Olaparib for Metastatic Castration-Resistant Prostate Cancer


ABSTRACT

BACKGROUND
Multiple loss-of-function alterations in genes that are involved in DNA repair, including homologous recombination repair, are associated with response to poly(adenosine diphosphate–ribose) polymerase (PARP) inhibition in patients with prostate and other cancers.

METHODS
We conducted a randomized, open-label, phase 3 trial evaluating the PARP inhibitor olaparib in men with metastatic castration-resistant prostate cancer who had disease progression while receiving a new hormonal agent (e.g., enzalutamide or abiraterone). All the men had a qualifying alteration in prespecified genes with a direct or indirect role in homologous recombination repair. Cohort A (245 patients) had at least one alteration in BRCA1, BRCA2, or ATM; cohort B (142 patients) had alterations in any of 12 other prespecified genes, prospectively and centrally determined from tumor tissue. Patients were randomly assigned (in a 2:1 ratio) to receive olaparib or the physician’s choice of enzalutamide or abiraterone (control). The primary end point was imaging-based progression-free survival in cohort A according to blinded independent central review.

RESULTS
In cohort A, imaging-based progression-free survival was significantly longer in the olaparib group than in the control group (median, 7.4 months vs. 3.6 months; hazard ratio for progression or death, 0.34; 95% confidence interval, 0.25 to 0.47; P<0.001); a significant benefit was also observed with respect to the confirmed objective response rate and the time to pain progression. The median overall survival in cohort A was 18.5 months in the olaparib group and 15.1 months in the control group; 81% of the patients in the control group who had progression crossed over to receive olaparib. A significant benefit for olaparib was also seen for imaging-based progression-free survival in the overall population (cohorts A and B). Anemia and nausea were the main toxic effects in patients who received olaparib.

CONCLUSIONS
In men with metastatic castration-resistant prostate cancer who had disease progression while receiving enzalutamide or abiraterone and who had alterations in genes with a role in homologous recombination repair, olaparib was associated with longer progression-free survival and better measures of response and patient-reported end points than either enzalutamide or abiraterone. (Funded by AstraZeneca and Merck Sharp & Dohme; PROfound ClinicalTrials.gov number, NCT02987543.)
METASTATIC CASTRATION-RESISTANT prostate cancer is a heterogeneous disease with poor outcomes.14 Tumors in up to 30% of patients harbor deleterious aberrations in genes involved in repairing DNA damage.1-3 Among the most common of these alterations, BRCA1 and BRCA2 are well-characterized genes involved in homologous recombination repair, and ATM functions as a DNA-damage checkpoint and indirectly activates homologous recombination repair.7,8 Loss-of-function alterations in these and other genes with a direct or indirect role in homologous recombination repair are associated with more aggressive prostate cancers.9,11 Such gene alterations confer sensitivity to poly(adenosine diphosphate–ribose) polymerase (PARP) inhibition in prostate and other cancers.12-19 The response to PARP inhibition may occur through multiple mechanisms, including PARP trapping, which is the physical obstruction of replication forks leading to DNA double-strand breaks and defects in homologous recombination repair.20

The PROfound trial is a prospective, biomarker-selected, phase 3 trial involving men with metastatic castration-resistant prostate cancer who had disease progression while receiving a new hormonal agent (e.g., enzalutamide or abiraterone). Patients with a qualifying alteration in prespecified genes with a direct or indirect role in homologous recombination repair were randomly assigned to receive the PARP inhibitor olaparib or the physician’s choice of either enzalutamide or abiraterone (control group). The primary objective was efficacy, as assessed by blinded independent central review of imaging-based progression-free survival in patients with alterations in BRCA1, BRCA2, or ATM.

METHODS

PATIENTS

Eligible patients were men (≥18 years of age) with confirmed metastatic castration-resistant prostate cancer whose disease had progressed during treatment with enzalutamide or abiraterone, administered for metastatic or nonmetastatic castration-resistant prostate cancer or for metastatic hormone-sensitive prostate cancer. Previous taxane chemotherapy was allowed. Men without previous surgical castration were required to continue luteinizing-hormone–releasing hormone analogue therapy. All the patients had adequate organ and bone marrow function. Full eligibility criteria are provided in the trial protocol, available with the full text of this article at NEJM.org. All the patients provided written informed consent.

An investigational clinical trial assay, based on the FoundationOne CDx next-generation sequencing test developed in partnership with Foundation Medicine, was used to prospectively identify patients with qualifying deleterious or suspected deleterious alterations in at least 1 of the 15 prespecified genes selected for their direct or indirect role in homologous recombination repair: BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L. Tumor testing was conducted centrally with the use of archival or recent biopsy tissue from primary or metastatic disease. The presence of a deleterious or suspected deleterious alteration according to the central tumor test was required for eligibility, irrespective of the zygosity of the alteration. Additional details are provided in the Supplementary Appendix, available at NEJM.org. Exploratory analyses of germline as compared with somatic origin and variant zygosity are being investigated and are not reported here.

TRIAL DESIGN AND INTERVENTIONS

This was a prospective, randomized, open-label, phase 3 trial. Eligible patients were included in one of two cohorts depending on their qualifying gene alteration. Patients with at least one alteration in BRCA1, BRCA2, or ATM were assigned to cohort A, regardless of co-occurring qualifying alterations in any of the other genes. Patients with alterations in any of the other 12 genes were assigned to cohort B. The overall population comprised patients from cohort A and cohort B (i.e., patients with a qualifying alteration in any of the 15 prespecified genes).

A central interactive voice-response or Web-response system was used to randomly assign patients in a 2:1 ratio to receive the standard dose of olaparib tablets (300 mg twice daily) or the prespecified physician’s choice of enzalutamide (160 mg once daily) or abiraterone (1000 mg once daily, plus prednisone at a dose of 5 mg twice daily) (control group). Randomization was stratified according to previous taxane use (yes or no) and measurable disease (yes or no). Measurable disease was determined by investigators at base-
line according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (longest diameter of soft-tissue lesions, ≥10 mm; short-axis diameter of lymph nodes, ≥15 mm). Treatment was continued until objective imaging-based disease progression, assessed by blinded central review by an independent third-party vendor, or until the occurrence of unacceptable toxic effects. Patients who were assigned to the control group were eligible to cross over to receive olaparib treatment after independent review–confirmed imaging-based progression (see the Supplementary Appendix).

**END POINTS**

The primary end point was imaging-based progression-free survival, assessed by an independent review committee, in patients with at least one alteration in BRCA1, BRCA2, or ATM (cohort A). Imaging-based progression-free survival was defined as the time from randomization until soft-tissue disease progression (by RECIST, version 1.1), bone lesion progression (by Prostate Cancer Clinical Trials Working Group 3 criteria), or death (see the Supplementary Appendix). A prespecified sensitivity analysis that was based on investigator assessment was performed. Imaging-based progression-free survival as assessed by independent review in the overall population was a key secondary end point.

Additional secondary end points included the confirmed objective response rate (defined as the percentage of patients who had an imaging-based complete response or partial response), the time to pain progression, overall survival (including a prespecified interim analysis, which is reported here), a reduction of at least 50% in the concentration of prostate-specific antigen (PSA) (PSA_{50} response), and the circulating-tumor-cell conversion rate (defined as the percentage of patients with a decrease in the number of circulating tumor cells from ≥5 cells per 7.5 ml of whole blood at baseline to <5 cells per 7.5 ml after baseline). The response rate was assessed among patients who could be evaluated and who had measurable disease at baseline as assessed by independent review according to RECIST, version 1.1. A prespecified sensitivity analysis for the crossover effect on overall survival was performed. Safety was assessed in the overall population through reporting of adverse events according to the Common Terminology Criteria Adverse Events, version 4.0, and collection of blood samples for clinical chemical and hematologic analyses. Assessments are described in the Supplementary Appendix.

**TRIAL OVERSIGHT**

This trial was performed in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca and Merck policies on bioethics. The trial was designed by representatives of AstraZeneca in collaboration with the trial steering committee. AstraZeneca was responsible for overseeing the collection, analysis, and interpretation of the data. All the authors had full access to the data. Merck provided input regarding the interpretation of the data. The manuscript was written with medical writing assistance funded by AstraZeneca and Merck Sharp & Dohme, with critical review and input by the authors. The authors attest to the accuracy and completeness of the data and the fidelity of the trial to the protocol.

**STATISTICAL ANALYSIS**

Efficacy data were analyzed on an intention-to-treat basis, and safety data were reported for all the patients who received at least one dose of a trial drug. With a sample size of approximately 240 patients in cohort A, 143 progression events or deaths (approximately 60% maturity) would provide the trial with 95% power, at a two-sided significance level of 5%, to show a significant difference in imaging-based progression-free survival between the olaparib group and the control group, under the assumption of a hazard ratio for progression or death of 0.53. For time-to-event end points, imaging-based progression-free survival, time to pain progression, and overall survival, P values were calculated with the use of stratified log-rank tests. Hazard ratios and 95% confidence intervals were calculated with the use of Cox proportional-hazards models, with stratification factors as covariates. The Kaplan–Meier method was used to calculate medians for each trial group. Logistic-regression models that were adjusted for stratification factors were used to analyze objective responses.

A multiple-testing procedure was used to control for the trial-wide type I error rate. If the primary end point in cohort A showed statistical significance, testing of key secondary end points was to be performed in a hierarchical manner:
objective response rate (in cohort A), imaging-based progression-free survival (in the overall population), time to pain progression (in cohort A), and overall survival (in cohort A), according to the sequential calculation of a two-sided alpha level of 0.05 (Fig. S1 in the Supplementary Appendix). For overall survival, the two-sided 5% level of alpha was split at the interim analysis (0.01) and final analysis (0.047) with the use of an O’Brien–Fleming spending function. Additional details are available in the Supplementary Appendix, and the statistical analysis plan is available with the protocol.

RESULTS

SCREENING AND RANDOMIZATION

Overall, 4425 patients were enrolled for screening at 206 sites in 20 countries; 4047 patients had tumor tissue available for testing. Of these samples, 2792 (69%) were successfully sequenced with a biomarker status outcome reported. A qualifying alteration in 1 or more of the 15 prespecified genes with a direct or indirect role in homologous recombination repair was detected in 778 of 2792 patients (28%). Of these patients, 387 (50%) met all eligibility criteria and thus underwent randomization from April 2017 through November 2018. (For details on screening, randomization, and follow-up, see Fig. S2.)

PATIENT CHARACTERISTICS

In cohort A, 162 patients were randomly assigned to receive olaparib and 83 to the control treatment. In cohort B, 94 patients were randomly assigned to receive olaparib and 48 to the control treatment. The alteration status for the prespecified genes is summarized in Table S2. Although baseline characteristics appeared balanced overall between the olaparib group and the control group, the control group had a higher percentage of patients with visceral metastases and a higher overall between the olaparib group and the control group (7.4 months vs. 3.6 months; hazard ratio for progression or death, 0.34; 95% confidence interval [CI], 0.25 to 0.47; P<0.001) (Fig. 1A). A prespecified sensitivity analysis that was based on investigator assessment yielded similar results to the primary analysis (hazard ratio, 0.24; 95% CI, 0.17 to 0.34) (Table S4). Prespecified subgroup analyses are shown in Figure 2.

The confirmed objective response rate among patients who could be evaluated was 33% (28 of 84 patients) in the olaparib group and 2% (1 of 43 patients) in the control group (odds ratio for a qualitative alteration in 1 or more of the 15 prespecified genes with a direct or indirect role in homologous recombination repair was detected in 778 of 2792 patients (28%). Of these patients, 387 (50%) met all eligibility criteria and thus underwent randomization from April 2017 through November 2018. (For details on screening, randomization, and follow-up, see Fig. S2.)

Efficacy

Patients with at Least One Alteration in BRCA1, BRCA2, or ATM (Cohort A)

Analysis of the primary endpoint was performed after 174 of 245 patients in cohort A had had imaging-based progression by independent review or had died (data maturity, 71%; data cutoff date, June 4, 2019). The median imaging-based progression-free survival was significantly longer in the olaparib group than in the control group (7.4 months vs. 3.6 months; hazard ratio for progression or death, 0.34; 95% confidence interval [CI], 0.25 to 0.47; P<0.001) (Fig. 1A). A prespecified sensitivity analysis that was based on investigator assessment yielded similar results to the primary analysis (hazard ratio, 0.24; 95% CI, 0.17 to 0.34) (Table S4). Prespecified subgroup analyses are shown in Figure 2.

The confirmed objective response rate among patients who could be evaluated was 33% (28 of 84 patients) in the olaparib group and 2% (1 of 43 patients) in the control group (odds ratio for a qualitative alteration in 1 or more of the 15 prespecified genes with a direct or indirect role in homologous recombination repair was detected in 778 of 2792 patients (28%). Of these patients, 387 (50%) met all eligibility criteria and thus underwent randomization from April 2017 through November 2018. (For details on screening, randomization, and follow-up, see Fig. S2.)

Overall Population (Cohorts A and B)

In the overall population, the median imaging-based progression-free survival by independent review was significantly longer in the olaparib group than in the control group (median, 5.8
Table 1. Characteristics of the Patients at Baseline.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort A</th>
<th>Cohorts A and B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Olaparib (N = 162)</td>
<td>Control (N = 83)</td>
</tr>
<tr>
<td>Median age at randomization (range) — yr</td>
<td>68 (47–86)</td>
<td>67 (49–86)</td>
</tr>
<tr>
<td>Age ≥65 yr at randomization — no. (%)</td>
<td>108 (67)</td>
<td>60 (72)</td>
</tr>
<tr>
<td>Metastatic disease at initial diagnosis — no. (%)</td>
<td>38 (23)</td>
<td>19 (23)</td>
</tr>
<tr>
<td>Missing data</td>
<td>7 (4)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Gleason score ≥8 — no./total no. (%)†</td>
<td>105/157 (67)</td>
<td>54/80 (67)</td>
</tr>
<tr>
<td>Patients with alterations in a single gene — no. (%)‡</td>
<td>BRCA1 8 (5)</td>
<td>5 (6)</td>
</tr>
<tr>
<td></td>
<td>BRCA2 80 (49)</td>
<td>47 (57)</td>
</tr>
<tr>
<td></td>
<td>ATM 60 (37)</td>
<td>24 (29)</td>
</tr>
<tr>
<td></td>
<td>CDK12 NA</td>
<td>NA</td>
</tr>
<tr>
<td>Median PSA at baseline (IQR) — μg/liter</td>
<td>62.2 (21.9–280.4)</td>
<td>112.9 (34.3–317.1)</td>
</tr>
<tr>
<td>Measurable disease at baseline — no. (%)§</td>
<td>95 (59)</td>
<td>46 (55)</td>
</tr>
<tr>
<td>Metastases at baseline — no. (%)§</td>
<td>Bone only 57 (35)</td>
<td>23 (28)</td>
</tr>
<tr>
<td></td>
<td>Visceral: lung or liver 46 (28)</td>
<td>32 (39)</td>
</tr>
<tr>
<td></td>
<td>Other 49 (30)</td>
<td>23 (28)</td>
</tr>
<tr>
<td>ECOG performance status — no. (%)</td>
<td>0 84 (52)</td>
<td>34 (41)</td>
</tr>
<tr>
<td></td>
<td>1 67 (41)</td>
<td>46 (55)</td>
</tr>
<tr>
<td></td>
<td>2 11 (7)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Missing data</td>
<td>0 0</td>
<td>0</td>
</tr>
<tr>
<td>Previous new hormonal agent — no. (%)¶</td>
<td>Enzalutamide only 68 (42)</td>
<td>40 (48)</td>
</tr>
<tr>
<td></td>
<td>Abiraterone only 62 (38)</td>
<td>29 (35)</td>
</tr>
<tr>
<td></td>
<td>Enzalutamide and abiraterone 32 (20)</td>
<td>14 (17)</td>
</tr>
<tr>
<td>Previous taxane use — no. (%)§</td>
<td>106 (65)</td>
<td>52 (63)</td>
</tr>
<tr>
<td></td>
<td>Docetaxel only 74 (46)</td>
<td>32 (39)</td>
</tr>
<tr>
<td></td>
<td>Cabazitaxel only 2 (1)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Docetaxel and cabazitaxel 29 (18)</td>
<td>20 (24)</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel only 1 (&lt;1)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Cohort A included patients with at least one alteration in BRCA1, BRCA2, or ATM. Cohort B included patients with alterations in any of 12 other prespecified genes: BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RADS1B, RADS1C, RADS1D, and RAD54L. In both cohorts, patients in the control group received the physician’s choice of enzalutamide or abiraterone. ECOG denotes Eastern Cooperative Oncology Group, IQR interquartile range, NA not applicable, and PSA prostate-specific antigen.

† In general, scores on the Gleason scale range from 6 to 10, with higher scores indicating a worse prognosis.

‡ A total of 28 patients (21 in cohort A and 7 in cohort B) had mutations in more than one gene. A total of 4 patients were incorrectly assigned to cohort B (1 in the olaparib group had an alteration in BRCA2, 1 in the control group had alterations in BRCA2 and CDK12, and 2 in the olaparib group had alterations in ATM).

§ Data were derived from electronic case-report forms as assessed by the investigator.

¶ A total of 13 patients received a new hormonal agent for disease before a diagnosis of metastatic castration-resistant prostate cancer; all others received a new hormonal agent after the development of metastatic castration-resistant prostate cancer.
The New England Journal of Medicine

A Imaging-Based Progression-free Survival in Cohort A

No. at Risk
Olaparib 162 149 126 116 102 101 82 77 56 53 42 37 26 24 18 11 11 3 2 0 0 0
Control 83 79 47 44 22 20 13 12 7 6 3 3 2 2 1 1 1 0 0 0

B Interim Overall Survival in Cohort A

No. at Risk
Olaparib 162 158 155 152 150 147 141 136 125 115 95 86 76 67 59 50 46 33 26 17 11 4 3 2 0 0
Control 83 82 79 76 74 72 69 69 54 50 44 40 34 29 25 23 18 15 11 9 6 3 1 1 0 0

C Imaging-Based Progression-free Survival in Cohorts A and B

No. at Risk
Olaparib 256 239 188 176 145 143 106 100 67 63 48 43 31 28 21 11 11 3 2 0 0 0
Control 131 123 73 67 38 35 20 19 9 8 5 5 5 3 3 2 2 1 1 0 0 0

Hazard ratio for progression or death,
0.34 (95% CI, 0.25–0.47)
P<0.001

Hazard ratio for death,
0.64 (95% CI, 0.43–0.97)
P=0.02

Hazard ratio for progression or death,
0.49 (95% CI, 0.38–0.63)
P<0.001
Among patients who could be evaluated, the confirmed objective response rate was 22% (30 of 138 patients) in the olaparib group and 4% (3 of 67 patients) in the control group (odds ratio, 5.93; 95% CI, 2.01 to 25.40). After 6 months, 85% of the patients in the olaparib group were free of pain progression, as compared with 75% in the control group (Fig. 3B). The median overall survival at interim analysis (data maturity, 41%) was 17.5 months in the olaparib group and 14.3 months in the control group (hazard ratio for death, 0.67; 95% CI, 0.49 to 0.93) (Fig. S3). Among patients in the control group with independent review—confirmed imaging-based progression, 82% crossed over to olaparib treatment.

Among patients who could be evaluated, a PSA$_{\text{m}}$ response was confirmed in 30% (73 of 243) in the olaparib group and 10% (12 of 123) in the control group. Among patients who could be evaluated, 27% (41 of 153) in the olaparib group and 10% (7 of 68) in the control group had conversion of circulating tumor cells. Results of exploratory analyses of efficacy in genomic subgroups and in patients with genes other than BRCA1, BRCA2, or ATM are provided in the Supplementary Appendix.

SAFETY

The median total duration of assigned treatment for patients in the overall population (cohorts A and B) was 7.4 months (range, 0 to 22.7) in the olaparib group and 3.9 months (range, 0.6 to 19.5) in the control group. The incidence of adverse events of grade 3 or higher — irrespective of attribution, dose modification, and treatment discontinuation owing to adverse events — was higher with olaparib than with the control treatment (Table 2). The most common adverse events of any grade were anemia, nausea, and fatigue or asthenia with olaparib and fatigue or asthenia with the control treatment. A total of 11 cases of pulmonary embolism (4% of patients) were reported in the olaparib group, as compared with 1 (1%) in the control group; none were fatal. No reports of myelodysplastic syndromes or acute myeloid leukemia were noted. Three patients reported new primary cancers: 1 in the olaparib group (glioma) and 2 in the control group (gastric cancer and transitional-cell carcinoma). One death in each group was considered by the investigators to be related to trial treatment. (For more details on safety, see the Supplementary Appendix.)

FIGURE 1 (facing page). Kaplan–Meier Estimates of Imaging-Based Progression-free Survival and Interim Overall Survival.

Panel A shows imaging-based progression-free survival, as assessed by blinded independent central review, in patients with at least one alteration in BRCA1, BRCA2, or ATM (cohort A), who received either olaparib or the physician’s choice of enzalutamide or abiraterone (control group); Panel B shows interim overall survival in the same cohort. For patients with censored data in cohort A, the median duration of follow-up for imaging-based progression-free survival was 7.5 months in the olaparib group and 5.4 months in the control group; the median duration of follow-up for overall survival was 12.6 months and 13.2 months, respectively. Panel C shows imaging-based progression-free survival in cohorts A and B (overall population); patients in cohort B had alterations in any of 12 other prespecified genes. For patients with censored data in the overall population, the median duration of follow-up for imaging-based progression-free survival was 7.4 months in the olaparib group and 5.5 months in the control group. Overall, at the time of the analysis of imaging-based progression-free survival by blinded independent central review, 10 patients (4%) in the olaparib group and 8 (6%) in the control group had withdrawn consent, and their data were censored. (For interim overall survival in the overall population, see Fig. S3.)

DISCUSSION

Our findings validate phase 1 and 2 data on the antitumor activity of olaparib in metastatic castration-resistant prostate cancer.\textsuperscript{14,15,19,22} Imaging-based progression-free survival was significantly longer in the olaparib group than in the control group among patients with at least one alteration in BRCA1, BRCA2, or ATM (cohort A), with a 66% lower risk of disease progression or death. Prespecified subgroup analyses of baseline demographic, disease, and clinical characteristics showed a consistency of treatment effect in favor of olaparib over the control treatment. Among patients with at least one alteration in BRCA1, BRCA2, or ATM, an interim analysis of overall

N ENGL J MED 382;22 NEJM.ORG MAY 28, 2020

The New England Journal of Medicine

Downloaded from nejm.org at Radboud University Nijmegen on October 8, 2021. For personal use only. No other uses without permission. Copyright © 2020 Massachusetts Medical Society. All rights reserved.
Figure 2. Prespecified Subgroup Analysis of Imaging-Based Progression-free Survival.

Shown is the subgroup analysis of patients in cohort A (Panel A) and those in the overall population (cohorts A and B) (Panel B). Subgroups in which fewer than five progression events or deaths occurred per group were not included in the analysis. The sizes of the circles are proportional to the number of events. The dashed line indicates the point of no effect (hazard ratio, 1.00). A hazard ratio of less than 1.00 favors olaparib. ECOG denotes Eastern Cooperative Oncology Group, and PSA prostate-specific antigen.
survival (secondary end point) showed a benefit for olaparib that was not significant. The survival benefit may have been obscured by the more than 80% crossover to olaparib among the patients in the control group whose disease had progressed. In addition to the imaging findings, the delay in pain progression in the olaparib group showed a direct patient benefit for olaparib as compared with the control treatment among patients with at least one alteration in \( BRCA1 \), \( BRCA2 \), or \( ATM \).

Olaparib was also associated with a significantly longer duration of imaging-based progression-free survival than the control treatment in the overall population (patients with an alteration in any of the 15 prespecified genes), although this finding may also reflect the benefit seen in a subgroup of patients including the population with \( BRCA1 \) or \( BRCA2 \) alterations. This treatment benefit was supported by findings on overall survival and other clinical end points in this broader population.

Our results in this randomized trial are broadly consistent with preliminary observations in a small number of patients receiving rucaparib or niraparib monotherapy in similar study popu-
The TOPARP-A and -B studies showed that tumors with BRCA1 or BRCA2 alterations were more sensitive to olaparib monotherapy than tumors harboring any of the other homologous recombination repair–related genes studied.\textsuperscript{15} Gene-level analyses in our trial are complex, and comparisons may be confounded by multiple considerations including sample size and treatment history; however, exploratory analyses suggest that patients with BRCA1 or BRCA2 alterations derived the most benefit. It is important that olaparib showed activity in patients with alterations in other prespecified genes with a direct or indirect role in homologous recombination repair; detailed analyses are ongoing.

Drug administration was nearly twice as long in the olaparib group as in the control group, which may have contributed to the higher incidence of certain adverse events (e.g., peripheral edema, back pain, and constipation) in the olaparib group. The safety profile of olaparib was similar to that described in other monotherapy studies.\textsuperscript{16,18} Pulmonary embolism is not a recognized complication of olaparib treatment, and the clinical significance of the occurrence of these cases is difficult to interpret.

The physician’s choice of either enzalutamide or abiraterone was selected as the comparator because switching between these agents does occur in practice, despite the lack of randomized

---

### Table 2. Adverse Events in the Overall Population (Cohorts A and B).*<sup>†</sup>

<table>
<thead>
<tr>
<th>Event</th>
<th>Olaparib (N = 256)</th>
<th>Control (N = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (number (percent))</td>
<td>Grade ≥3 (number (percent))</td>
</tr>
<tr>
<td>Any</td>
<td>244 (95)</td>
<td>130 (51)</td>
</tr>
<tr>
<td>Anemia†</td>
<td>119 (46)</td>
<td>55 (21)</td>
</tr>
<tr>
<td>Nausea</td>
<td>106 (41)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>105 (41)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>77 (30)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>54 (21)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>47 (18)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>45 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>35 (14)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>32 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>28 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>26 (10)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>24 (9)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>18 (7)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Interruption of intervention due to adverse event</td>
<td>115 (45)</td>
<td>NA</td>
</tr>
<tr>
<td>Dose reduction due to adverse event</td>
<td>57 (22)</td>
<td>NA</td>
</tr>
<tr>
<td>Discontinuation of intervention due to adverse event</td>
<td>46 (18)</td>
<td>NA</td>
</tr>
<tr>
<td>Death due to adverse event</td>
<td>10 (4)</td>
<td>NA</td>
</tr>
</tbody>
</table>

* The table shows adverse events of any grade (≥10% of patients in either group) with corresponding adverse events of grade 3 or higher according to the Common Terminology Criteria for Adverse Events and irrespective of attribution, dose modifications owing to adverse events, and dose discontinuations owing to adverse events.

† The anemia category includes anemia, decreased hemoglobin level, decreased red-cell count, decreased hematocrit level, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, and normocytic anemia. Anemia was reported in 46% of the patients, and a decreased hemoglobin level was reported in less than 1%.
evidence to support this approach. The sequencing of the new hormonal agents is not defined, and the antitumor activity that has been reported in prospective and retrospective studies has varied. Our trial included both patients who had not previously received chemotherapy and those who had, with nearly two thirds having previously received taxane therapy. Efficacy in cohort A and in the overall population was seen regardless of whether olaparib monotherapy was administered before chemotherapy or after chemotherapy.

In men with metastatic castration-resistant prostate cancer who had BRCA1, BRCA2, or ATM mutations and who had disease progression while receiving a new hormonal agent, olaparib led to a significantly longer imaging-based progression-free survival than the physician’s choice of enzalutamide or abiraterone. A benefit was also observed in the overall trial population with an alteration in any of the 15 prespecified genes with a direct or indirect role in homologous recombination repair. The most frequent adverse events with olaparib were anemia and nausea, as previously noted with the drug.16-18

Supported by AstraZeneca and Merck Sharp & Dohme (a subsidiary of Merck).

Dr. de Bono reports receiving consulting fees and advisory board fees from Astellas Pharma, AstraZeneca, Bayer HealthCare, Boehringer Ingelheim, Daiichi Sankyo, Genentech, GlaxoSmithKline, Janssen Global Services, Menarini Silicon Biosystems, Merck, Merck Sharp & Dohme, Orion, Pfizer, Qiagen Sciences, Sanofi-Aventis U.S., Sierra Oncology, Taiho Pharmaceutical, and Vertex Pharmaceuticals and holding a patent (WO/2005/053662) on DNA damage repair inhibitors for treatment of cancer, held by the Institute of Cancer Research and licensed to AstraZeneca, and a patent (US604213) on 17-substituted steroids useful in cancer treatment, held by the Institute of Cancer Research and licensed to Janssen Global Services; Dr. Mateo, receiving advisory board fees from Amgen, Clovis Oncology, and Janssen Pharmaceuticals, fees for serving on a speakers bureau from Astellas Pharma, and grant support and advisory board fees from AstraZeneca; Dr. Fizazi, receiving consulting fees from Astellas Pharma, Bayer, Janssen Global Services, and Sanofi Pasteur, consulting fees and writing assistance from AstraZeneca, Bristol-Myers Squibb, Merck, and Myovant Sciences, and consulting fees, advisory board fees, and writing assistance from Pfizer; Dr. Shore, receiving consulting fees from Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Clovis Oncology, Dendreon Pharmaceuticals, Ferring Pharmaceuticals, Janssen Global Services, Merck, Myovant Sciences, Nymox Pharmaceutical, Pfizer, Sanofi Pasteur Biologics, and Tolmar Pharmaceuticals; Dr. Sandhu, receiving grant support, paid to the Peter MacCallum Cancer Centre, from Amgen, Endocyte, and Genentech, grant support, paid to the Peter MacCallum Cancer Centre, and advisory fees from AstraZeneca and Merck, and advisory fees from Bristol-Myers Squibb and Merck Serono; Dr. Chi, receiving grant support, paid to BC Cancer, consulting fees, and lecture fees from Astellas Pharma, Janssen Pharmaceuticals, and Sanofi, grant support, paid to BC Cancer, and consulting fees from AstraZeneca, Bayer, and Roche, and consulting fees from Daiichi Sankyo, Pfizer, and Point Biopharma; Dr. Sartor, receiving grant support, paid to Tulane University, and consulting fees from AstraZeneca, Bayer, and Janssen Biotech and consulting fees from Clovis Oncology, Invitae, and Pfizer; Dr. Agarwal, receiving advisory board fees from Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Clovis Oncology, Eisai, Eli Lilly, EMD Serono, Exelixis, Foundation Medicine, Genentech, Janssen Biotech, Merck, Nektar Therapeutics, Novartis, Pfizer, Pharmacyclics (an AbbVie company), and Seattle Genetics; Dr. Olmos, receiving lecture fees, advisory board fees, and travel support from Astellas Pharma, receiving grant support, advisory board fees, and travel support from and serving on a steering committee for AstraZeneca, receiving grant support, advisory board fees, lecture fees, and travel support from Bayer HealthCare, receiving advisory board fees from Clovis Oncology and Daiichi Sankyo, serving on a steering committee for and receiving travel support from F. Hoffmann–La Roche, receiving advisory board fees and lecture fees and travel support from and serving on a steering committee for Genentech, receiving grant support, advisory board fees, lecture fees, and travel support from Janssen Pharmaceuticals, and receiving grant support, lecture fees, and advisory board fees from Sanofi; Dr. Thierry-Vuillemin, receiving consulting fees from Astellas Pharma, Ipsen Pharma, Janssen Biotech, Novartis, and Sanofi-Aventis U.S., consulting fees and travel support from AstraZeneca, Bristol-Myers Squibb, F. Hoffmann–La Roche, Merck Sharp & Dohme, and Pfizer, and travel support from Janssen Pharmaceuticals; Dr. Twardowski, receiving lecture fees and fees for serving on a speakers bureau from Astellas Pharma and Janssen Biotech; Dr. Mehra, receiving grant support, paid to Radboud University Medical Center, and advisory fees from Astellas Pharma Europe, Janssen Pharmaceuticals, Pfizer, and Roche, advisory fees from Bristol-Myers Squibb, advisory fees and travel support from Merck Sharp & Dohme, and grant support, paid to Radboud University Medical Center, from Sanofi; Drs. Goessl and Kang, being employed by and owning stock in AstraZeneca; Dr. Burgents, being employed by AstraZeneca and Merck Sharp & Dohme; Dr. Wu, being employed by and owning stock in AstraZeneca; Dr. Kohlmann, being employed by and owning shares and stock options in AstraZeneca; Dr. Adelman, being employed by and owning stock in AstraZeneca; Dr. Hussain, receiving lecture fees and travel support from Astellas Pharma, grant support, paid to Northwestern University, from AstraZeneca, grant support, paid to Northwestern University, and advisory board fees from Bayer, advisory board fees from Daiichi Sankyo, grant support, paid to Northwestern University, and advisory board fees from Genentech, grant support, paid to the University of Michigan, from Pfizer, and lecture fees from Sanofi and Genzyme. No other potential conflict of interest relevant to this article was reported.

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 who participated in the PROfound trial, their families and caregivers, and our coinvestigators; Allison Allen, Ph.D., of Global Medicines Development at AstraZeneca for her role as the trial medical scientist; Claire Corcoran, Ph.D., and Caroline Sibilla, Ph.D., of Precision Medicine, AstraZeneca, for their contributions in enabling delivery of diagnostic test results in the trial; and Debbi Gorman, Ph.D., of Mudskipper Business for medical writing assistance.
APPENDIX

The authors’ full names and academic degrees are as follows: Johann de Bono, M.B., Ch.B., Ph.D., Joaquin Mateo, M.D., Ph.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Neal Shore, M.D., Shahneen Sandhu, M.D., Kim N. Chi, M.D., Oliver Sartor, M.D., Neeraj Agarwal, M.D., David Olmos, M.D., Ph.D., Antoine Thiery-Vuillenem, M.D., Ph.D., Przemyslaw Twardowski, M.D., Niven Mehra, M.D., Ph.D., Carsten Goessl, M.D., Jin Yu Kang, M.D., Joseph Burgents, Ph.D., Wenting Wu, Ph.D., Alexander Kohlmann, Ph.D., Carrie A. Adelman, Ph.D., and Maha Hussain, M.B., Ch.B.

The authors’ affiliations are as follows: the Institute of Cancer Research and Royal Marsden Hospital, London (J. de Bono), and AstraZeneca, Translational Medicine, Cambridge (C.A.A.) — all in the United Kingdom; Vall d’Hebron Institute of Oncology and Vall d’Hebron University Hospital, Barcelona (J.M.), the Spanish National Cancer Research Center, Madrid (D.O.), and Hospitals Universitarios Virgen de la Victoria y Regional de Málaga, Málaga (D.O.) — all in Spain; Institut Gustave Roussy, University of Paris Sud, Villejuif (K.F.), and the Department of Cancer Medicine, Centre Hospitalier Universitaire Besançon, Besançon (A.T.-V.) — all in France; Centre Hospitalier de l’Université de Montréal—Centre de Recherche du Centre Hospitalier de l’Université de Montréal, Montreal (F.S.), and BC Cancer Organization, Vancouver (K.N.C.) — all in Canada; Carolina Urologic Research Center, Myrtle Beach, SC (N.S.); Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (S.S.); Tulane University School of Medicine, New Orleans (O.S.); Huntsman Cancer Institute, University of Utah Comprehensive Cancer Center, Salt Lake City (N.A.); John Wayne Cancer Institute, Santa Monica, CA (P.T.); Radboud University Medical Center, Nijmegen, the Netherlands (N.M.); AstraZeneca, Global Medicines Development, Oncology, Gaithersburg, MD (C.G., J.K., W.W.); Mereck, Kenilworth, NJ (J. Burgents); AstraZeneca, Precision Medicine, Oncology Research and Development, Gaithersburg, MD (A.K.); and the Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago (M.H.).

REFERENCES


Copyright © 2020 Massachusetts Medical Society.