BACKGROUND
Abiraterone acetate, a drug that blocks endogenous androgen synthesis, plus prednisone is indicated for metastatic castration-resistant prostate cancer. We evaluated the clinical benefit of abiraterone acetate plus prednisone with androgen-deprivation therapy in patients with newly diagnosed, metastatic, castration-sensitive prostate cancer.

METHODS
In this double-blind, placebo-controlled, phase 3 trial, we randomly assigned 1199 patients to receive either androgen-deprivation therapy plus abiraterone acetate (1000 mg daily, given once daily as four 250-mg tablets) plus prednisone (5 mg daily) (the abiraterone group) or androgen-deprivation therapy plus dual placebos (the placebo group). The two primary end points were overall survival and radiographic progression-free survival.

RESULTS
After a median follow-up of 30.4 months at a planned interim analysis (after 406 patients had died), the median overall survival was significantly longer in the abiraterone group than in the placebo group (not reached vs. 34.7 months) (hazard ratio for death, 0.62; 95% confidence interval [CI], 0.51 to 0.76; P<0.001). The median length of radiographic progression-free survival was 33.0 months in the abiraterone group and 14.8 months in the placebo group (hazard ratio for disease progression or death, 0.47; 95% CI, 0.39 to 0.55; P<0.001). Significantly better outcomes in all secondary end points were observed in the abiraterone group, including the time until pain progression, next subsequent therapy for prostate cancer, initiation of chemotherapy, and prostate-specific antigen progression (P<0.001 for all comparisons), along with next symptomatic skeletal events (P=0.009). These findings led to the unanimous recommendation by the independent data and safety monitoring committee that the trial be unblinded and crossover be allowed for patients in the placebo group to receive abiraterone. Rates of grade 3 hypertension and hypokalemia were higher in the abiraterone group.

CONCLUSIONS
The addition of abiraterone acetate and prednisone to androgen-deprivation therapy significantly increased overall survival and radiographic progression-free survival in men with newly diagnosed, metastatic, castration-sensitive prostate cancer. (Funded by Janssen Research and Development; LATITUDE ClinicalTrials.gov number, NCT01715285.)

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METASTATIC, CASTRATION-SENSITIVE prostate cancer accounts for approximately 3% of all new prostate-cancer diagnoses in the United States.1 Historically, androgen-deprivation therapy consisting of bilateral orchiectomy or luteinizing hormone–releasing hormone analogues, with or without first-generation androgen-receptor inhibitors, has been the standard of care.2 Although the majority of patients have an initial response to androgen-deprivation therapy, most men with metastases have progression to castration-resistant prostate cancer within a median of approximately 1 year.3,5 Resistance to androgen-deprivation therapy is largely driven by the reactivation of androgen-receptor signaling through persistent adrenal androgen production, up-regulation of intratumoral testosterone production, modification of the biologic characteristics of androgen receptors, and steroidogenic parallel pathways.2

The clinical benefit of adding docetaxel to androgen-deprivation therapy versus treatment with androgen-deprivation therapy alone has been shown in three randomized, phase 3 trials — Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED),5,6 Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE),7 and GETUG-153,8 — which collectively included more than 3000 men with metastatic, castration-sensitive prostate cancer. Androgen-deprivation therapy plus docetaxel is now a standard of care for men with metastatic, castration-sensitive prostate cancer who are eligible for chemotherapy, particularly those with a high metastatic burden, as defined in the respective studies.3-11 Barriers to the use of docetaxel include advanced patient age, poor performance status, coexisting illnesses, and patient preferences.9,12 Retrospective analyses exploring real-world practice patterns13,14 indicate that men with newly diagnosed, metastatic, castration-sensitive prostate cancer who are not being treated in clinical trials may be nearly a decade older than those treated in clinical trials. The concern with respect to chemotherapy-related toxicity and the effect of coexisting illnesses on complications is based on the severity of the toxicity that has been observed. Chemotherapy-related deaths were documented in all three randomized trials in which docetaxel was added to androgen-deprivation therapy.3,5,7

Abiraterone acetate, the prodrug of abiraterone, inhibits cytochrome P-450c17, a critical enzyme in androgen biosynthesis.15,16 Recent studies implicate its active D4A metabolite in antitumor effects, presumably through blockade of multiple steroidogenic enzymes and antagonism of the androgen receptor.17 Abiraterone acetate (hereafter referred to as abiraterone) in combination with prednisone has been shown to significantly increase overall survival and provide additional clinical benefits in patients with metastatic, castration-resistant prostate cancer who have not received chemotherapy and in those who have received previous docetaxel.18-22 The combination of abiraterone plus prednisone and androgen-deprivation therapy has been shown to reduce tumor burden in men with high-risk, localized prostate cancer who are receiving neoadjuvant therapy, which suggests a potential role for inhibiting extragonadal androgen biosynthesis before the emergence of castration resistance in men with newly diagnosed, metastatic, castration-sensitive prostate cancer.23,24 In LATITUDE, a multinational, randomized, double-blind, placebo-controlled, phase 3 trial, we evaluated the addition of abiraterone plus prednisone to androgen-deprivation therapy, as compared with androgen-deprivation therapy and dual placebos, on overall survival, radiographic progression-free survival, and clinically relevant measures in men with newly diagnosed, metastatic, castration-sensitive prostate cancer.

METHODS

TRIAL DESIGN AND CONDUCT

The trial was conducted at 235 sites in 34 countries in Europe, the Asia–Pacific region, Latin America, and Canada. The trial protocol (available with the full text of this article at NEJM.org) was approved by the review board at each participating institution. The trial was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. All the patients provided written informed consent.

An independent data and safety monitoring committee was commissioned by the sponsor, Janssen Research and Development, to review safety data on a regular basis and review efficacy data at planned interim analyses. The trial...
was designed by the senior academic authors and employees of the sponsor. Data were transcribed by trial personnel from source documents onto an electronic data-capture system prepared by the sponsor. The data analyses were performed by statisticians employed by the sponsor. All the authors assume responsibility for the completeness and integrity of the data and for the fidelity of the trial to the protocol. All the academic authors had full access to all parts of the data and drafted the manuscript with sponsor input, and all the coauthors subsequently provided input. The sponsor provided funding for editorial assistance. All the authors and participating institutions have agreements with the sponsor regarding data confidentiality.

PATIENTS AND TREATMENTS

Eligible patients were required to be at least 18 years of age and to have an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 to 2 (on a 5-point scale, with higher numbers indicating greater disability) with newly diagnosed (≤3 months before randomization), pathologically confirmed prostate cancer without neuroendocrine differentiation or small-cell histologic features. All the patients had high-risk, metastatic, castration-sensitive prostate cancer, as documented by a positive bone scan or metastatic lesions at the time of diagnosis on computed tomography (CT) or magnetic resonance imaging (MRI), according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. In addition, the patients were required to have at least two of the three following high-risk factors associated with poor prognosis: a Gleason score of 8 or more (on a scale of 2 to 10, with higher scores indicating more aggressive disease), at least three bone lesions, and the presence of measurable visceral metastasis. Patients were excluded if they had received previous chemotherapy, radiation therapy, or surgery for metastatic prostate cancer, with the exception of 3 months or less of androgen-deprivation therapy with luteinizing hormone–releasing hormone analogues or orchietomy with or without concurrent first-generation androgen-receptor antagonists before baseline or one course of palliative radiation or surgical therapy to treat symptoms associated with metastatic disease.

Patients were randomly assigned in a 1:1 ratio to receive androgen-deprivation therapy and abiraterone acetate (1000 mg daily, given once daily as four 250-mg tablets) and prednisone (5 mg daily) (the abiraterone group) or androgen-deprivation therapy and placebos (the placebo group). Patients were stratified according to the presence or absence of measurable visceral disease and ECOG performance-status score (0 or 1 vs. 2). Abiraterone or placebo was administered at least 1 hour before or 2 hours after a meal. All the patients who had not undergone surgical castration received ongoing androgen-deprivation therapy to reach or maintain a serum testosterone level of less than 50 ng per deciliter (1.7 nmol per liter). Safety and dosing adherence were evaluated during each trial visit, at treatment discontinuation (if applicable), and at the end-of-trial visit.

END POINTS

The two primary efficacy end points were overall survival and radiographic progression-free survival. Overall survival was defined as the time from randomization to death from any cause, and radiographic progression-free survival as the time from randomization to the occurrence of radiographic progression or death from any cause. Radiographic progression of soft-tissue lesions was evaluated by either CT or MRI on the basis of RECIST, version 1.1. Progression on bone scanning was assessed by adaptation of Prostate Cancer Working Group 2 criteria,25 and radiographic progression or death from any cause was defined as a clinical or pathological fracture, spinal-cord compression, palliative radiation to bone, or surgery involving bone), time to progression with respect to prostate-specific antigen (PSA) level on the basis of Prostate Cancer Working Group 2 criteria,25 time to the next therapy for prostate cancer, time to initiation of chemotherapy, and time to pain progression. Pain progression was defined as an increase of at least 30% from baseline in the worst pain
category on the Brief Pain Inventory—Short Form as observed at two consecutive evaluations performed at least 4 weeks apart.

**ASSESSMENTS**

Efficacy assessments included sequential radiographic imaging to assess radiographic progression-free survival (CT or MRI and bone scanning) performed every 4 months, starting at week 16. PSA levels were measured at baseline, monthly in the first year, and then every 2 months until end-of-trial treatment. Patients underwent serial monitoring of vital signs, serum hematologic and chemical findings, liver-function tests, and serum testosterone levels. Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 4.0.

**STATISTICAL ANALYSIS**

The overall level of significance was 0.05, with allocation between the two primary end points of overall survival (0.049) and radiographic progression-free survival (0.001) (Table S2 in the Supplementary Appendix). For overall survival, 852 events were required at the final analysis to detect a hazard ratio of 0.81 at a two-tailed significance level of 0.049, with a statistical power of 85%. An analysis of radiographic progression-free survival was planned when 565 progressions or deaths had been observed, which would provide a statistical power of 94% to detect a hazard ratio of 0.667 at a two-tailed significance level of 0.001. Two interim analyses were included (Table S2 in the Supplementary Appendix). The overall survival analyses incorporated the group sequential design with an alpha spending function that was calculated as Wang–Tsiatis power boundaries of shape parameter 0.2 (which shape the probability distribution). Secondary end points were tested with the use of the Hochberg test procedure to control the familywise type I error rate. The primary statistical method of comparison for time-to-event end points was the stratified log-rank test, according to the stratification factors. The Cox proportional-hazards model was used to estimate the hazard ratio and its associated 95% confidence interval.

**RESULTS**

**PATIENTS AND TREATMENTS**

A total of 1199 patients underwent randomization from February 12, 2013, through December 11, 2014. Of these patients, 597 were assigned to the abiraterone group and 602 to the placebo group (Fig. S1 in the Supplementary Appendix). The baseline demographic and disease characteristics were well balanced between the two groups (Table S3 in the Supplementary Appendix). The results presented here are based on the clinical cutoff date of October 31, 2016, for the...
first interim analysis of overall survival, at which time 406 deaths and 593 radiographic progressions or deaths had occurred. At a median follow-up of 30.4 months, the median time that the patients received the intervention was 24 months in the abiraterone group and 14 months in the placebo group. As a result of the findings at the time of the interim analysis, the independent data and safety monitoring committee unanimously recommended on January 12, 2017, that the trial be unblinded to allow crossover among the patients in the placebo group to receive abiraterone.

**End Points**

**Overall Survival**
The first interim analysis was performed after 406 deaths (48% of the 852 deaths that were included in the final analysis) and a median follow-up of 30.4 months. Of these deaths, 169 of 597 (28%) occurred in the abiraterone group and 237 of 602 (39%) in the placebo group. The overall rate of survival at 3 years was 66% in the abiraterone group and 49% in the placebo group (Fig. 1A). The rate of death from any cause was 28% in the abiraterone group and 39% in the placebo group (Table S4 in the Supplementary Appendix). The relative risk of death was 38% lower in the abiraterone group than in the placebo group (hazard ratio, 0.62; 95% confidence interval [CI], 0.51 to 0.76; P<0.001). The treatment effect of abiraterone on overall survival was consistently favorable across nearly all prespecified subgroups (Fig. S2 in the Supplementary Appendix).

**Radiographic Progression-free Survival**
At the time of the analysis, the median progression-free survival was 33.0 months in the abiraterone group and 14.8 months in the placebo group (239 events vs. 354 events) — a 53% lower relative risk of radiographic progression or death in the abiraterone group than in the placebo group (hazard ratio, 0.47; 95% CI, 0.39 to 0.55; P<0.001) (Fig. 1B). The treatment effect in the abiraterone group was consistent across nearly all prespecified subgroups (Fig. S3 in the Supplementary Appendix).

**Secondary and Exploratory End Points**
The superiority of abiraterone over placebo was shown for all secondary end points (Table 1 and Fig. 2, and Figs. S4 and S5 in the Supplementary Appendix). The numbers of patients who received one or multiple life-prolonging subsequent therapies were 125 (21%) in the abiraterone group and 246 (41%) in the placebo group (Table S5 in the Supplementary Appendix). Docetaxel was the most common post-progression treatment in the two groups.

**Safety**
Grade 3 or 4 adverse events were reported in 63% of the patients in the abiraterone group and

| Table 1. Prespecified Secondary and Exploratory Efficacy End Points.† |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **End Point**                  | **Abiraterone Group** (N = 597) | **Placebo Group** (N = 602) | **Hazard Ratio (95% CI)** | **P Value†** |
| Secondary end points           |                               |                               |                               |                |
| Median time to pain progression (mo) | NR                      | 16.6                         | 0.70 (0.58–0.83)             | <0.001         |
| Median time to PSA progression (mo) | 33.2                    | 7.4                          | 0.30 (0.26–0.35)             | <0.001         |
| Median time to next symptomatic skeletal event (mo) | NR                      | NR                           | 0.70 (0.54–0.92)             | 0.009          |
| Median time to chemotherapy (mo) | NR                      | 38.9                         | 0.44 (0.35–0.56)             | <0.001         |
| Median time to subsequent prostate cancer therapy (mo) | NR                      | 21.6                         | 0.42 (0.35–0.50)             | <0.001         |
| Exploratory end point          |                               |                               |                               |                |
| Patients with a PSA response (%)‡ | 91                       | 67                           | 1.36 (1.28–1.45)             | <0.001         |

* CI denotes confidence interval, PSA prostate-specific antigen, and NR not reached.
† P values for secondary end points were calculated by means of a stratified log-rank test and those for the exploratory end point by means of a chi-square test.
‡ A PSA response was defined as a decrease of at least 50% from the baseline value. The comparison for this exploratory end point was calculated as an odds ratio.
The numbers of patients with serious adverse events were similar in the two groups. The frequency of adverse events leading to treatment discontinuation was 12% in the abiraterone group and 10% in the placebo group (Table S6 in the Supplementary Appendix). Adverse events that led to a dose modification or interruption were reported in 32% of the patients in the abiraterone group and in 17% of those in the placebo group. Grade 3 mineralocorticoid-related toxic effects of special interest, including hypertension and hypokalemia, occurred at a higher frequency in the abiraterone group than in the placebo group; rates of grade 3 and grade 4 hypertension were 20% and 0%, respectively, in the abiraterone group and 10% and 0.2%, respectively, in the placebo group; rates of hypokalemia were 10% and 0.8% in the abiraterone group and of 1% and 0.2% in the placebo group (Table 2).

**Discussion**

In this phase 3 trial involving men with high-risk, newly diagnosed, metastatic, castration-sensitive prostate cancer, the rate of overall survival was significantly higher among those who received androgen-deprivation therapy plus abiraterone and prednisone than among those who received androgen-deprivation therapy plus placebos, with a 38% lower relative risk of death in 48% of those in the placebo group (Table 2). The numbers of patients with serious adverse events were similar in the two groups. The frequency of adverse events leading to treatment discontinuation was 12% in the abiraterone group and 10% in the placebo group (Table S6 in the Supplementary Appendix). Adverse events that led to a dose modification or interruption were reported in 32% of the patients in the abiraterone group and in 17% of those in the placebo group. Grade 3 mineralocorticoid-related toxic effects of special interest, including hypertension and hypokalemia, occurred at a higher frequency in the abiraterone group than in the placebo group; rates of grade 3 and grade 4 hypertension were 20% and 0%, respectively, in the abiraterone group and 10% and 0.2%, respectively, in the placebo group; rates of hypokalemia were 10% and 0.8% in the abiraterone group and of 1% and 0.2% in the placebo group (Table 2).
The addition of abiraterone plus prednisone to androgen-deprivation therapy also significantly prolonged radiographic progression-free survival (hazard ratio, 0.47) and all secondary endpoints. Since the between-group difference for overall survival was significant at the time of the first interim analysis and unblinding of the trial, this analysis is considered to be final.

We explored the utility of more effective blockade of the androgen-receptor axis with the addition of abiraterone to androgen-deprivation therapy in men with metastatic, castration-sensitive prostate cancer. Our data support the hypothesis that more effective inhibition of androgen-receptor signaling as a component of the initial systemic therapy in patients with castration-sensitive prostate cancer leads to improved outcomes. The clinical benefit that we observed contrasts with that from the many previous attempts with castration and first-generation androgen-receptor inhibitors,27,28 which showed only a small improvement with a combined androgen-blockade approach,29 presumably owing to the lower potency and partial agonist activity of these drugs. Several other ongoing randomized, phase 3 trials in this patient population are examining androgen receptor–signaling combina-

### Table 2. Adverse Events.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Abiraterone Group (N = 597)</th>
<th>Placebo Group (N = 602)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>558 (93)</td>
<td>557 (93)</td>
</tr>
<tr>
<td>Grade 3 or 4 adverse event</td>
<td>374 (63)</td>
<td>287 (48)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>165 (28)</td>
<td>146 (24)</td>
</tr>
<tr>
<td>Any adverse event leading to treat-</td>
<td>73 (12)</td>
<td>61 (10)</td>
</tr>
<tr>
<td>ment discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event leading to death</td>
<td>28 (5)</td>
<td>24 (4)</td>
</tr>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>219 (37)</td>
<td>121 (20)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>122 (20)</td>
<td>57 (10)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>98 (16)</td>
<td>31 (5)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>75 (13)</td>
<td>26 (4)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>87 (15)</td>
<td>25 (4)</td>
</tr>
<tr>
<td>AST increased</td>
<td>74 (12)</td>
<td>20 (3)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>74 (12)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8 (1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>54 (9)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>110 (18)</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>77 (13)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Spinal-cord compression</td>
<td>14 (2)</td>
<td>12 (2)</td>
</tr>
</tbody>
</table>

* Listed are the most common adverse events and events of special interest. The latter were selected on the basis of the safety profile of phase 2 and phase 3 studies of abiraterone. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

† Listed in descending order are events that were reported in at least 2% of the patients in either group. Among other events of special interest, grade 3 peripheral edema was reported in 0.3% of the patients in the abiraterone group and in 0.5% of those in the placebo group; grade 3 or 4 fluid retention or congestive heart failure was not reported in either group. Grade 3 hot flush was reported in one patient in the placebo group, and grade 1 irritability was reported in three patients in the abiraterone group.
tion therapies with androgen-deprivation therapy (Table S7 in the Supplementary Appendix) and are exploring whether these treatments can be added to androgen-deprivation therapy plus docetaxel in patients with metastatic, castration-sensitive prostate cancer. The assessment of efficacy of subsequent therapies, including the types of disease progression in patients who were receiving treatment, will require more long-term analysis.

Men with newly diagnosed, metastatic, castration-sensitive prostate cancer can have variable outcomes, so we purposely enrolled those who were considered to have at least two high-risk prognostic features (e.g., a Gleason score of ≥8, the presence of ≥3 bone lesions, or the presence of measurable visceral metastasis), all of which are associated with poor survival. In addition, 50% of the patients had symptomatic disease at baseline. The patient population appears to be similar to high-burden disease populations in the three randomized trials that evaluated androgen-deprivation therapy plus docetaxel, since the outcomes in the control groups were similar across those studies. After a median follow-up of 7 years in GETUG-15, a nonsignificant 22% reduction in the relative risk of death was observed in patients with high-volume disease. A significant 27% reduction in the relative risk of death (and a reduction of 37% in patients with high-volume disease) with androgen-deprivation therapy plus docetaxel was observed after a 53.7-month follow-up (approximately 50% of deaths) in CHAARTED. In STAMPEDE, a significant 24% risk reduction in death was observed among patients with metastatic, castration-sensitive prostate cancer. The STAMPEDE investigators now report in the journal the results of another trial of abiraterone plus prednisone in men with locally advanced or metastatic prostate cancer. In our trial, the efficacy of abiraterone, with a 38% reduction in the risk of death among patients who had not received previous treatment for metastatic disease, compares favorably with previous findings. Of note, the early use of abiraterone plus prednisone resulted in increased survival, even though more patients in the placebo group received life-prolonging treatments after progression.

The overall safety profile in the abiraterone group was consistent with those in previous studies involving patients with metastatic, castration-resistant prostate cancer, with an anticipated elevated incidence of mineralocorticoid-related hypertension and hypokalemia. The incidence of grade 3 hypertension in the abiraterone group as compared with the placebo group (20% vs. 10%) was greater than that observed in previous studies of abiraterone involving patients with metastatic, castration-resistant prostate cancer. However, this difference may be attributable to our use of stricter grading with version 4.0 of the Common Terminology Criteria for Adverse Events.

The increased rate of hypertension in the abiraterone group did not appear to have any serious sequelae; 2 patients in each group died of stroke, and 10 patients in the abiraterone group and 6 in the placebo group died of cardiac disorders. The incidence of hypokalemia was also higher than that reported in previous phase 3 studies of abiraterone involving patients with metastatic, castration-sensitive prostate cancer, but only 2 patients discontinued treatment because of hypokalemia and there were no hypokalemia-related deaths. The apparent increase in mineralocorticoid-associated adverse events may reflect the fact that the prednisone dose used in our trial was lower than that used in previous studies of abiraterone (5 mg vs. 10 mg) but may also be related to the longer duration of abiraterone treatment in our trial than in previous trials (24 months in the LATITUDE trial vs. 13.8 months in COU-AA-302). The observed degrees of hypertension and hypokalemia were both medically manageable, only rarely required treatment discontinuation, and seldom led to serious consequences, all factors that point to the need for proper and timely management.

In conclusion, among men with newly diagnosed, metastatic, castration-sensitive prostate cancer, the addition of abiraterone plus prednisone to androgen-deprivation therapy was associated with longer overall survival and longer radiographic progression-free survival than was androgen-deprivation therapy alone. Rates of grade 3 hypertension and hypokalemia were higher in the abiraterone group.

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

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