ORIGINAL ARTICLE

Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer

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ABSTRACT

BACKGROUND

We previously reported that olaparib led to significantly longer imaging-based progression-free survival than the physician's choice of enzalutamide or abiraterone among men with metastatic castration-resistant prostate cancer who had qualifying alterations in homologous recombination repair genes and whose disease had progressed during previous treatment with a next-generation hormonal agent. The results of the final analysis of overall survival have not yet been reported.

METHODS

In an open-label, phase 3 trial, we randomly assigned patients in a 2:1 ratio to receive olaparib (256 patients) or the physician's choice of enzalutamide or abiraterone plus prednisone as the control therapy (131 patients). Cohort A included 245 patients with at least one alteration in *BRCA1*, *BRCA2*, or *ATM*, and cohort B included 142 patients with at least one alteration in any of the other 12 prespecified genes. Crossover to olaparib was allowed after imaging-based disease progression for patients who met certain criteria. Overall survival in cohort A, a key secondary end point, was analyzed with the use of an alpha-controlled, stratified log-rank test at a data maturity of approximately 60%. The primary and other key secondary end points were reported previously.

RESULTS

The median duration of overall survival in cohort A was 19.1 months with olaparib and 14.7 months with control therapy (hazard ratio for death, 0.69; 95% confidence interval [CI], 0.50 to 0.97; P=0.02). In cohort B, the median duration of overall survival was 14.1 months with olaparib and 11.5 months with control therapy. In the overall population (cohorts A and B), the corresponding durations were 17.3 months and 14.0 months. Overall, 86 of 131 patients (66%) in the control group crossed over to receive olaparib (56 of 83 patients [67%] in cohort A). A sensitivity analysis that adjusted for crossover to olaparib showed hazard ratios for death of 0.42 (95% CI, 0.19 to 0.91) in cohort A, 0.83 (95% CI, 0.11 to 5.98) in cohort B, and 0.55 (95% CI, 0.29 to 1.06) in the overall population.

CONCLUSIONS

Among men with metastatic castration-resistant prostate cancer who had tumors with at least one alteration in *BRCA1*, *BRCA2*, or *ATM* and whose disease had progressed during previous treatment with a next-generation hormonal agent, those who were initially assigned to receive olaparib had a significantly longer duration of overall survival than those who were assigned to receive enzalutamide or abiraterone plus prednisone as the control therapy, despite substantial crossover from control therapy to olaparib. (Funded by AstraZeneca and Merck Sharp & Dohme; PROfound ClinicalTrials.gov number, NCT02987543.)

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

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Metastatic castration-resistant prostate cancer remains lethal.[1] Men with deleterious alterations in genes involved in homologous recombination repair, such as *BRCA1* and *BRCA2*, have more aggressive disease and higher mortality than those with proficient homologous recombination repair.[2-12] The goal of treatment is to prolong survival while maintaining or improving quality of life.[13] Tumors with gene alterations that affect homologous recombination repair are sensitive to poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitors.[14-21] Findings from a phase 2 trial of the PARP inhibitor olaparib in patients with metastatic castration-resistant prostate cancer and homologous recombination deficiency were confirmed in the PROfound trial, a phase 3, randomized trial.[17,21,22]

The PROfound trial enrolled patients with metastatic castration-resistant prostate cancer who had alterations in at least 1 of 15 prespecified genes with a direct or indirect role in homologous recombination repair and whose disease had progressed during previous treatment with a next-generation hormonal agent. The overall population comprised patients who had at least one alteration in *BRCA1*, *BRCA2*, or *ATM* (cohort A) and patients with at least one alteration in any of the other 12 prespecified genes (cohort B). In cohort A, the patients who received olaparib had a significantly longer duration of imaging-based progression-free survival than those who received the physician's choice of enzalutamide or abiraterone plus prednisone (control) (hazard ratio for progression or death, 0.34; 95% confidence interval [CI], 0.25 to 0.47; P<0.001).[22] Benefits with olaparib were also shown with respect to the key secondary end points of confirmed objective response rate, defined as the percentage of patients who had an imaging-based complete response or partial response (higher with olaparib than with control), and time to pain progression in cohort A (longer with olaparib than control).[22] An exploratory analysis in cohort B revealed a hazard ratio (olaparib vs. control) for imaging-based progression or death of 0.88 (95% CI, 0.58 to 1.36) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[22] An interim analysis of overall survival in cohort A at a data maturity of 38% showed a median duration of overall survival of 18.5 months in the olaparib group, as compared with 15.1 months in the control group, despite substantial crossover from control therapy to olaparib.[22] Here, we report the results of the final prespecified analyses of overall survival in cohort A, a key secondary end point.

Methods

Trial Design and Patients

A detailed account of the methods, including all eligibility criteria, has been published previously.[22] Briefly, the trial enrolled men with metastatic castration-resistant prostate cancer whose disease had progressed during previous treatment with enzalutamide, abiraterone, or both. Previous taxane chemotherapy was allowed. All the patients provided written informed consent.

An investigational clinical trial assay, based on the FoundationOne CDx next-generation sequencing test that was developed in partnership with Foundation Medicine, was used to prospectively identify patients with a qualifying deleterious or suspected deleterious alteration in at least 1 of the following 15 prespecified genes, which were selected on the basis of 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* (Fig. S2). Confirmation of homologous recombination deficiency by means of a genomic instability test was not a requirement for patient eligibility.

Patients were randomly assigned in a 2:1 ratio to receive olaparib (300 mg twice daily) or the physician's choice of enzalutamide (160 mg once daily) or abiraterone (1000 mg once daily) plus prednisone (5 mg twice daily) (control). Subsequent therapies were administered at the discretion of the investigators. Patients who were assigned to the control group were allowed to cross over to receive olaparib as a first subsequent anticancer therapy if they had disease progression (verified by blinded, independent central review if it occurred before the primary analysis data cutoff date of June 4, 2019, or by site investigator review if it occurred thereafter), had not received other subsequent anticancer therapy, had no unresolved toxic effects from previous therapy that were uncontrolled or greater than grade 1 at the time of initiating treatment with olaparib, and had agreed to continue attending the scheduled trial visits.

END POINTS

Primary and key secondary end points were reported previously.[22] Overall survival (defined as the time from randomization to death from any cause regardless of whether the patient withdrew from the assigned therapy or received another anticancer therapy) in cohort A was a key alpha-controlled secondary end point. A prespecified sensitivity analysis was performed to explore the effect of crossover from control therapy to olaparib on overall survival. Prespecified subgroup analyses were also performed to assess the consistency of the treatment effect across potential prognostic factors. Central assessment of tumor response was stopped when imaging-based disease progression occurred during the assigned treatment. Imaging-based disease progression was defined as soft-tissue disease progression according to the Response Evaluation Criteria in Solid Tumors, version 1.1, or bone lesion progression according to the criteria of the Prostate Cancer Clinical Trials Working Group 3.

The time from randomization to a second progression (after a first event) or death was a secondary end point and was based on investigator assessment of either imaging-based or clinical disease progression or death; assessment was commenced after patients had begun a subsequent anticancer treatment. Adverse events were monitored throughout the trial and were graded according to the Common Terminology Criteria for Adverse Events, version 4.03.[23]

TRIAL OVERSIGHT

The trial was performed in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and the AstraZeneca and Merck policies on bioethics. Representatives of AstraZeneca designed the trial in collaboration with the trial steering committee and were responsible for overseeing the collection, analysis, and interpretation of the data. All the authors had full access to the data. Merck provided input regarding data interpretation. 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 vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org.

STATISTICAL ANALYSIS

A hierarchical multiple-testing procedure was used to control for the trial-wide type I error rate in the analyses of the primary end point of imaging-based progression-free survival (assessed by blinded independent central review), the key secondary end point of overall survival in cohort A, and the other key secondary end points, as reported previously (Fig. S3).[22] The final analysis of overall survival was performed on an intention-to-treat basis and was planned when approximately 60% of the patients in cohort A had died. According to the multiple testing procedure, overall survival in cohort A was analyzed with the use of a stratified log-rank test, with the two-sided alpha level of 5% split at the interim analysis (0.01) and final analysis (0.047) on the basis of an O'Brien–Fleming spending function.[24] The prespecified sensitivity analysis of overall survival that adjusted for the effect of crossover of patients from control therapy to olaparib was performed with the use of rank-preserving structural failure time models.[25,26] Because the statistical analysis plan (available with the protocol) did not include a provision for correcting for multiplicity when conducting tests for other secondary or exploratory end points, the results are reported as point estimates with 95% confidence intervals, and the widths of the confidence intervals should not be used to infer treatment effects.

The safety population comprised all patients who had undergone randomization and received at least one dose of a trial drug. Safety data were also collected from all the patients in the control group who had crossed over to receive olaparib in accordance with the protocol and received at least one dose of olaparib. Safety data were analyzed with the use of descriptive statistics. Additional details of the statistical methods are provided in the Supplementary Appendix and in the statistical analysis plan in the protocol. The data cutoff date for the final analysis of overall survival was March 20, 2020.

RESULTS

PATIENTS AND TREATMENT

The demographic and clinical characteristics of the patients at baseline are provided in Table S1.[22] At the time of the final analysis, 68 patients in the olaparib group and 33 in the control group remained in the trial; of these patients, 14 and 2,

respectively, were receiving olaparib or control therapy as assigned (Fig. S4). The crossover-adjusted analysis included 86 of 131 patients (66%) in the control group who had crossed over to receive olaparib; this subgroup included 83 of 99 patients (84%) who had disease progression and chose to cross over in accordance with the protocol and 3 additional patients who did not meet the crossover eligibility criteria and received olaparib outside of the trial.

OVERALL SURVIVAL

Cohort A

At the time of the final analysis of overall survival, 148 of 245 patients (60%) in cohort A had died, so the prespecified criteria for significance of the overall survival end point were met. The median duration of overall survival was 19.1 months with olaparib and 14.7 months with control therapy (hazard ratio for death, 0.69; 95% CI, 0.50 to 0.97; P=0.02) (Fig. 1A). A sensitivity analysis that adjusted for crossover from control therapy to olaparib showed a hazard ratio of 0.42 (95% CI, 0.19 to 0.91) (Fig. 1B).

Cohort B

At the time of the final analysis of overall survival, 100 of 142 patients (70%) in cohort B had died. The median duration of overall survival was 14.1 months with olaparib and 11.5 months with control therapy (hazard ratio for death, 0.96; 95% CI, 0.63 to 1.49) (Fig. 2A). After adjustment for crossover from control therapy to olaparib, the hazard ratio was 0.83 (95% CI, 0.11 to 5.98) (Fig. 2B). The role of *PPP2R2A* as a homologous recombination repair gene could not be validated on the basis of preclinical data (Fig. S9), and no benefit of olaparib over control therapy with respect to overall survival was noted among patients who had alterations in *PPP2R2A* (hazard ratio for death, 5.11; 95% CI, 1.10 to 35.73) (Fig. S5B). In a post hoc exploratory sensitivity analysis that excluded these patients from cohort B, the hazard ratio for death was 0.79 (95% CI, 0.51 to 1.25) for the comparison between olaparib and control therapy, and the median duration of overall survival was 14.2 months with olaparib and 10.8 months with control therapy (Fig. S10A).

Overall Population

After the death of 248 of 387 patients (64%) in the overall population (cohorts A and B), the median duration of overall survival was 17.3 months with olaparib and 14.0 months with control therapy (hazard ratio for death, 0.79; 95% CI, 0.61 to 1.03) (Fig. 3A). After adjustment for crossover from control therapy to olaparib, the hazard ratio was 0.55 (95% CI, 0.29 to 1.06) (Fig. 3B). In a sensitivity analysis that excluded patients who had alterations in *PPP2R2A*, the hazard ratio was 0.76 (95% CI, 0.58 to 1.00), and the median duration of overall survival was 17.4 months with olaparib and 13.6 months with control therapy (Fig. S10B).

Prespecified Subgroup Analyses

In cohort A, prespecified subgroup analyses according to demographic and clinical characteristics at baseline, including previous use of taxane (yes vs. no), are shown in Figure 4. When these same prespecified analyses were performed in the overall population, the benefit of olaparib over control therapy with respect to overall survival was less clear than in cohort A (Fig. S5A).

Exploratory Gene-Level Analyses

Exploratory gene-level analyses showed hazard ratios for death (olaparib vs. control) of 0.42 (95% CI, 0.12 to 1.53) among patients with an alteration in only *BRCA1* and 0.59 (95% CI, 0.37 to 0.95) among patients with an alteration only in *BRCA2*; exploratory gene-level analyses of other genes were also performed when there were sufficient numbers of patients and events (Figs. S5B and S6). The hazard ratio for death among patients with an alteration in any non-*BRCA* gene was 0.95 (95% CI, 0.68 to 1.34) in the intention-to-treat population; after adjustment for crossover, the hazard ratio was 0.82 (95% CI, 0.25 to 2.68) (Fig. S7A). Findings from exploratory analyses that included patients with an alteration in only *ATM* or *CDK12* are shown in Figure S7B and S7C. Post hoc subgroup analyses according to previous use of taxane in patients with an alteration in only *BRCA1* or *BRCA2*, *ATM*, or *CDK12* are shown in Figure S8.

TIME TO SECOND PROGRESSION OR DEATH

The median time until a second progression or death in cohort A, as assessed by the investigators, was 15.5 months with olaparib and 10.6 months with control therapy (hazard ratio for second progression or death, 0.64; 95% CI, 0.45 to 0.93) (Fig. S11A). The corresponding values in cohort B were 9.9 months and 7.9 months (hazard ratio, 0.77; 95% CI, 0.50 to 1.21) (Fig. S11B); in the overall population, the values were 13.4 months

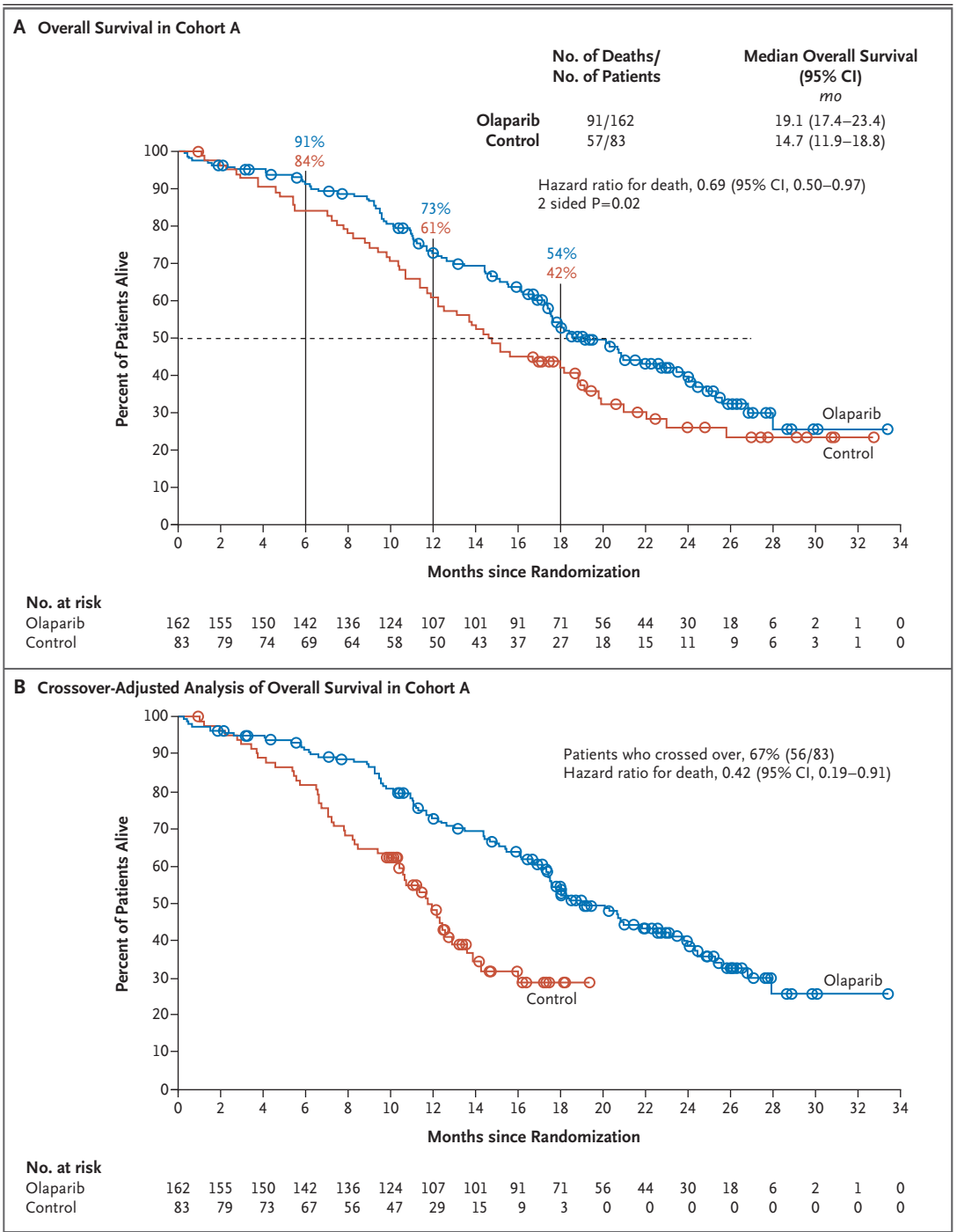
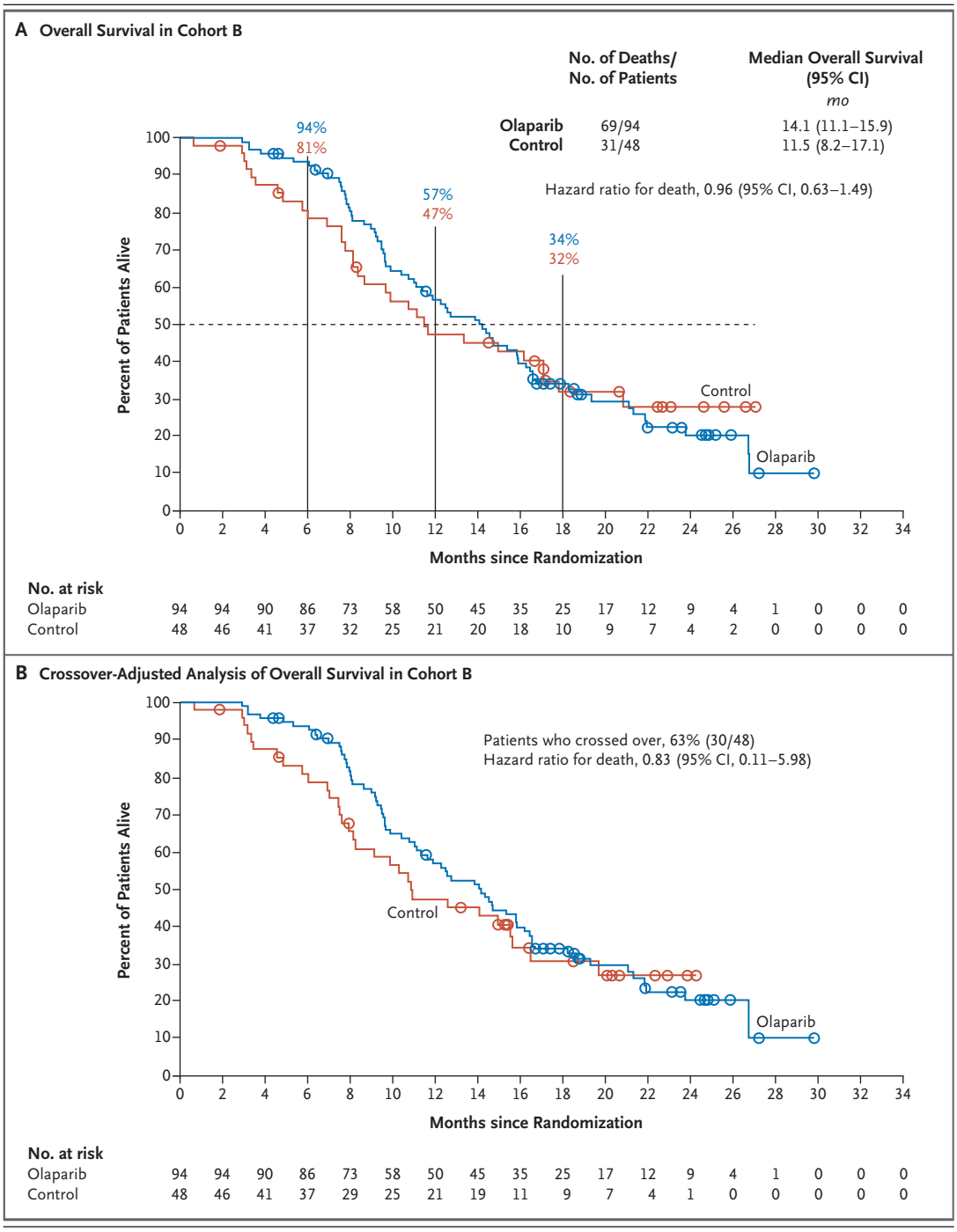


Figure 1. Kaplan–Meier Estimates of Overall Survival and Corresponding Crossover-Adjusted Sensitivity Analyses in Cohort A.

Panel A shows overall survival among the patients in the intention-to-treat population who had at least one alteration in *BRCA1*, *BRCA2*, or *ATM* (cohort A). Panel B shows overall survival in cohort A, as adjusted with the use of a rank-preserving structural failure time model (with a recensoring approach to avoid possible informative censoring bias) to show the effect of crossover of patients from control therapy to olaparib as a subsequent anticancer therapy. For the patients who had censored data, the median duration of follow-up was 21.9 months among those in the olaparib group and 21.0 months among those in the control group. The alpha spent at the final analysis of overall survival was 0.047. Among the 83 patients in cohort A who were assigned to the control group, 56 (67%) crossed over to receive olaparib.



and 9.7 months (hazard ratio, 0.68; 95% CI, 0.51 to 0.90) (Fig. S11C).

SUBSEQUENT ANTICANCER THERAPIES

In cohort A, 79 of 162 patients (49%) in the olaparib group and 64 of 83 patients (77%) in the control group received a subsequent anticancer therapy; the corresponding values in the overall population were 129 of 256 patients (50%) and 96 of 131 patients (73%) (Table S2). Among the 64 patients in the control group in cohort A who received a subsequent anticancer therapy, 56 (67%) received olaparib and 8 (10%) received a different anticancer therapy, with no use of olaparib. The most common subsequent therapies other than olaparib were docetaxel

Figure 2 (facing page). Kaplan–Meier Estimates of Overall Survival and Corresponding Crossover-Adjusted Sensitivity Analyses in Cohort B.

Panel A shows overall survival among the patients in the intention-to-treat population who had at least one alteration in one of the prespecified genes with a direct or indirect role in homologous recombination repair other than *BRCA1*, *BRCA2*, or *ATM* (cohort B). The 12 other prespecified genes included *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. Panel B shows overall survival in cohort B, as adjusted with the use of a rank-preserving structural failure time model (with a recensoring approach to avoid possible informative censoring bias) to show the effect of crossover of patients from control therapy to olaparib as a subsequent anticancer therapy. For the patients who had data that were censored, the median duration of follow-up was 18.7 months among those in the olaparib group and 18.3 months in the control group. Among the 48 patients in cohort B who were assigned to the control group, 30 (63%) crossed over to receive olaparib. The analyses performed in cohort B were not alpha-controlled, and definitive treatment effects should not be inferred.

(11 patients [13%]) and cabazitaxel (10 patients [12%]); these patients included those who received docetaxel or cabazitaxel as a first subsequent therapy and those who had crossed over to receive olaparib as a first subsequent therapy and also received docetaxel or cabazitaxel as further therapy. A subsequent anticancer therapy was not initiated in 19 of the 83 patients (23%) in the control group. The most common subsequent anticancer therapies among the 162 patients in the olaparib group in cohort A were docetaxel (26 patients [16%]), cabazitaxel (19 patients [12%]), and enzalutamide (16 patients [10%]). The findings were similar in the overall population.

SAFETY

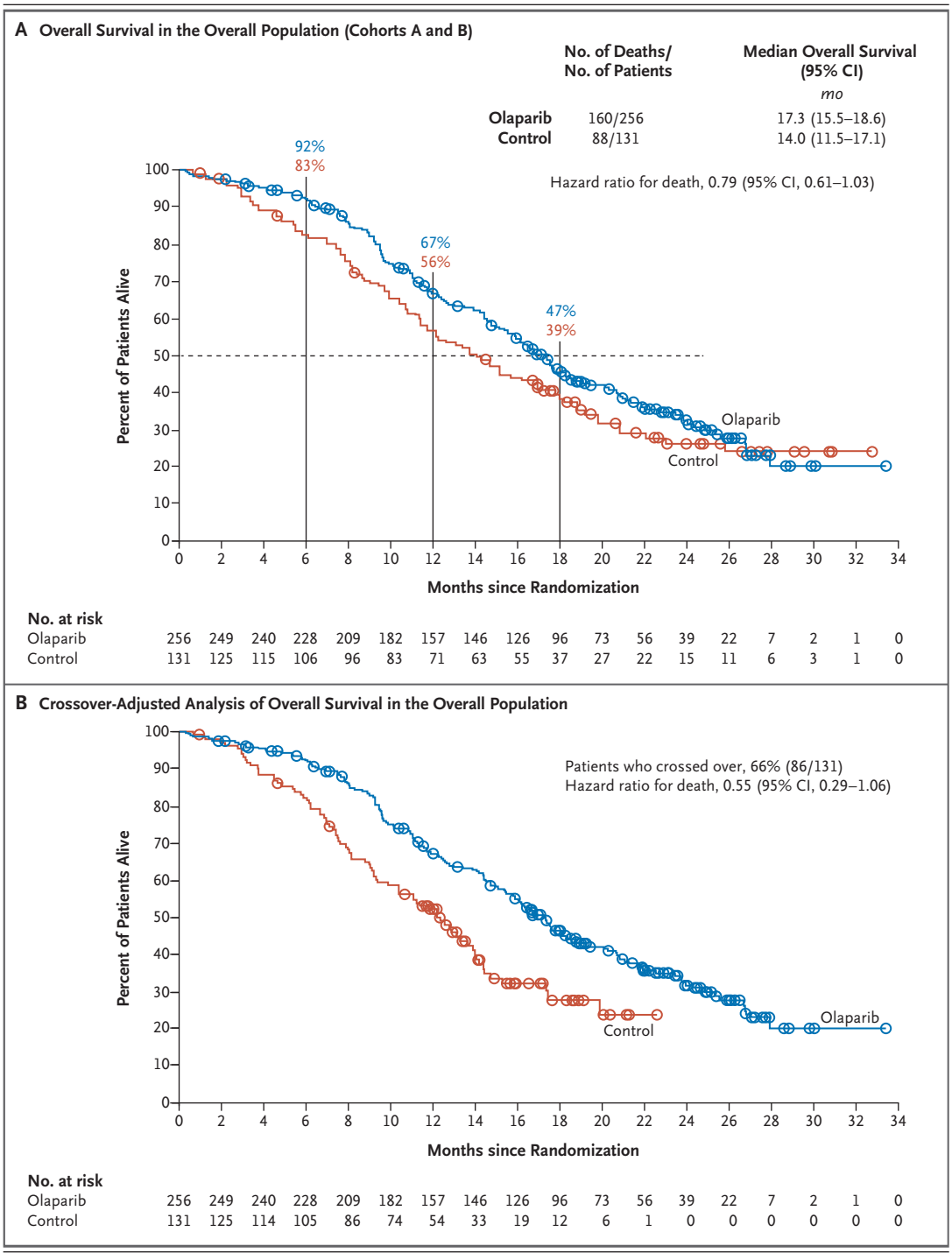
The median duration of treatment was 7.6 months (range, 0.03 to 28.9) in the olaparib group and 3.9 months (range, 0.6 to 29.1) in the control group; the median duration of treatment with olaparib among the 83 patients in the control group who crossed over to receive olaparib in accordance with the protocol was 4.8 months (range, 0.2 to 28.9). No new safety signals were observed after the longer follow-up, as compared with the follow-up period in the primary analysis (Table S3). The most common adverse events among the patients in the olaparib group and those who crossed over to receive olaparib were anemia, nausea, and fatigue or asthenia; among those in the control group, the most common adverse events were anemia, fatigue or asthenia, and decreased appetite (Table 1 and Table S5). Adverse events that were suspected by the site investigators to be causally related to olaparib were most frequently anemia (occurring in 39% of the patients), nausea (in 36%), and fatigue or asthenia (in 32%); olaparib was discontinued because of anemia in 7% of the patients and because of neutropenia, thrombocytopenia, nausea, vomiting, or fatigue or asthenia in 1% of the patients for each (Table S8). The most common adverse events that were suspected to be causally related to control therapy were fatigue or asthenia (occurring in 21% of the patients), nausea (in 11%), and decreased appetite (in 7%). Fatigue or asthenia that was considered to be causally related to control therapy led to treatment discontinuation in 2% of the patients.

No additional cases of a second new primary malignant tumor, pneumonitis, or myelodysplastic syndrome or acute myeloid leukemia were noted during the 30-day safety follow-up period. One case of fatal acute myeloid leukemia was reported in a 75-year-old White male patient who had a germline *BRCA2* alteration that was diagnosed 54 days after the discontinuation of olaparib (duration of olaparib exposure, 15.7 months).

Adverse events led to death in 10 of 256 patients (4%) in the olaparib group, in 6 of 130 patients (5%) in the control group, as well as in 3 of 83 patients (4%) who crossed over from control therapy to receive olaparib in accordance with the protocol (Table S9). Two deaths were considered to be causally related to a trial treatment: one from pneumonia and neutropenia in the olaparib group and one from pleural effusion in the control group.

DISCUSSION

In this trial involving men with metastatic castration-resistant prostate cancer whose disease had progressed during previous treatment with a next-generation hormonal agent, overall survival in cohort A (those who had an alteration in *BRCA1*, *BRCA2*, or *ATM*) was a prespecified key alpha-controlled secondary end point. In cohort A, the patients who received olaparib had a significantly longer duration of overall survival than those who received a control therapy (enzalutamide or abiraterone plus prednisone) (19.1 months vs. 14.7 months; hazard ratio for death, 0.69; 95% CI, 0.50 to 0.97; P=0.02). The risk of death was 31%



lower with olaparib than with control therapy, despite substantial crossover from control therapy to olaparib. The median duration of treatment with olaparib among the patients who crossed over was 4.8 months, and the median duration of treatment with control therapy was 3.9 months. These findings support the previously reported result of a significantly longer duration of imaging-based progression-free survival with olaparib than with control therapy in the same patient population.[22]

Phase 2 trials have shown that antitumor activity with PARP inhibition in patients with metastatic castration-resistant prostate cancer varies

Figure 3 (facing page). Kaplan–Meier Estimates of Overall Survival and Corresponding Crossover-Adjusted Sensitivity Analyses in the Overall Population.

Panel A shows overall survival among the patients in the intention-to-treat population who had at least one alteration in any of the 15 prespecified genes with a direct or indirect role in homologous recombination repair (overall population). Panel B shows overall survival in the overall population, as adjusted with the use of a rank-preserving structural failure time model (with a recensoring approach to avoid possible informative censoring bias) to show the effect of crossover of patients from control therapy to olaparib as a subsequent anticancer therapy. For the patients who had data that were censored, the median duration of follow-up was 20.7 months among those in the olaparib group and 20.5 months among those in the control group. Among the 131 patients in the overall population who were assigned to the control group, 86 (66%) crossed over to receive olaparib (83 crossed over in accordance with the protocol and 3 received olaparib outside the trial). The analyses performed in the overall population were not alpha-controlled, and definitive treatment effects should not be inferred.

according to the DNA-repair gene alterations they express, with consistently higher response rates among those with *BRCA2* alterations.[14,21] Patients in cohort A, and particularly the high percentage of patients who had tumors with a *BRCA1* or *BRCA2* alteration,[22] appeared to derive the greatest benefit from olaparib with respect to overall survival. The trial was not designed to test the benefit of therapy with respect to overall survival at the individual gene level. However, a clinical benefit was not observed for olaparib in the population of patients who had other homologous recombination repair gene alterations. These data, including the results of sensitivity analyses that excluded patients with *PPP2R2A* alterations, and the recent regulatory approval of olaparib for metastatic castration-resistant prostate cancer in which this gene alteration was excluded[27] highlight that additional studies are now required to further delineate genomic indicators of response to PARP inhibition.

Post hoc, gene-level subgroup analyses according to previous use of taxane in patients who had an alteration in only *BRCA1*, *BRCA2*, *ATM*, or *CDK12* provide some insight into the potential effect of previous therapy on the treatment effect of olaparib. The effect of previous use of taxane on overall survival was observed predominantly in the analysis that included patients with only *ATM* loss, in which olaparib seemed to show a benefit over control therapy in those who had previously received taxane therapy, as compared with those who had not. However, this trial was not powered to detect a treatment effect across any subgroup; moreover, the patient number and number of events in some subgroups were limited, and the analyses were not adjusted for confounding factors (e.g., baseline prognostic factors, differences in disease burden and treatment history at baseline, and crossover from control therapy to olaparib after disease progression). Therefore, the results of these subgroup analyses should be interpreted with caution.

The safety profile of olaparib in this final analysis was consistent with that in the primary analysis,[22] with no cumulative toxic effects observed during the extended exposure period. During the 30-day safety follow-up period, the number of cases of a second new primary malignant tumor or pneumonitis did not increase over those reported in the primary analysis; however, one case of acute myeloid leukemia was reported during follow-up for overall survival.

These data on overall survival are supported by the observation that the interval between a first progression and a second progression or death was longer with olaparib than with control therapy, despite substantial crossover from control therapy to olaparib. However, this was an investigator-assessed end point and thereby potentially subject to reporting bias. Patients who crossed over from control therapy to receive olaparib had a shorter median duration of olaparib exposure (4.8 months) than those who were randomly assigned to receive olaparib (7.6 months). Thus, earlier treatment with olaparib may have an advantage over its use later in the disease course.

When the PROfound trial was designed, data from phase 3 randomized trials that would validate the efficacy of switching from one next-generation hormonal therapy directed at androgen signaling to another were lacking, although such sequential use has been commonly applied in clinical practice. Small clinical studies that assessed sequential next-generation hormonal therapy had shown some antitumor activity, and because patients with disease progression had restricted options for systemic treatment,[28,29] this approach was incorporated into clinical guidelines and adopted as a standard of care.[30] With the caveat that cross-trial comparisons should be considered with caution, we note that recently reported data from the CARD trial have shown

Subgroup	Olaparib	Control	Hazard Ratio for Death (95% CI)
	no. of deaths/no. of patients		
All patients	91/162	57/83	0.69 (0.50–0.97)
Previous use of taxane			
Yes	60/106	41/52	0.56 (0.38–0.84)
No	31/56	16/31	1.03 (0.57–1.92)
Measurable disease at baseline			
Yes	55/95	33/46	0.73 (0.47–1.13)
No	36/67	24/37	0.67 (0.40–1.15)
Metastases at baseline			
Bone only	30/57	15/23	0.64 (0.35–1.22)
Visceral	29/46	22/32	0.99 (0.57–1.74)
Other	27/49	16/23	0.62 (0.34–1.18)
ECOG performance-status score at baseline			
0	46/84	18/34	0.94 (0.55–1.66)
1	35/67	36/46	0.55 (0.35–0.88)
2	10/11	3/3	0.98 (0.30–4.37)
Age at randomization			
<65 yr	29/54	16/23	0.62 (0.34–1.17)
≥65 yr	62/108	41/60	0.74 (0.50–1.10)
Region			
Asia	32/57	18/28	0.86 (0.49–1.55)
Europe	36/68	29/38	0.52 (0.32–0.85)
North America or South America	23/37	10/17	0.99 (0.48–2.18)
Race			
White	61/109	38/55	0.69 (0.46–1.04)
Black	1/2	1/1	NC
Asian	23/43	12/19	0.76 (0.39–1.59)
Other	1/1	1/1	NC
PSA level at baseline			
≥Median	43/68	37/48	0.65 (0.42–1.01)
<Median	46/92	19/33	0.88 (0.52–1.53)

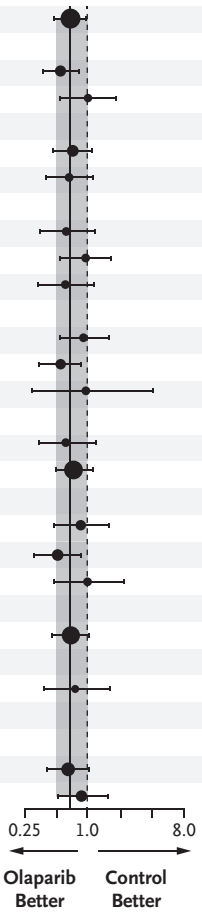


Figure 4. Subgroup Analyses of Overall Survival in Cohort A, According to Baseline Demographic and Clinical Characteristics of the Patients.

Subgroups in which fewer than five patients had died were not included in the analysis. The sizes of the circles are proportional to the number of events. The dashed vertical line indicates the point of no effect (hazard ratio, 1.00). The solid vertical line indicating the point estimate in all the patients who were included in the analysis has been added. Subgroup analyses were not alpha-controlled, and definitive treatment effects should not be inferred. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers reflecting greater disability). Data on race were gathered by the site investigators and reported on the electronic case-report forms. NC denotes not calculated, and PSA prostate-specific antigen.

that the efficacy of cabazitaxel was superior to that of a second androgen-signaling–directed, next-generation hormonal agent in patients (not selected on the basis of biomarkers) who had previously been treated with docetaxel and whose disease had progressed during 12 months of previous treatment with a next-generation hormonal agent.[31] However, data to guide treatment sequencing for patients with metastatic castration-resistant prostate cancer and homologous recombination deficiency remain sparse outside of that trial. In addition, cabazitaxel was not considered to be an appropriate choice for the control treatment in the PROfound trial, because it is only approved for use after docetaxel,[32] and patients were included in our trial regardless of previous receipt of chemotherapy.

In this analysis of overall survival among patients with metastatic castration-resistant prostate cancer who had tumors with at least one alteration in *BRCA1*, *BRCA2*, or *ATM* and whose disease had progressed during previous treatment with a next-

Table 1. Adverse Events in the Overall Population (Cohorts A and B) and in the Subgroup of Patients Who Crossed Over from Control Therapy to Receive Olaparib.*

Event	Olaparib (N=256)		Control (N=130)†		Crossover (N=83)‡	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients with event (percent)					
Any adverse event	246 (96)	133 (52)	115 (88)	52 (40)	77 (93)	49 (59)
Anemia§	127 (50)	58 (23)	20 (15)	7 (5)	43 (52)	24 (29)
Nausea	110 (43)	4 (2)	27 (21)	0	24 (29)	2 (2)
Fatigue or asthenia¶	107 (42)	8 (3)	43 (33)	7 (5)	21 (25)	8 (10)
Decreased appetite	80 (31)	4 (2)	24 (18)	1 (<1)	15 (18)	2 (2)
Diarrhea	55 (21)	2 (<1)	9 (7)	0	12 (14)	0
Vomiting	51 (20)	6 (2)	17 (13)	1 (<1)	16 (19)	1 (1)
Constipation	49 (19)	0	19 (15)	0	12 (14)	0
Back pain	36 (14)	2 (<1)	18 (14)	2 (2)	8 (10)	0
Peripheral edema	34 (13)	0	10 (8)	0	3 (4)	0
Cough	29 (11)	0	3 (2)	0	4 (5)	0
Dyspnea	27 (11)	6 (2)	5 (4)	0	4 (5)	1 (1)
Arthralgia	26 (10)	1 (<1)	14 (11)	0	4 (5)	0
Urinary tract infection	21 (8)	5 (2)	15 (12)	5 (4)	12 (14)	3 (4)
Any serious adverse event‖	94 (37)	NA	39 (30)	NA	27 (33)	NA
Interruption of treatment because of adverse event	119 (46)	NA	25 (19)	NA	44 (53)	NA
Dose reduction because of adverse event	60 (23)	NA	7 (5)	NA	27 (33)	NA
Discontinuation of treatment due to adverse event	51 (20)	NA	11 (8)	NA	11 (13)	NA
Death due to adverse event	10 (4)	NA	6 (5)	NA	3 (4)	NA

* Adverse events, regardless of the investigators' assessment of causality, are reported for those that occurred in at least 10% of the patients in either treatment group. Patients who reported multiple adverse events were counted once for each type of adverse event, even if they reported multiple occurrences of a particular adverse event. The safety analysis set included all the patients who had been randomly assigned to receive olaparib or the physician's choice of enzalutamide or abiraterone plus prednisone (control) and received at least one dose of a trial drug. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.03.[23] NA denotes not applicable.

† One patient in the control group did not receive treatment.

‡ Patients in the control group were allowed to cross over to receive olaparib after disease progression in accordance with the protocol. Three patients in the control group who received olaparib outside of the trial were not included in the safety analysis set.

§ 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. Among the patients in the overall population, anemia was reported in 49% and a decreased hemoglobin level in less than 1%. Among the patients who crossed over to receive olaparib, anemia was reported in 49%, a decreased hemoglobin level in 1%, decreased red-cell count in 1%, and macrocytic anemia in 1%.

¶ Fatigue or asthenia is a grouped term that includes fatigue, asthenia, or both.

‖ The most common serious adverse events, regardless of the investigators' assessment of causality, are listed in Table S7 in the Supplementary Appendix.

generation hormonal agent, olaparib led to significantly longer overall survival than enzalutamide or abiraterone plus prednisone. This improvement was noted despite substantial crossover from control therapy to olaparib. Previously defined adverse effects of olaparib (e.g., anemia, nausea, and fatigue or asthenia) were observed in this trial.

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APPENDIX

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