | 232 (21.9) | 193 (18.3) | 1.25 (1.01–1.55)§‡‡ | 0.04¶ |
| 95% CI — % | 19.5–24.4 | 16.0–20.7 | | |
| Metastasis-free survival assessed with conventional imaging — mo | NR | NR | 0.84 (0.67–1.07) | — |
| PSA-free survival with testosterone recovery (95% CI) — mo | 35.4 (33.4–38.1) | 30.3 (28.4–33.0) | 0.83 (0.73–0.94) | — |
| **Exploratory end points** | | | | |
| Low residual cancer burden — no. (%) | 323 (30.6) | 123 (11.7) | 3.36 (2.67–4.23)§ | — |
| Time to castration-resistant prostate cancer (95% CI) — mo | NR | NR (71.8–NE) | 0.59 (0.46–0.76) | — |
| Time to testosterone recovery from baseline (95% CI) — mo§§ | 19.4 (19.0–20.3) | 18.7 (18.3–19.1) | 0.93 (0.84–1.02) | — |
| Time to distant metastasis detected on conventional imaging — mo | NR | NR | 0.63 (0.46–0.85) | — |
| Time to distant metastasis detected on PSMA PET — mo | NR | NR | 0.72 (0.57–0.89) | — |
| Time to testosterone recovery from end of 12-mo perioperative treatment period (95% CI) — mo§§ | 8.1 (7.1–8.6) | 6.6 (6.3–7.1) | 0.92 (0.84–1.01) | — |
| **Post hoc end points** | | | | |
| Investigator-assessed metastasis-free survival (95% CI) — mo | NR | NR (73.6–NE) | 0.74 (0.62–0.87) | — |
| Distant metastasis assessed by blinded independent central review in patients with biochemical failure — no./total no. (%) | 134/156 (85.9) | 189/221 (85.5) | NA | — |

* Data are shown for the intention-to-treat population unless otherwise indicated. Detailed definitions of secondary, exploratory, and post hoc end points are provided in the Supplementary Appendix. For end points assessed in time-to-event analyses, the median number of months is reported. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing. NA denotes not available, NE not estimable, and NR not reached.

† Unless otherwise specified, values are hazard ratios from a proportional-hazards model stratified according to region (Europe, North America, or the rest of the world), nodal status (N0 vs. N1), and Gleason score (7 vs. ≥8). A hazard ratio of less than 1 favors apalutamide over placebo.

‡ Pathological complete response or minimal residual disease (MRD), assessed by blinded independent central review, was defined as having no residual tumor or minimal residual tumor that was no more than 5 mm in size in the greatest dimension of the largest tumor lesion and was confined to the prostate (stage ypT2 or lower).

§ The comparison was calculated as an odds ratio with the use of a logistic-regression analysis adjusted for region, nodal status, and Gleason score. An odds ratio of greater than 1 favors apalutamide over placebo.

¶ The P value was calculated on the basis of a Cochran–Mantel–Haenszel test stratified according to region, nodal status, and Gleason score.

‖ Metastasis-free survival, assessed by blinded independent central review, was defined as the time from randomization to the first occurrence of distant metastasis detected on conventional imaging (computed tomography, magnetic resonance imaging, or bone scan) or prostate-specific membrane antigen positron-emission tomography (PSMA PET), a pathological finding of distant metastasis, or death from any cause.

** The P value is from a log-rank test stratified according to region, nodal status, and Gleason score.

†† Data were partially missing for 28 of 1057 patients (2.6%) in the apalutamide group and 23 of 1052 (2.2%) in the placebo group who received subsequent therapy.

‡‡ The values reported are for the intention-to-treat population; however, approximately 10% of the patients could not be evaluated for this end point by the clinical cutoff date and were therefore classified as having evidence of disease.

§§ Data are shown for the safety population, which included all the patients who received at least one dose of apalutamide or placebo (1050 in each group).

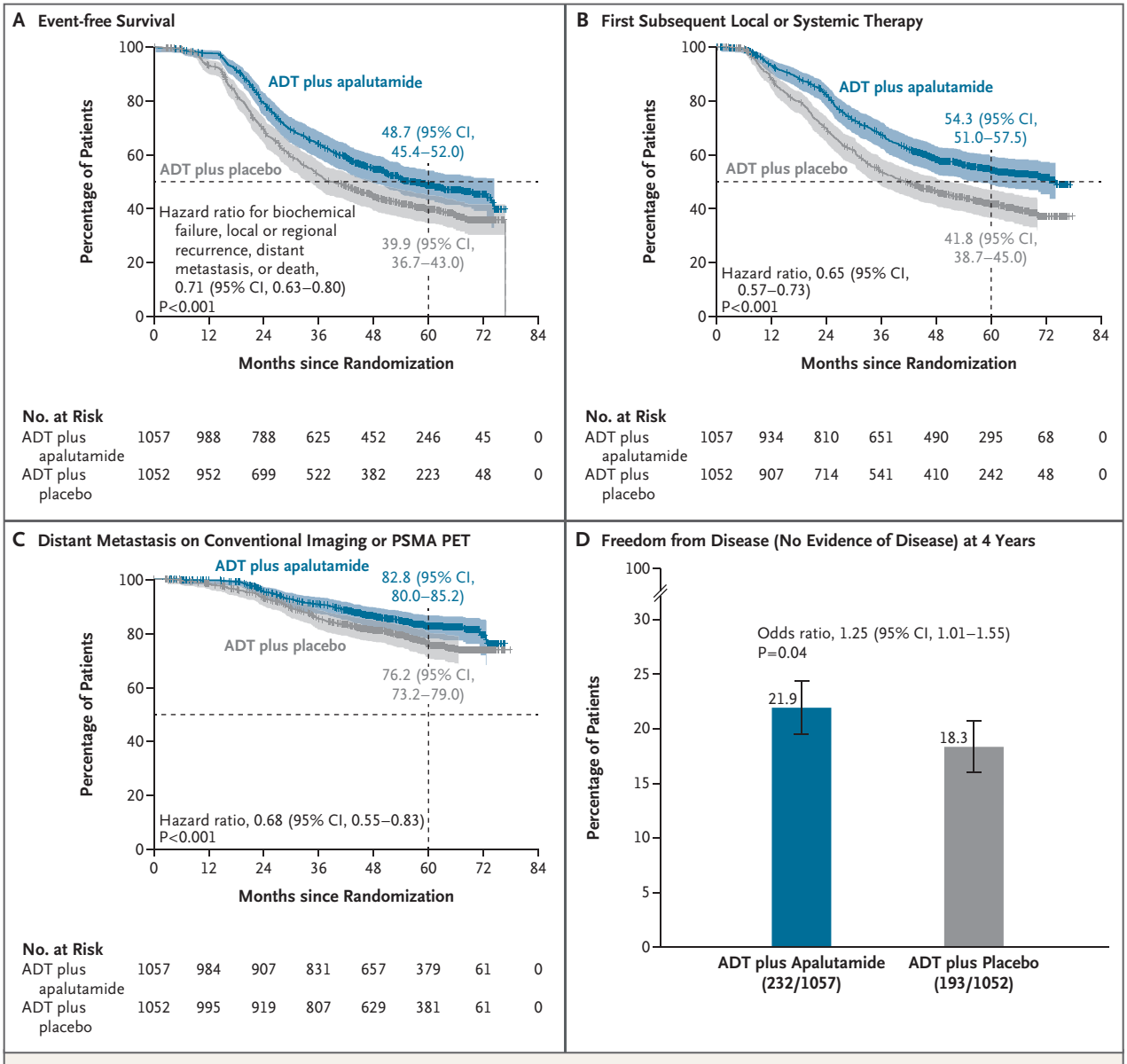


**Figure 2. Key Secondary End Points.**

Shown are Kaplan–Meier estimates for key end points assessed in time-to-event analyses: event-free survival (defined as the time from randomization to the first occurrence of biochemical failure, local or regional recurrence, distant metastasis, or death) (Panel A), first subsequent local or systemic therapy (assessed as the time from randomization to the initiation of any subsequent local, regional, or systemic treatment for prostate cancer, including reinitiation of androgen-deprivation therapy) (Panel B), and distant metastasis detected on conventional imaging (computed tomography, magnetic resonance imaging, or bone scan) or prostate-specific membrane antigen positron-emission tomography (PSMA PET) (Panel C). The percentage of patients with freedom from disease (defined as having no evidence of disease) at 4 years is also shown (Panel D). Data shown are for the intention-to-treat population. As of the clinical cutoff date, approximately 10% of the patients were not evaluable for freedom from disease at 4 years and were classified as having evidence of disease. Hazard ratios in Panels A, B, and C are from a stratified proportional-hazards model, and P values are from a log-rank test stratified according to the prespecified stratification factors (region, nodal status, and Gleason score). The odds ratio in Panel D is from a logistic-regression analysis adjusted for the prespecified stratification factors, and the P value is based on a Cochran–Mantel–Haenszel test stratified according to the prespecified stratification factors. An odds ratio of greater than 1 and a hazard ratio of less than 1 favor apalutamide over placebo. Shading in Panels A, B, and C and I bars in Panel D indicate 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

in Table 2 and in the Supplementary Appendix. After a median follow-up of 5 years, with an overall mortality of 8.5%, the analysis of overall survival in the apalutamide group as compared with the placebo group (evaluated as an alternative measure of safety) showed a hazard ratio for death of 1.08, a finding that is below the prespecified threshold for an unacceptable level of detriment.[26]

#### POST HOC END POINTS

Metastasis-free survival after radical prostatectomy as indicated by a low residual cancer burden (stage ypT2 or lower, with ≤0.25 $cm^3$ of residual disease) is shown in Figure S7. Subsequent therapy was received by 42.4% of the patients in the apalutamide group and 56.7% of those in the placebo group; the most common therapies were hormonal therapy (in 34.0% and 46.5%, respectively) and postoperative radiotherapy (in 26.6% and 36.8%), primarily salvage radiotherapy (Table S4).

#### SAFETY

The median duration of the treatment period was similar in the two trial groups (apalutamide group, 11.0 months; placebo group, 11.1 months). Grade 3 or 4 adverse events that occurred during the treatment period were reported in 39.6% of the patients in the apalutamide group and in 31.0% of those in the placebo group (Table 3); differences between the two groups were driven primarily by differences in the incidence of rash. Rash was managed with the use of topical antihistamines, oral antihistamines, or both, as well as glucocorticoids; 2.2% of the patients in the apalutamide group discontinued apalutamide owing to skin reactions. The most common adverse events that occurred during the treatment period were hot flush (in 63.4% of the patients in the apalutamide group vs. 56.5% of those in the placebo group), urinary incontinence (in 50.2% vs. 50.9%, respectively), erectile dysfunction (in 41.6% vs. 41.4%), fatigue (in 27.7% vs. 26.8%), arthralgia (in 22.6% vs. 19.4%), and rash (in 21.2% vs. 10.0%). Urinary incontinence and erectile dysfunction were mostly grade 1 or 2. All-grade adverse events of special interest are listed in Table S5. Serious adverse events that occurred during the treatment period were reported in 19.3% of the patients in the apalutamide group and in 16.4% of those in the placebo group (Table S6). Adverse events that occurred during the treatment period and led to discontinuation of apalutamide or placebo were reported in 7.4% of the patients in the apalutamide group and in 2.7% of those in the placebo group (Table 3 and Tables S7 and S8).

Overall, 92 of 1050 patients (8.8%) in the apalutamide group and 87 of 1050 patients (8.3%) in the placebo group died during the treatment period or during follow-up. Among patients younger than 75 years of age, death occurred in 76 of 945 (8.0%) of those in the apalutamide group and in 75 of 956 (7.8%) in the placebo group. Among patients 75 years of age or older, 16 of 105 (15.2%) of those in the apalutamide group died, as did 12 of 94 (12.8%) in the placebo group. Adverse events that led to death during the treatment period occurred in 1.3% of the patients in the apalutamide group and in 0.5% of those in the placebo group (Table S9). Serious adverse events that occurred during the treatment period and led to death were determined by the investigator to be related to treatment with apalutamide, ADT, or radical prostatectomy or a combination of these treatments in 7 of 1050 patients (0.7%) in the apalutamide group and in 1 of 1050 (0.1%) in the placebo group. The percentage of patients with venous thromboembolism was balanced in the two groups (2.0% vs. 3.4%) (Table S10), as was the percentage with cardiac disorders that occurred during the treatment period (6.8% [71 patients] vs. 5.9% [62 patients]).

## DISCUSSION

Among patients with high-risk localized or locally advanced prostate cancer, treatment with ADT plus apalutamide was associated with greater success of radical prostatectomy than treatment with ADT plus placebo. A significant benefit with 12 cycles of perioperative ADT plus apalutamide as compared with ADT plus placebo was observed for pathological complete response or minimal residual disease and metastasis-free survival, the dual primary end points. The percentage of patients with a pathological complete response or minimal residual disease in surgical specimens after 6 cycles of neoadjuvant ADT plus apalutamide was approximately 9 times as high as the percentage after treatment with ADT plus placebo

**Table 3. Adverse Events That Occurred during the Treatment Period.***

| Adverse Event | ADT plus Apalutamide (N=1050) | | | | | ADT plus Placebo (N=1050) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Total | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Total |
| | *number of patients (percent)* | | | | | *number of patients (percent)* | | | | |
| Any adverse event | — | — | — | — | 1037 (98.8) | — | — | — | — | 1027 (97.8) |
| Grade 3 or 4 adverse event | — | — | — | — | 416 (39.6) | — | — | — | — | 325 (31.0) |
| Any serious adverse event | — | — | — | — | 203 (19.3) | — | — | — | — | 172 (16.4) |
| Any adverse event leading to discontinuation of apalutamide or placebo | — | — | — | — | 78 (7.4) | — | — | — | — | 28 (2.7) |
| Any adverse event leading to dose interruption | — | — | — | — | 154 (14.7) | — | — | — | — | 81 (7.7) |
| Any adverse event leading to death | — | — | — | — | 14 (1.3) | — | — | — | — | 5 (0.5) |
| Most common adverse events† | | | | | | | | | | |
| At least 1 adverse event | 96 (9.1) | 525 (50.0) | 393 (37.4) | 23 (2.2) | 1037 (98.8) | 122 (11.6) | 580 (55.2) | 313 (29.8) | 12 (1.1) | 1027 (97.8) |
| Hot flush | 550 (52.4) | 109 (10.4) | 7 (0.7) | 0 | 666 (63.4) | 514 (49.0) | 79 (7.5) | 0 | 0 | 593 (56.5) |
| Urinary incontinence | 232 (22.1) | 279 (26.6) | 16 (1.5) | 0 | 527 (50.2) | 248 (23.6) | 269 (25.6) | 17 (1.6) | 0 | 534 (50.9) |
| Erectile dysfunction | 200 (19.0) | 202 (19.2) | 35 (3.3) | 0 | 437 (41.6) | 192 (18.3) | 216 (20.6) | 27 (2.6) | 0 | 435 (41.4) |
| Fatigue | 248 (23.6) | 39 (3.7) | 4 (0.4) | 0 | 291 (27.7) | 266 (25.3) | 14 (1.3) | 1 (0.1) | 0 | 281 (26.8) |
| Arthralgia | 165 (15.7) | 68 (6.5) | 4 (0.4) | 0 | 237 (22.6) | 143 (13.6) | 59 (5.6) | 2 (0.2) | 0 | 204 (19.4) |
| Rash | 123 (11.7) | 69 (6.6) | 31 (3.0) | 0 | 223 (21.2) | 90 (8.6) | 13 (1.2) | 2 (0.2) | 0 | 105 (10.0) |
| Constipation | 117 (11.1) | 83 (7.9) | 0 | 0 | 200 (19.0) | 98 (9.3) | 68 (6.5) | 0 | 0 | 166 (15.8) |
| Hypertension | 19 (1.8) | 70 (6.7) | 80 (7.6) | 0 | 169 (16.1) | 13 (1.2) | 80 (7.6) | 91 (8.7) | 0 | 184 (17.5) |
| Pruritus | 114 (10.9) | 44 (4.2) | 7 (0.7) | 0 | 165 (15.7) | 75 (7.1) | 15 (1.4) | 0 | 0 | 90 (8.6) |
| Procedural pain | 35 (3.3) | 78 (7.4) | 6 (0.6) | 0 | 119 (11.3) | 28 (2.7) | 112 (10.7) | 3 (0.3) | 0 | 143 (13.6) |
| Urinary tract infection | 8 (0.8) | 90 (8.6) | 18 (1.7) | 0 | 116 (11.0) | 5 (0.5) | 108 (10.3) | 11 (1.0) | 0 | 124 (11.8) |
| Covid-19 | 60 (5.7) | 35 (3.3) | 5 (0.5) | 2 (0.2) | 102 (9.7) | 67 (6.4) | 35 (3.3) | 2 (0.2) | 1 (0.1) | 105 (10.0) |

* Data are shown for the safety population. Adverse events that occurred during the treatment period were specified as those events that occurred on or after the date of the first dose of apalutamide or placebo and before the start of subsequent therapy or no more than 30 days after the last dose of apalutamide or placebo, whichever occurred first, or as adverse events that were considered to be related to treatment, regardless of the start date of the event. Adverse events were defined according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 28.0, and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. For each system organ class and preferred term, patients are counted only once, even if they had multiple events that would be categorized according to the same system organ class or preferred term. In such cases, the highest-grade event is reported. If grades were unknown for all events for a given patient, the patient is counted only in the total column. Covid-19 denotes coronavirus disease 2019.

† The most common adverse events were reported in at least 10% of the patients in either group. Grade 5 events are excluded.

(8.9% vs. 1.0%). Combined neoadjuvant treatment (6 cycles) and adjuvant treatment (6 cycles) with ADT plus apalutamide led to a significantly longer time to the development of distant metastasis (detected with conventional imaging, PSMA PET, or histopathological analysis) or death than treatment with ADT plus placebo, as assessed by blinded independent central review. Although Kaplan–Meier curves for metastasis-free survival converged late in follow-up, this finding probably reflects the sparse data during the follow-up period. The proportional-hazards assumption was assessed graphically with log-log plots (see the Supplementary Appendix), which showed approximately parallel lines throughout follow-up, an indication that the statistical assumption regarding metastasis-free survival was reasonably met despite the late Kaplan–Meier convergence.

With a median time to subsequent therapy of 6 years in the apalutamide group, the significant delay in disease recurrence or progression with ADT plus apalutamide as compared with ADT plus placebo was a clinical benefit for patients, as was the higher likelihood of being without evidence of disease at 4 years after treatment with ADT plus apalutamide than after treatment with ADT plus placebo. These benefits were corroborated by apparent improvement in additional patient-centered end points, including time to distant metastasis and time to development of castration-resistant prostate cancer.

The benefit of perioperative ADT plus apalutamide with radical prostatectomy in our trial extends findings from phase 2 trials. In a previous phase 2 trial, neoadjuvant abiraterone acetate plus prednisone with ADT led to a significantly greater reduction in intraprostatic androgens than ADT alone, with higher percentages of patients having a pathological complete response, minimal residual disease, or low residual cancer burden, findings that showed a strong on-target effect of the addition of androgen pathway inhibitors.[14] Consistent with the results of phase 2 trials,[14-17] the results of the present trial showed benefit in measures of prostate cancer and prospectively correlated pathological response with metastasis-free survival after neoadjuvant therapy and radical prostatectomy.[27] This approach aligns with the findings of a pooled analysis showing that the depth of the pathological response, evaluated as the residual cancer burden, was highly prognostic for metastasis-free survival in high-risk patients receiving a neoadjuvant androgen-receptor pathway inhibitor.[28] The meta-analysis by the Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) group showed that, in trials involving localized prostate cancer (treated with radiation therapy and radical prostatectomy), metastasis-free survival as assessed with conventional imaging correlated with overall survival.[29]

Use of PSMA PET in this trial represents an advance in practice; PSMA PET is now the standard in some regions of the world, owing to improved staging accuracy.[1,2] Given its higher sensitivity at low PSA levels, PSMA PET detects metastases at biochemical failure earlier than conventional imaging,[1,2,8,30,31] and positive PSMA PET findings have been shown to affect treatment management.[30,32] Metastasis-free survival assessed by PSMA PET at biochemical recurrence after radical prostatectomy was shown to be three times shorter than metastasis-free survival assessed by conventional imaging.[33] In our trial, the between-group difference in metastasis-free survival as assessed by conventional imaging alone was not significant. The increasing use of PSMA PET since the inception of our trial[34] may limit the power of assessment of metastasis-free survival by conventional imaging alone in early-stage disease. PSMA PET is recommended for consideration in future trials to generate results relevant to clinical practice.[35] Patients enrolled in our trial were evaluated in accordance with the latest evolving standards in diagnostics, and results are broadly generalizable to those with high-risk localized or locally advanced prostate cancer who are candidates for radical prostatectomy.

Owing to wide approval around the world and the adoption of PSMA PET as standard care, the present trial allowed the use of PSMA PET for staging by protocol amendment, which added complexity to the trial design and interpretation, including the lack of baseline PET staging. Another limitation is that perioperative ADT plus apalutamide was compared with perioperative ADT plus placebo; the use of perioperative ADT represents intensification of treatment beyond current clinical guideline recommendations of radical prostatectomy alone.[2] This design feature enabled the assessment of pathological complete response or minimal residual disease and

metastasis-free survival between trial groups with maintenance of blinding and was aligned with regulatory input. The comparison of ADT plus apalutamide plus radical prostatectomy with radical prostatectomy alone is ongoing in a complementary PROTEUS substudy (ClinicalTrials.gov number, NCT03767244). Further limitations are that the primary and secondary end points for this trial did not formally evaluate perioperative systemic therapy with radical prostatectomy as compared with radical prostatectomy followed by possible adjuvant or salvage therapy.

The safety profile of ADT plus apalutamide in the present trial was consistent with that in previous trials involving patients with more advanced prostate cancer.[20-22] Adverse events were more common with ADT plus apalutamide than with ADT plus placebo, with a higher incidence of rash in the apalutamide group accounting for much of the difference. Rash-related outcomes may be improved by following a rash-management guide, which is commonly used in real-world practice and, as shown in the Apa-RP trial, can reduce the incidence, duration, and severity of rash.[36,37] Treatment with 12 cycles of ADT plus apalutamide did not show any new safety signals in patients with high-risk localized or locally advanced prostate cancer. The frequency of adverse events that led to discontinuation of apalutamide or placebo was low overall but was higher in the apalutamide group (7.4% vs. 2.7%). With appropriate management of cardiovascular and perioperative thromboembolic risk, ADT plus apalutamide before and after radical prostatectomy was associated with mainly low-grade adverse events, especially in the context of the more impactful sequelae of radical prostatectomy.

Overall survival was evaluated as an alternative measure of safety and showed no detrimental treatment effect, although the length of follow-up in this trial was short to assess a survival outcome in this disease context. Overall mortality, including death from prostate cancer and non–treatment-related death, was 8.5%, which is similar to the mortality of 8.0% among 945 patients in the apalutamide group who were younger than 75 years of age. However, among 105 patients in the apalutamide group who were 75 years of age or older, mortality was nearly twice as high, at 15.2%, a finding that underscores the importance of careful selection of suitable candidates for both systemic therapy and surgery. The incidence of adverse events that led to death during the treatment period was low (1.3% in the apalutamide group vs. 0.5% in the placebo group) but important in the context of treatment of localized disease.

In this trial, androgen-receptor pathway inhibition with 6 cycles of ADT plus apalutamide both before and after radical prostatectomy in patients with high-risk localized or locally advanced prostate cancer led to significantly greater disease-control success than treatment with ADT plus placebo, as well as better patient-relevant long-term oncologic outcomes. New therapeutic approaches, particularly those with a well-established safety profile, that have the potential to prevent or delay metastatic disease are crucial to improving the lives of patients with prostate cancer.

Supported by Johnson & Johnson.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients and their families who participated in the trial and the trial coordinators, trial teams, nurses, and all others who have been involved in the trial since its inception in 2018. Writing assistance with the first draft of the manuscript was provided by Breanne Landry, Ph.D., and Larissa Belova, Ph.D., of Parexel, with funding provided by Johnson & Johnson.

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