ORIGINAL ARTICLE

Olaparib for Metastatic Castration-Resistant Prostate Cancer

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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.)

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A 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 is a heterogeneous disease with poor outcomes.[1-6] 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-

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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:

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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.[21] 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 median baseline PSA concentration, and the olaparib group had a higher percentage of patients with an *ATM* alteration (Table 1).

EFFICACY

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

Analysis of the primary end point 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 an objective response, 20.86; 95% CI, 4.18 to 379.18; P<0.001). The median time to pain progression was significantly longer in the olaparib group than in the control group (hazard ratio, 0.44; 95% CI, 0.22 to 0.91; P=0.02) (Fig. 3A). A sensitivity analysis including death as an event in the absence of pain progression yielded similar results (Table S7). At this time, an interim analysis for overall survival was also conducted when 93 of 245 patients had died (data maturity, 38%) and yielded a median overall survival of 18.5 months with olaparib and 15.1 months with the control treatment (hazard ratio for death, 0.64; 95% CI, 0.43 to 0.97; P=0.02) (Fig. 1B). Among patients in the control group with independent review–confirmed imaging-based disease progression, 81% crossed over to receive olaparib treatment at the investigators' discretion. The results of a sensitivity analysis for overall survival with adjustment for switching to olaparib treatment are shown in Table S8.

Among patients who could be evaluated, 43% (66 of 153) in the olaparib group and 8% (6 of 77) in the control group had a PSA_{50} response. Clearance of circulating tumor cells was observed in 30% (29 of 97) and 11% (5 of 44) of patients who could be evaluated in the olaparib and control groups, respectively.

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

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Cohort A		Cohorts A and B	
	Olaparib (N=162)	Control (N=83)	Olaparib (N=256)	Control (N=131)
Median age at randomization (range) — yr	68 (47–86)	67 (49–86)	69 (47–91)	69 (49–87)
Age ≥65 yr at randomization — no. (%)	108 (67)	60 (72)	174 (68)	97 (74)
Metastatic disease at initial diagnosis — no. (%)	38 (23)	19 (23)	66 (26)	25 (19)
Missing data	7 (4)	4 (5)	11 (4)	7 (5)
Gleason score ≥8 — no./total no. (%)†	105/157 (67)	54/80 (67)	183/251 (73)	95/127 (75)
Patients with alterations in a single gene — no. (%)‡				
BRCA1	8 (5)	5 (6)	8 (3)	5 (4)
BRCA2	80 (49)	47 (57)	81 (32)	47 (36)
ATM	60 (37)	24 (29)	62 (24)	24 (18)
CDK12	NA	NA	61 (24)	28 (21)
Median PSA at baseline (IQR) — μg/liter	62.2 (21.9–280.4)	112.9 (34.3–317.1)	68.2 (24.1–294.4)	106.5 (37.2–326.6)
Measurable disease at baseline — no. (%)§	95 (59)	46 (55)	149 (58)	72 (55)
Metastases at baseline — no. (%)§				
Bone only	57 (35)	23 (28)	86 (34)	38 (29)
Visceral: lung or liver	46 (28)	32 (39)	68 (27)	44 (34)
Other	49 (30)	23 (28)	88 (34)	41 (31)
ECOG performance status — no. (%)				
0	84 (52)	34 (41)	131 (51)	55 (42)
1	67 (41)	46 (55)	112 (44)	71 (54)
2	11 (7)	3 (4)	13 (5)	4 (3)
Missing data	0	0	0	1 (1)
Previous new hormonal agent — no. (%)¶				
Enzalutamide only	68 (42)	40 (48)	105 (41)	54 (41)
Abiraterone only	62 (38)	29 (35)	100 (39)	54 (41)
Enzalutamide and abiraterone	32 (20)	14 (17)	51 (20)	23 (18)
Previous taxane use — no. (%)	106 (65)	52 (63)	170 (66)	84 (64)
Docetaxel only	74 (46)	32 (39)	115 (45)	58 (44)
Cabazitaxel only	2 (1)	0	3 (1)	0
Docetaxel and cabazitaxel	29 (18)	20 (24)	51 (20)	26 (20)
Paclitaxel only	1 (<1)	0	1 (<1)	0

* Cohort A included patients with at least one alteration in *BRCA1*, *BRCA2*, or *ATM*. Cohort B included patient with alterations in any of 12 other prespecified genes: *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, 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.

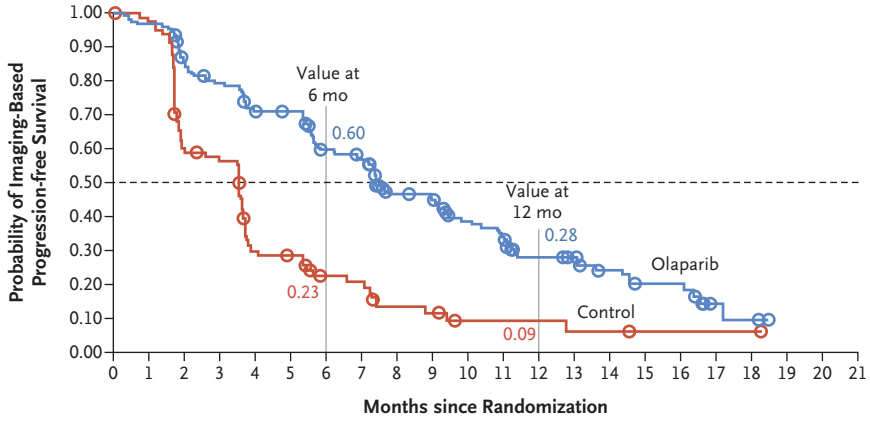
‡ A total of 28 patients (21 in cohort A and 7 in cohort B) had mutations in more than one gene. A total of 4 patients were incorrectly assigned to cohort B (1 in the olaparib group had an alteration in *BRCA2*, 1 in the control group had alterations in *BRCA2* and *CDK12*, and 2 in the olaparib group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

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A Imaging-Based Progression-free Survival in Cohort A



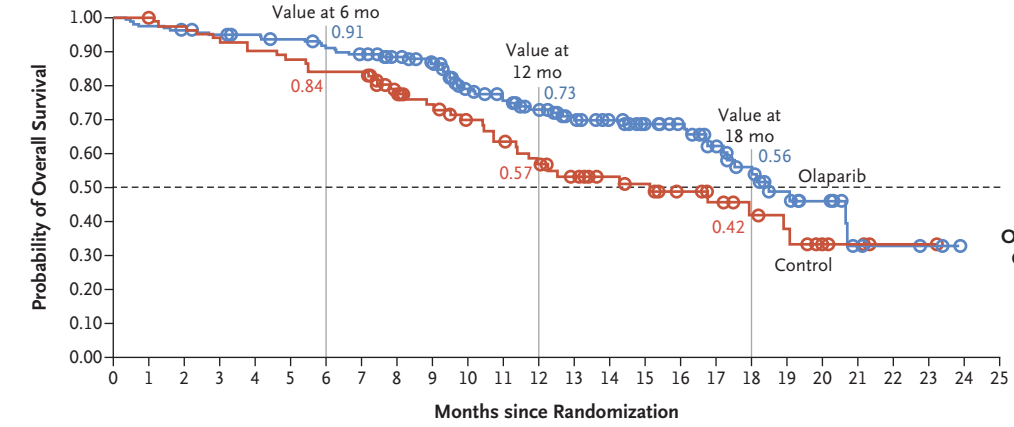
	Median *mo*
Olaparib	7.4
Control	3.6

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

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	3	2	2	1	1	1	1	0	0	0

B Interim Overall Survival in Cohort A



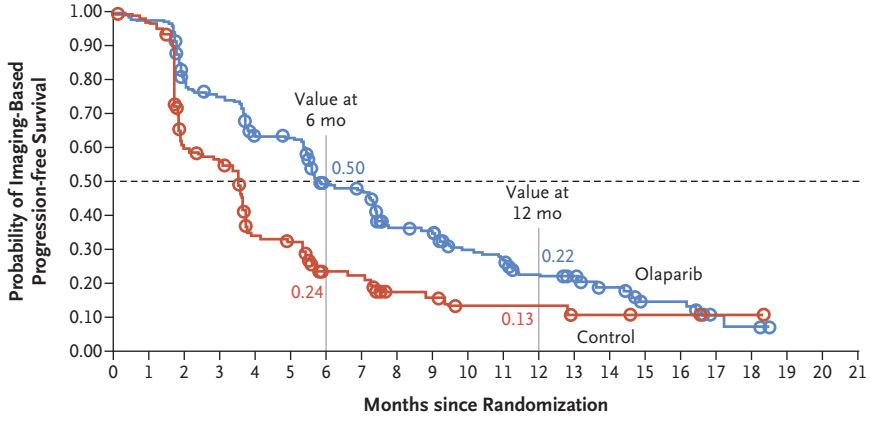
	Median *mo*
Olaparib	18.5
Control	15.1

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

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



	Median *mo*
Olaparib	5.8
Control	3.5

Hazard ratio for progression or death, 0.49 (95% CI, 0.38–0.63)
P<0.001

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

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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.)

months vs. 3.5 months; hazard ratio, 0.49; 95% CI, 0.38 to 0.63; P<0.001) (Fig. 1C). This finding was supported by sensitivity analysis by investigator assessment (Table S4). Exploratory findings with respect to imaging-based progression-free survival for individual genes are reported in Figure 2B, with additional details in the Supplementary Appendix.

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_{50} 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.)

DISCUSSION

Our findings validate phase 1 and 2 data on the antitumor activity of olaparib in metastatic castration-resistant prostate cancer.[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

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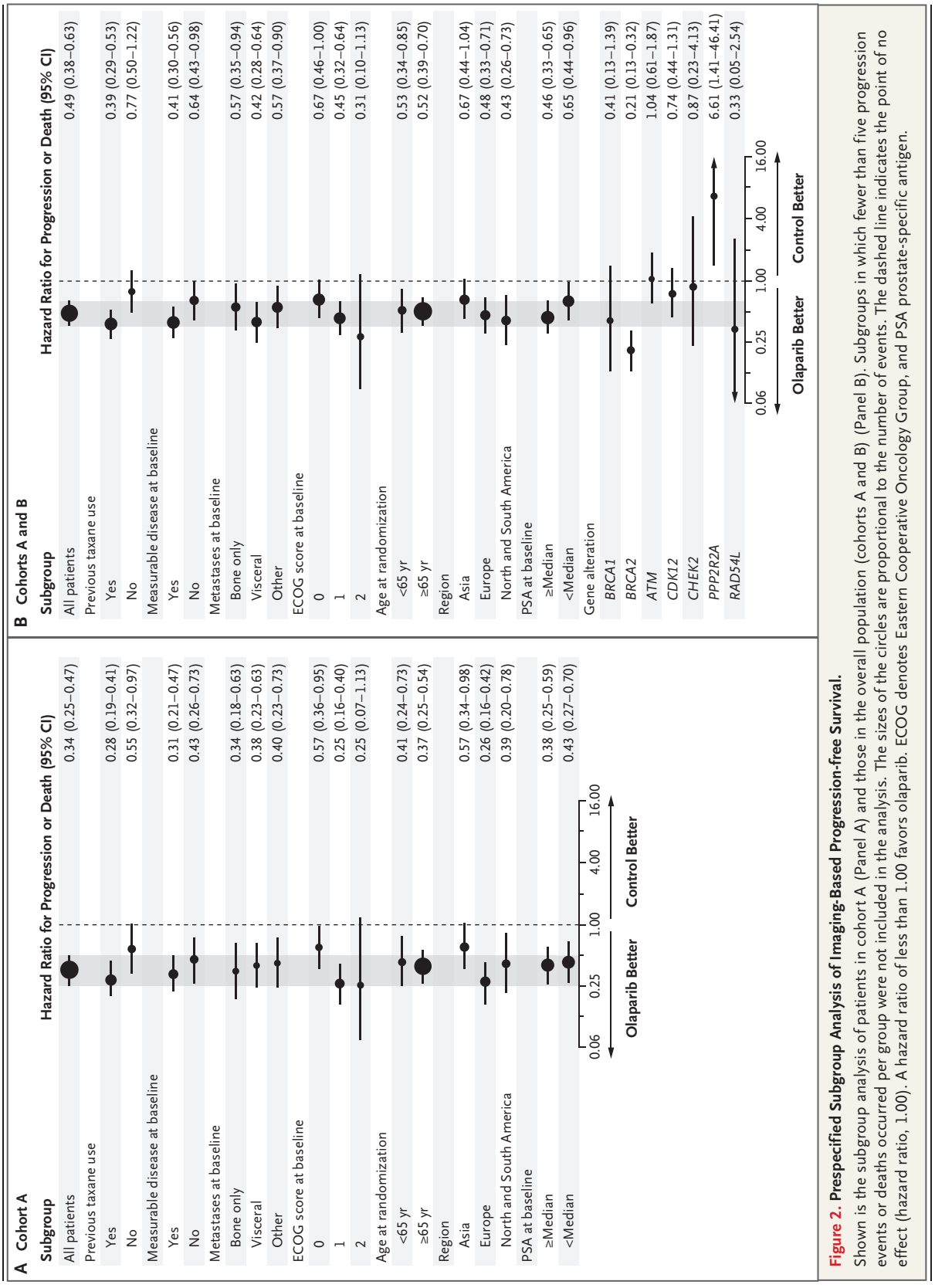


Figure 2. Prespecified Subgroup Analysis of Imaging-Based Progression-free Survival.

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.

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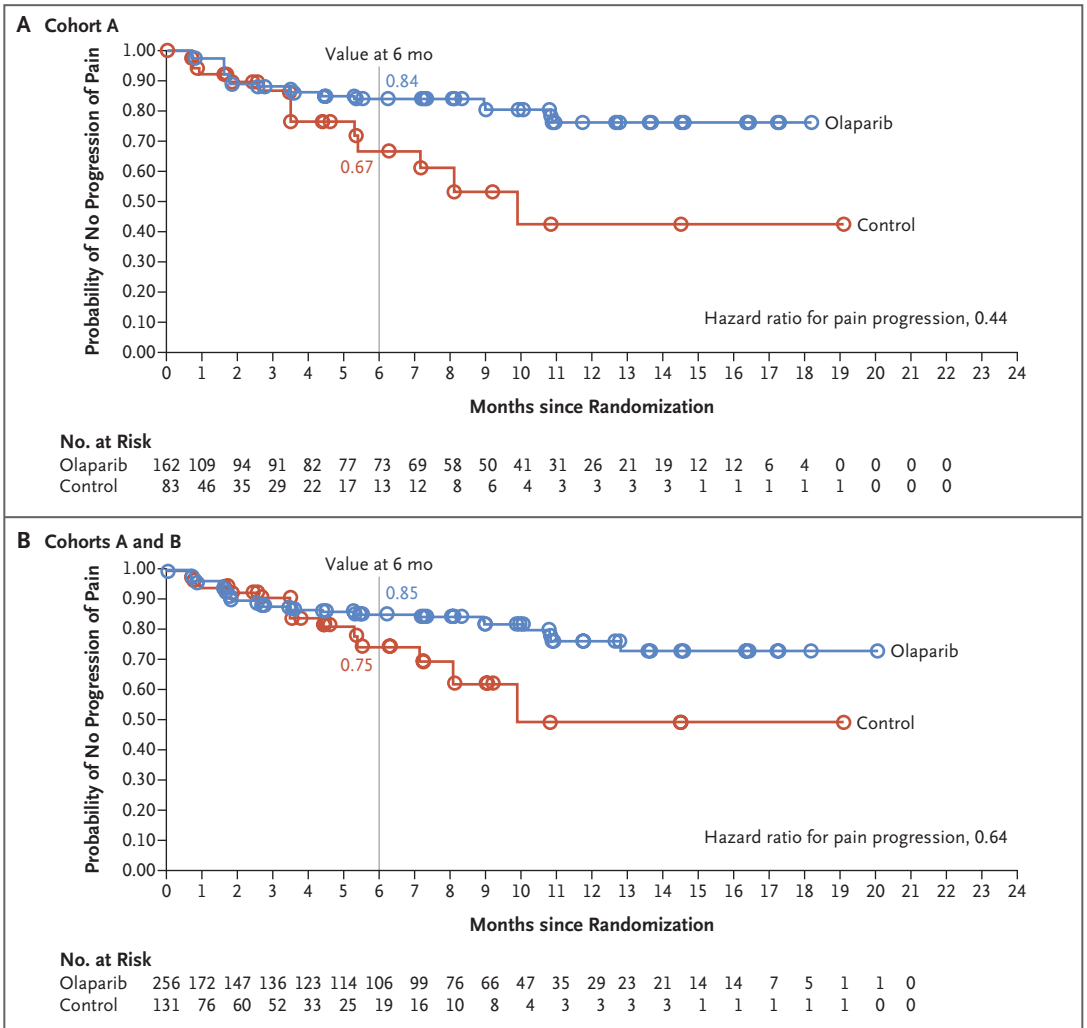


Figure 3. Time to Pain Progression.

Shown is the probability that patients had no progression of pain during treatment with olaparib or the control drug in cohort A (Panel A) and in cohorts A and B (Panel B). In this analysis, death was not considered as a competing risk. Time to pain progression was based on the worst-pain score (item 3) on the Brief Pain Inventory–Short Form and on opioid use.

analysis of overall 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[13] or niraparib[12] monotherapy in similar study popu-

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Table 2. Adverse Events in the Overall Population (Cohorts A and B).*

Event	Olaparib (N=256)		Control (N=130)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number (percent)			
Adverse event				
Any	244 (95)	130 (51)	114 (88)	49 (38)
Anemia†	119 (46)	55 (21)	20 (15)	7 (5)
Nausea	106 (41)	3 (1)	25 (19)	0
Fatigue or asthenia	105 (41)	7 (3)	42 (32)	7 (5)
Decreased appetite	77 (30)	3 (1)	23 (18)	1 (<1)
Diarrhea	54 (21)	2 (<1)	9 (7)	0
Vomiting	47 (18)	6 (2)	16 (12)	1 (<1)
Constipation	45 (18)	0	19 (15)	0
Back pain	35 (14)	2 (<1)	15 (12)	2 (2)
Peripheral edema	32 (12)	0	10 (8)	0
Cough	28 (11)	0	3 (2)	0
Dyspnea	26 (10)	6 (2)	4 (3)	0
Arthralgia	24 (9)	1 (<1)	14 (11)	0
Urinary tract infection	18 (7)	4 (2)	15 (12)	5 (4)
Interruption of intervention due to adverse event	115 (45)	NA	24 (18)	NA
Dose reduction due to adverse event	57 (22)	NA	5 (4)	NA
Discontinuation of intervention due to adverse event	46 (18)	NA	11 (8)	NA
Death due to adverse event	10 (4)	NA	5 (4)	NA

* 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%.

lations. 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.[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.[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 evidence to support this approach.[23] Appropriate sequencing of the new hormonal agents is not defined, and the antitumor activity that has been reported in prospective and retrospective studies

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has varied.[23-27] 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]

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APPENDIX

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REFERENCES

1. Abida W, Armenia J, Gopalan A, et al. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol 2017 May 31 (Epub ahead of print).

2. Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;161:1215-28.

3. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443-53.

4. Beltran H, Beer TM, Carducci MA, et al. New therapies for castration-resistant prostate cancer: efficacy and safety. Eur Urol 2011;60:279-90.

5. Sartor O, de Bono JS. Metastatic prostate cancer. N Engl J Med 2018;378:645-57.

6. Nuhn P, De Bono JS, Fizazi K, et al. Update on systemic prostate cancer therapies: management of metastatic castration-resistant prostate cancer in the era of precision oncology. Eur Urol 2019;75:88-99.

7. Walsh CS. Two decades beyond *BRCA1/2*: homologous recombination, hereditary cancer risk and a target for ovarian cancer therapy. Gynecol Oncol 2015;137:343-50.

8. Blackford AN, Jackson SP. ATM, ATR, and DNA-PK: the trinity at the heart of the DNA damage response. Mol Cell 2017;66:801-17.

9. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013;31:1748-57.

10. Na R, Zheng SL, Han M, et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. Eur Urol 2017;71:740-7.

11. Castro E, Romero-Laorden N, Del Pozo A, et al. PROREPAIR-B: a prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. J Clin Oncol 2019;37:490-503.

12. Smith MR, Sandhu SK, Kelly WK, et al. Phase II study of niraparib in patients with metastatic castration-resistant prostate cancer (mCRPC) and biallelic DNA-repair gene defects (DRD): preliminary results of GALAHAD. J Clin Oncol 2019;37:202. abstract.

13. Abida W, Bryce AH, Vogelzang NJ, et al. Preliminary results from TRITON2: a phase II study of rucaparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination repair (HRR) gene alterations. Ann Oncol 2018;29:viii271-viii302.

14. Mateo J, Carreira S, Sandhu S, et al.

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DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015; 373:1697-708.
15. Mateo J, Porta N, Bianchini D, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol 2020;21:162-74.
16. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline *BRCA* mutation. N Engl J Med 2017;377:523-33.
17. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline *BRCA*-mutated metastatic pancreatic cancer. N Engl J Med 2019;381:317-27.
18. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2018;379:2495-505.
19. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 2015;33:244-50.
20. O'Connor MJ. Targeting the DNA damage response in cancer. Mol Cell 2015;60:547-60.
21. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
22. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009;361:123-34.
23. de Bono JS, Chowdhury S, Feyerabend S, et al. Antitumour activity and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate plus prednisone for ≥24 weeks in Europe. Eur Urol 2018;74:37-45.
24. Khalaf D, Annala M, Finch DL, et al. Phase 2 randomized cross-over trial of abiraterone + prednisone (ABI+P) vs enzalutamide (ENZ) for patients (pts) with metastatic castration resistant prostate cancer (mCPRC): results for 2nd-line therapy. J Clin Oncol 2018;36:5015.
25. Terada N, Maughan BL, Akamatsu S, et al. Exploring the optimal sequence of abiraterone and enzalutamide in patients with chemotherapy-naïve castration-resistant prostate cancer: the Kyoto-Baltimore collaboration. Int J Urol 2017;24: 441-8.
26. Matsubara N, Yamada Y, Tabata KI, et al. Abiraterone followed by enzalutamide versus enzalutamide followed by abiraterone in chemotherapy-naive patients with metastatic castration-resistant prostate cancer. Clin Genitourin Cancer 2018; 16:142-8.
27. Maughan BL, Luber B, Nadal R, Antonarakis ES. Comparing sequencing of abiraterone and enzalutamide in men with metastatic castration-resistant prostate cancer: a retrospective study. Prostate 2017;77:33-40.
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