Olaparib for the Treatment of Patients With Metastatic Castration-Resistant Prostate Cancer and Alterations in *BRCA1* and/or *BRCA2* in the PROfound Trial

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ABSTRACT

PURPOSE Phase III PROfound trial (ClinicalTrials.gov identifier: NCT02987543) met its primary and key secondary objectives, demonstrating significantly longer radiographic progression-free survival (rPFS) and overall survival (OS) with olaparib monotherapy versus abiraterone or enzalutamide (control) in patients with metastatic castration-resistant prostate cancer (mCRPC) with alterations in *BRCA1*, *BRCA2* (BRCA), and/or *ATM* (cohort A) whose disease had progressed on prior next-generation hormonal agent (NHA). We report exploratory post hoc analysis of the subgroup of patients with mCRPC with BRCA alterations in PROfound.

METHODS All patients had an alteration in a homologous recombination repair gene by tumor tissue testing, of which 160 had underlying BRCA alterations. rPFS and OS were estimated using the Kaplan-Meier method. Confirmed objective response rate and safety were also assessed.

RESULTS Olaparib was associated with longer rPFS (hazard ratio [HR], 0.22 [95% CI, 0.15 to 0.32]) and OS (HR, 0.63 [95% CI, 0.42 to 0.95]) than control. There was an rPFS benefit with olaparib in all zygosity subgroups (biallelic [n = 88]; HR, 0.08 [95% CI, 0.04 to 0.16], heterozygous [n = 15] and unknown [n = 57]; HR, 0.30 [95% CI, 0.16 to 0.60]). Patients with *BRCA2* homozygous deletions experienced prolonged responses to olaparib (n = 16; median rPFS, 16.6 months [95% CI, 9.3 to not reached]). Some evaluations are limited by small patient numbers. Germline DNA analysis was performed for 112 (70%) patients; risk of disease progression was similar for patients with germline (n = 61; HR, 0.08 [95% CI, 0.03 to 0.18]) and somatic (n = 51; HR, 0.16 [95% CI, 0.07 to 0.37]) BRCA alterations.

CONCLUSION In all subgroups assessed, olaparib improved outcomes versus abiraterone or enzalutamide for patients with mCRPC with BRCA alterations whose disease had progressed on previous NHA.

ACCOMPANYING CONTENT

Appendix

Protocol

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INTRODUCTION

Although multiple treatment options exist for patients with metastatic castration-resistant prostate cancer (mCRPC), outcomes remain poor, with clinical trials reporting median overall survival (OS) of approximately 3 years after diagnosis and life expectancy in real-world practice of closer to 2 years.[1-4] Therefore, developing new strategies, including precision medicine approaches, to treat these patients is important.

Approximately 20%-25% of patients with mCRPC have alterations in genes associated with homologous recombination repair (HRR; approximately 1% *BRCA1* and 7%-13% *BRCA2*)[5,6] and HRR gene alterations, particularly in *BRCA1* and *BRCA2* (BRCA), are associated with a more aggressive prostate cancer phenotype,[7,8] as well as increased tumor sensitivity to poly(ADP-ribose) polymerase (PARP) inhibitors.[9-11]

PROfound (ClinicalTrials.gov identifier: NCT02987543) was a phase III randomized, open-label trial of olaparib versus physicians' choice of abiraterone or enzalutamide for patients with mCRPC with a deleterious or suspected deleterious alteration in ≥1 of 15 genes with a direct or indirect role

CONTEXT

Key Objective

How effective is olaparib in the treatment of patients with BRCA-altered metastatic castration-resistant prostate cancer (mCRPC) that has progressed on previous treatment with a next-generation hormonal agent (NHA)?

Knowledge Generated

Analysis of PROfound trial end points in patients with BRCA-altered mCRPC whose disease had progressed on previous NHA shows consistent clinical benefits with olaparib versus abiraterone or enzalutamide. These benefits were observed for all BRCA subgroups within the population of PROfound.

Relevance *(M.A. Carducci)*

This post hoc subset analysis highlights the outcomes of patients with advanced mCRPC who will have the most benefit from olaparib treatment, given their BRCA alterations. Individuals with BRCA2 alterations, either of germline or somatic origin, appear to have prolonged or exceptional responses reinforcing recommendations for poly(ADP-ribose) polymerase inhibition in these men.*

*Relevance section written by *JCO* Associate Editor Michael A. Carducci, MD, FACP, FASCO.

in HRR who had experienced disease progression on a previous next-generation hormonal agent (NHA). Patients with alterations in BRCA and/or *ATM* genes (cohort A) treated with olaparib versus abiraterone or enzalutamide (control) had significantly longer radiographic progression-free survival (rPFS; median, 7.4 *v* 3.6 months; hazard ratio [HR], 0.34 [95% CI, 0.25 to 0.47]; $P < .001$) and OS (median, 19.1 *v* 14.7 months; HR, 0.69 [95% CI, 0.50 to 0.97]; $P = .02$). A statistically significant rPFS benefit with olaparib was observed in the overall trial population (cohorts A + B, patients with alterations in ≥1 of 15 HRR genes; median, 5.8 *v* 3.5 months; HR, 0.49 [95% CI, 0.38 to 0.63]; $P < .001$). The HR for OS in the overall trial population was 0.79 (95% CI, 0.61 to 1.03).[12,13]

Trials evaluating PARP inhibitor monotherapy in patients with HRR alterations have reported the greatest response rates in patients with BRCA alterations.[14-18] For PROfound, some rPFS and OS data, including those by previous taxane, have been reported.[12,13] We present consolidated exploratory analyses on safety and efficacy outcomes specifically for patients with BRCA alterations, pursuing further analyses by germline versus somatic (tumor-only) origin and zygosity status of the BRCA alterations.

METHODS

Patient Population, Methods, and Trial End Points

The design of PROfound has been reported.[12] The prespecified genes assessed were *BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*, assessed using a clinical trial assay based on the FoundationOne CDx next-generation sequencing (NGS) test developed in partnership with Foundation Medicine Inc (FMI; Cambridge, MA). Evaluation of the NGS tissue test outcome against preanalytical factors for patients screened for PROfound has been reported.[19]

Patients were randomly assigned 2:1 to olaparib monotherapy (300 mg twice a day) or physician's choice of either enzalutamide (160 mg once daily) or abiraterone (1,000 mg once daily, plus prednisone 5 mg twice a day; control), stratified by whether patients had received previous taxane (yes/no) and had measurable disease (yes/no).

The primary end point was rPFS by blinded independent central review (BICR) in cohort A (BRCA and/or *ATM*), defined as time from random assignment until soft-tissue disease progression (by RECIST, v1.1), bone lesion progression (by Prostate Cancer Clinical Trials Working Group 3 [PCWG3] criteria), or death. Additional end points included OS (time from random assignment to death by any cause), confirmed objective response rate (ORR; response was based on RECIST v1.1 in the absence of progression on bone scan by PCWG3 criteria, confirmed by repeat imaging no <4 weeks later), confirmed prostate-specific antigen (PSA) response (a reduction in PSA level of ≥50% compared with baseline on two consecutive occasions at least 3 weeks apart), and circulating tumor cell (CTC) conversion (the proportion of patients achieving a decline in the number of CTCs from ≥5 cells/7.5 mL at baseline to <5 cells/7.5 mL at any visit after baseline).

When a patient in the control arm experienced radiographic disease progression, they could crossover to receive olaparib, provided they met the study criteria (had not received other subsequent anticancer therapy and had no grade ≥1 toxicities from previous therapy) and agreed to comply with the study requirements. Sensitivity analyses were conducted to assess the effect of treatment switching.

Exploratory Biomarker Subgroup Analyses

This analysis focuses on the patients from PROfound with tumor BRCA alterations (*BRCA1* only, *BRCA2* only, or *BRCA1* and/or *BRCA2* with another co-occurring HRR alteration; Fig 1). Details of tumor testing are provided in Appendix 1 (online only).

Germline Versus Somatic (tumor-only) BRCA Alteration

For patients in cohort A who consented to germline testing, a blood sample was collected at screening for retrospective central germline testing using the Myriad BRACAnalysis CDx assay. Patients were categorized as having a germline BRCA alteration on the basis of the presence of a deleterious or suspected deleterious alteration in BRCA in germline DNA, or as having a somatic BRCA alteration if they had a BRCA alteration by tumor testing and negative germline BRCA alteration status by central germline testing.

Gene-Specific Zygosity

Gene-specific zygosity was determined using an investigational computational algorithm developed at FMI from the FoundationOne CDx tissue test.[20,21] Patients were classified into subgroups on the basis of the evidence for a second hit in the same BRCA gene: biallelic, heterozygous, or unknown. Details of patient classification are available in Appendix Table A1. In brief, the biallelic subgroup included patients with homozygous deletions, two pathogenic mutations, a pathogenic mutation with no evidence of a wild-type allele, or two pathogenic alterations but no evidence of whether they occurred in the same or different alleles (suspected biallelic inactivation). Patients in the heterozygous subgroups were considered suspected heterozygous because, although the presence of a wild-type allele was determined, it was not possible to rule out that the other allele may have been inactivated by alterations not detectable by the targeted NGS assay.

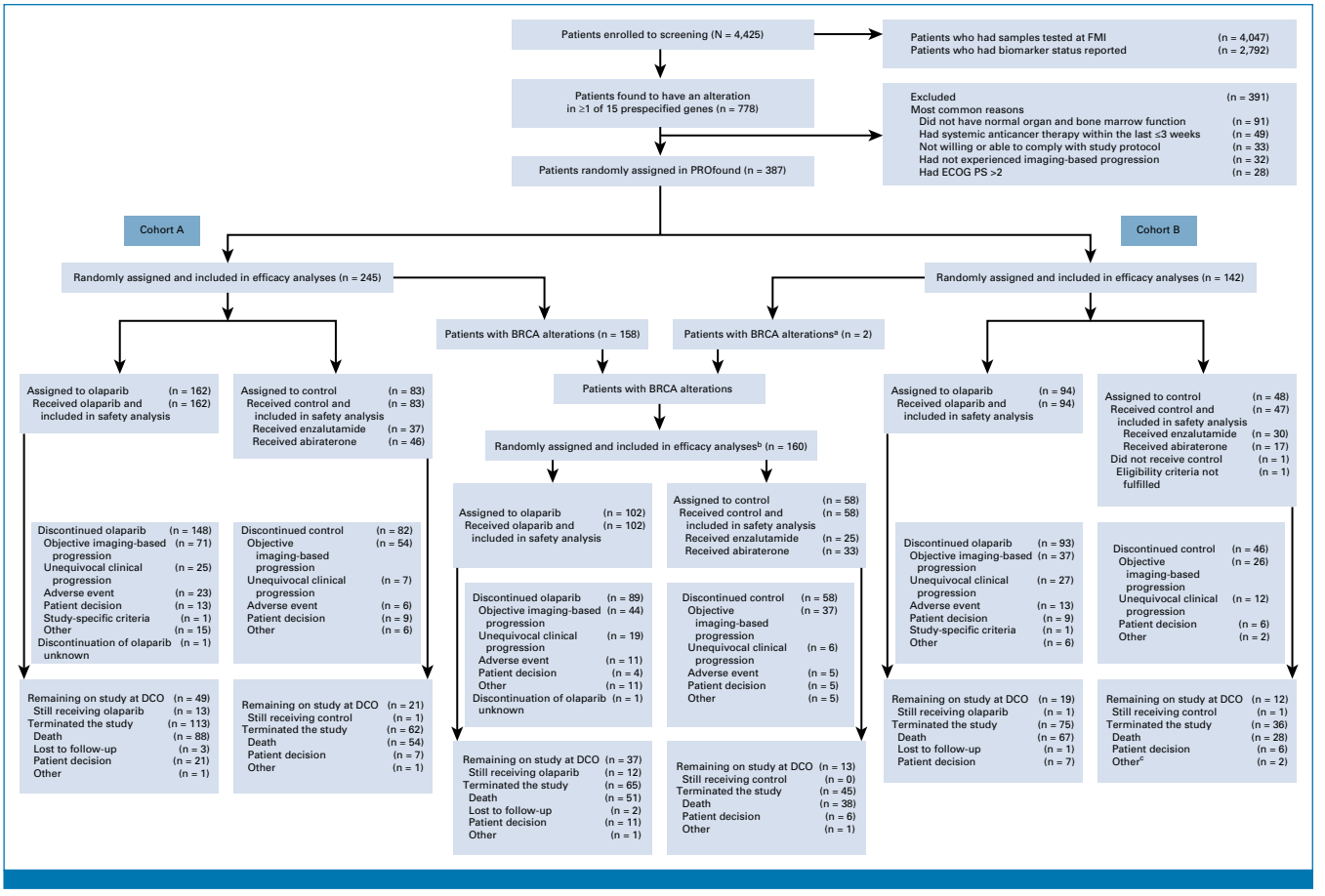

FIG 1. CONSORT diagram. Cohort A included patients with alterations in *BRCA1*, *BRCA2* (BRCA), and/or *ATM*. Cohort B included patients with alterations in *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D,* and *RAD54L*. Control refers to investigator's choice of next-generation hormonal agent (either abiraterone or enzalutamide). BRCA comprises *BRCA1* and/or *BRCA2* including co-occurring alterations in other HRR genes. [a]Two patients with BRCA alterations were incorrectly assigned to cohort B. [b]BRCA alteration status was not a stratification factor. [c]Status was unknown for one patient. DCO, data cutoff; ECOG PS, Eastern Cooperative Oncology Group performance status; FMI, Foundation Medicine Inc; HRR, homologous recombination repair.

TABLE 1. Characteristics of Patients at Baseline

Characteristic	All BRCA Alterations (combined including co-occurring alterations),[a] No. (%)		*BRCA1* Alteration Only, No. (%)		*BRCA2* Alteration Only, No. (%)	
	Olaparib (n = 102)	Control (n = 58)	Olaparib (n = 8)	Control (n = 5)	Olaparib (n = 81)	Control (n = 47)
Age ≥65 years	69 (67.6)	37 (63.8)	7 (87.5)	3 (60.0)	53 (65.4)	32 (68.1)
Previous taxane	72 (70.6)	35 (60.3)	8 (100.0)	4 (80.0)	58 (71.6)	28 (59.6)
Measurable disease	62 (60.8)	35 (60.3)	7 (87.5)	1 (20.0)	47 (58.0)	29 (61.7)
Metastases at baseline						
Bone only	34 (33.3)	15 (25.9)	1 (12.5)	3 (60.0)	27 (33.3)	11 (23.4)
Visceral (lung/liver)	30 (29.4)	22 (37.9)	4 (50.0)	0	24 (29.6)	19 (40.4)
Other	33 (32.4)	18 (31.0)	3 (37.5)	2 (40.0)	25 (30.9)	14 (29.8)
ECOG performance status						
0	51 (50.0)	22 (37.9)	3 (37.5)	3 (60.0)	40 (49.4)	18 (38.3)
1	43 (42.2)	33 (56.9)	5 (62.5)	2 (40.0)	34 (42.0)	27 (57.4)
2	8 (7.8)	3 (5.2)	0	0	7 (8.6)	2 (4.3)
Previous therapies						
Immunotherapy	7 (6.9)	7 (12.1)				
Hormonal therapy	102 (100)	58 (100)				
Taxane chemotherapy	72 (70.6)	35 (60.3)				
Radiotherapy	65 (63.7)	38 (65.5)				
Other	24 (23.5)	15 (25.9)				

NOTE. Patients can be counted in more than one previous disease-related treatment modality. Control refers to investigator's choice of next-generation hormonal agent (either abiraterone or enzalutamide).
Abbreviations: BRCA, *BRCA1* and/or *BRCA2* including co-occurring alterations in other HRR genes; *BRCA1* only, alteration in *BRCA1* gene only; *BRCA2* only, alteration in *BRCA2* gene only; ECOG, Eastern Cooperative Oncology Group; HRR, homologous recombination repair.
[a]Nineteen patients with a BRCA alteration also had a co-occurring alteration (*BRCA1* + *ATM*, n = 1, *BRCA1* + *RAD54L*, n = 1, *BRCA2* + *ATM*, n = 2, *BRCA2* + *BARD1*, n = 2, *BRCA2* + *CDK12*, n = 5, *BRCA2* + *CDK12* + *CHEK2*, n = 1, *BRCA2* + *CHEK2*, n = 2, *BRCA2* + *CHEK2* + *RAD51D*, n = 1, *BRCA2* + *PPP2R2A*, n = 3, *BRCA2* + *RAD51B*, n = 1).

Trial Oversight

PROfound was performed in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca and Merck policies on bioethics. All patients provided written informed consent.

Data Analysis

This was a post hoc analysis in patients with BRCA alterations, including patients with co-occurring alterations in the 13 other prespecified HRR genes in PROfound. As the analysis was not preplanned in the trial protocol, it was not alpha-controlled or powered. Subgroup analyses were not stratified. Most efficacy end points were evaluated for the entire population with BRCA alterations (including those with co-occurring alterations). For consistency with previous publications, rPFS and final OS evaluated by previous taxane status were analyzed for patients with an alteration in *BRCA1* only or *BRCA2* only. Germline versus somatic analysis is restricted to patients with germline DNA results (n = 112). All other analyses presented include all patients with BRCA alterations on the basis of tissue testing.

The data cutoff date for rPFS, confirmed ORR, symptomatic skeletal-related event (SSRE), CTC, and PSA analyses was June 4, 2019. OS, exposure, safety, and subsequent therapies were assessed based on a final data cutoff date of March 20, 2020.

rPFS by BICR, OS, and time to first SSRE were estimated using the Kaplan-Meier method. Related HRs and 95% CIs were calculated using the Cox proportional hazards model. Confirmed radiologic ORR by BICR was analyzed by logistic regression. Crossover-adjusted OS was assessed in sensitivity analyses using rank-preserving structural failure time models (RPSFTMs).[22]

Adverse events (AEs) were assessed by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.03).

RESULTS

Demographics and Characteristics

Of the 387 patients randomly assigned, 160 had an alteration in a BRCA gene (13 alterations in *BRCA1* only, 128 in *BRCA2*

only, and 19 *BRCA1* and/or *BRCA2* plus another gene: two *BRCA1* and 17 *BRCA2*; Table 1).

Before the trial, 66.9% of patients had received previous taxane chemotherapy and NHA; the proportion of patients was higher in the olaparib arm (70.6%) than in the control arm (60.3%).

Treatment Duration

At final analysis, median treatment duration was 9.6 months (range, <0.1-28.9) in the olaparib arm and 3.8 months (range, 0.7-14.7) in the control arm. For patients who crossed over from control to olaparib, median treatment duration of subsequent olaparib was 8.9 months (range, 0.2-28.9). At data cutoff date March 20, 2020, 12 patients (7.5%) were receiving study treatment (12 olaparib and zero control); 87.3% of patients receiving olaparib and 100% receiving control had discontinued treatment. Reasons for discontinuation, AEs (Appendix Table A2), and time to first SSRE analyses (Appendix Fig A1) are included in the Appendix 1.

Eighty-six patients (53.8%) received a subsequent anticancer therapy after discontinuation of the original study drug, most commonly taxane chemotherapy and hormonal therapies for patients treated with olaparib and PARP inhibitors and taxane chemotherapy for patients originally in the control arm (Appendix Table A3).

Olaparib Efficacy in Patients With BRCA Alterations

rPFS and OS

rPFS was longer for olaparib-treated patients with BRCA alterations than for patients in the control arm (median, 9.8 *v* 3.0 months; HR, 0.22 [95% CI, 0.15 to 0.32]; Fig 2A).[12] For patients with *BRCA2*-only alterations (n = 128), median rPFS favored olaparib over control (10.8 *v* 3.5 months) and was 2.1 versus 1.8 months for patients with *BRCA1*-only alterations (n = 13).[12]

When these patients were assessed based on whether they had received previous taxane or not, an rPFS benefit with olaparib versus control was observed in both subgroups (previous taxane; median, 9.0 *v* 1.9 months; HR, 0.20 [95% CI, 0.12 to 0.34]; no previous taxane; median, 14.6 *v* 3.7 months; HR, 0.13 [95% CI, 0.05 to 0.31]; Appendix Fig A2).

For the overall population of patients with BRCA alterations, OS was longer in the olaparib arm than in the control arm (median, 20.1 *v* 14.4 months; HR, 0.63 [95% CI, 0.42 to 0.95]; Fig 2B). For the *BRCA2*-only (n = 128) and *BRCA1*-only (n = 13) populations, the HR for OS favored olaparib versus control (HR, 0.59 [95% CI, 0.37 to 0.95] and HR, 0.42 [95% CI, 0.12 to 1.53], respectively).[13]

Of the patients with a BRCA alteration in the control arm, 40 (69%) crossed over to olaparib after confirmed disease progression. Sensitivity analyses using RPSFTMs, a method used to adjust for crossover, showed that the HR for olaparib versus control was between 0.27 (95% CI, 0.19 to 0.75) and 0.40 (95% CI, 0.27 to 0.90), depending on the model selected (Appendix Fig A3A without recensoring, and Fig A3B with recensoring).[23]

At the time of final OS analysis, we reported that in patients with BRCA alterations, there was a reduction in risk of death with olaparib versus control for both subgroups of patients who had or had not received previous taxane therapy (previous taxane; median, 17.4 *v* 12.6 months; HR, 0.64 [95% CI, 0.39 to 1.08]; no previous taxane; median, not reached [NR] *v* 18.8 months; HR, 0.30 [95% CI, 0.10 to 0.78]; Appendix Fig A4).[13]

Confirmed ORR, PSA, and CTCs

A higher proportion of patients in the olaparib arm than in the control arm had reductions from baseline in target lesions, PSA levels, and CTC levels, indicating that more patients in this arm responded to treatment (Fig 3). In patients who were evaluable by RECIST v1.1, confirmed ORR was 43.9% (n = 25/57) and 0% (n = 0/33) in the olaparib and control arms, respectively (neither the odds ratio nor the corresponding 95% CI was calculable). Confirmed PSA response was 61.7% (n = 58/94 [95% CI, 51.1 to 71.5]) and 0% (n = 0/54) in the olaparib and control arms, respectively. CTC conversion was 69.0% (n = 20/29 [95% CI, 49.2 to 84.7]) for olaparib-treated patients and 23.5% (n = 4/17 [95% CI, 6.8 to 49.9]) for patients receiving control.

Olaparib Efficacy and Tolerability in the Population of Patients With BRCA Alterations by Germline Versus Somatic Alteration Type

Of the patients with a BRCA alteration, including those with coalterations in other HRR genes, 112 (70.0%) were evaluable for germline/somatic alteration status (Appendix Table A4).

Seventy-three of 112 patients were evaluable for genomics zygosity analysis. The proportion of tumors with biallelic inactivation was high (84%) for germline (31/40 [78%]) and somatic (30/33 [91%]) BRCA alterations.

Olaparib was associated with prolonged rPFS and OS and higher confirmed ORR for patients with either germline or somatic BRCA alterations compared with control (Table 2; Fig 4).

AE profiles in patients by germline or somatic BRCA alteration were similar: the rate of patients discontinuing olaparib due to an AE was 19% (n = 8/42) and 21% (n = 7/33) with germline and somatic mutations, respectively (Appendix Table A5).

Fifteen patients (78.9%) and 13 (72.2%) patients with germline and somatic alterations, respectively, crossed over from control to olaparib after disease progression.

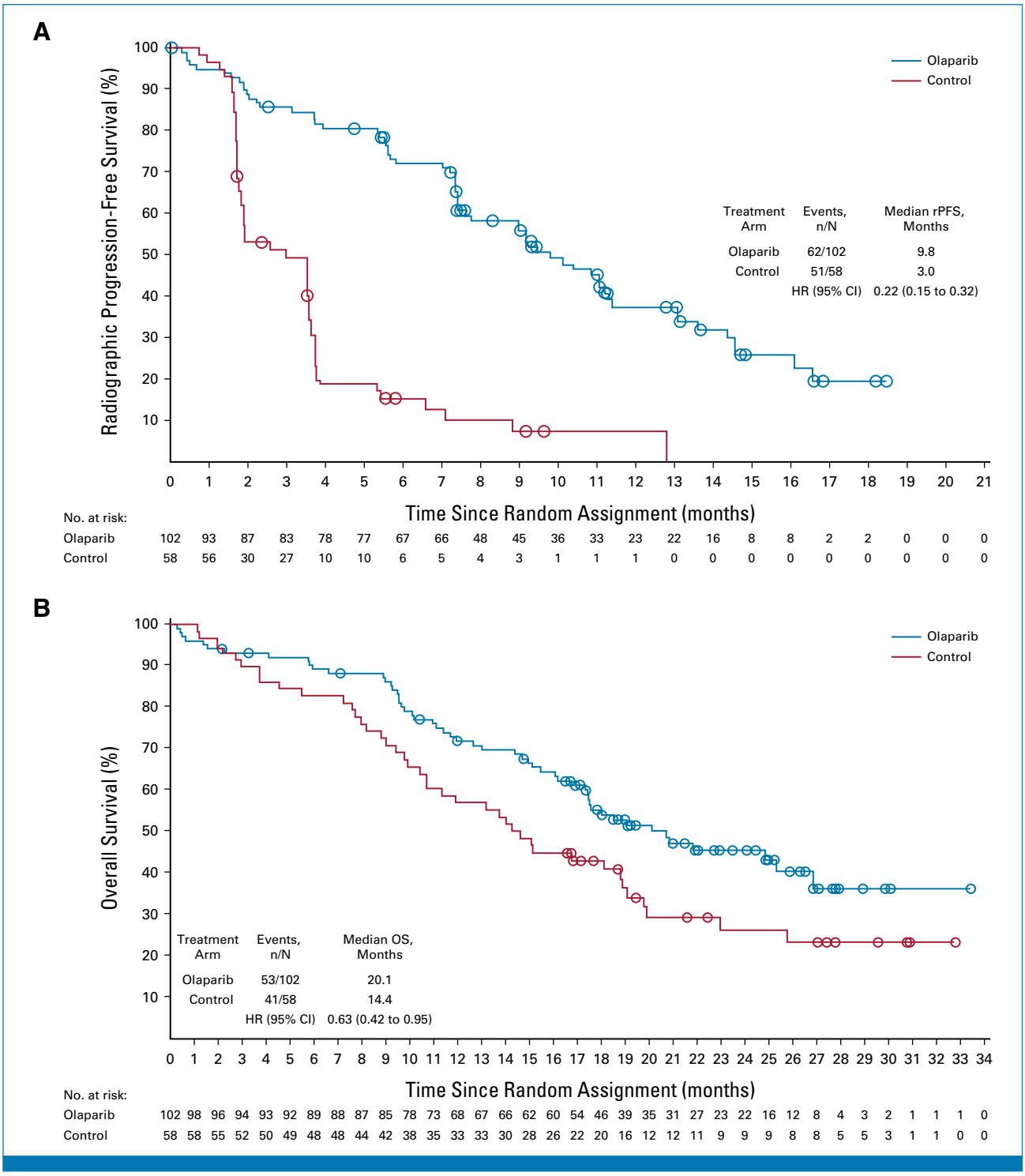

FIG 2. Kaplan-Meier curves for the population of patients with BRCA alterations (combined including co-occurring alterations; N = 160) of (A) rPFS and (B) OS. BRCA comprises *BRCA1* and/or *BRCA2* including co-occurring alterations in other HRR genes. A circle indicates a censored observation. Figure 2A from de Bono J et al, Olaparib for metastatic castration-resistant prostate cancer, New England Journal of Medicine 382:2091–102. Copyright © 2020, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. HR, hazard ratio; HRR, homologous recombination repair; OS, overall survival; rPFS radiographic progression-free survival.

Olaparib Efficacy in Patients With BRCA Alterations by Zygosity of the Detected Alteration

Of the patients with a BRCA alteration, 64.4% (n = 103/160) were evaluable for zygosity on the basis of targeted NGS. Of those, 85% (n = 88/103) of alterations were predicted to associate with biallelic inactivation of a BRCA gene. The suspected heterozygous subgroup was small (n = 15). Of the patients evaluable for zygosity status with a *BRCA1* alteration (n = 6), one had biallelic inactivation and five had a

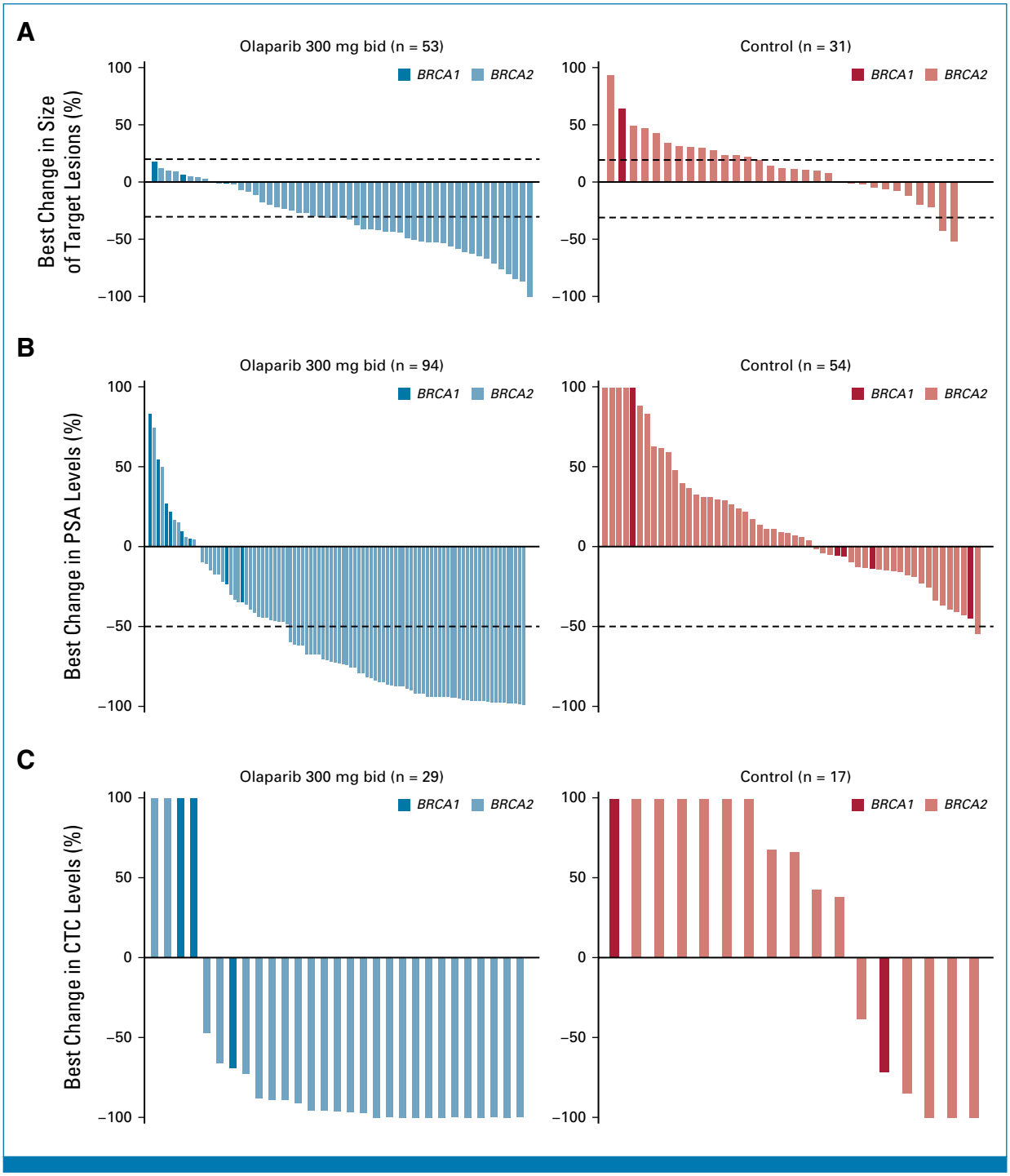

FIG 3. Best percentage change from baseline in (A) target lesions, (B) PSA, and (C) CTC levels for patients with BRCA alterations (combined including co-occurring alterations). These figures include data from patients with *BRCA1* and/or *BRCA2* including co-occurring alterations in other HRR genes. Analysis of best percentage change from baseline in target lesions includes patients with measurable disease at baseline (as assessed by blinded independent central review) and a valid baseline and postbaseline RECIST assessment. The dashed line at +20 indicates the threshold for progressive disease, and the dashed line at −30 indicates the threshold for partial response. Analysis of best percentage change from baseline in PSA includes patients with a valid baseline and postbaseline PSA measurement. The dashed line at −50 indicates the threshold for PSA response. Analysis of best percentage change from baseline in CTC includes patients with ≥5 cells/7.5 mL at baseline and a postbaseline CTC measurement. Patients with values less than −100 have an imputed value of −100. Patients with values >100 have an imputed value of 100. Control refers to investigator's choice of next-generation hormonal agent (either abiraterone or enzalutamide). bid, twice a day; CTC, circulating tumor cell; HRR, homologous recombination repair; PSA, prostate-specific antigen.

TABLE 2. Efficacy Results by Germline or Somatic Status for the Population of Patients With BRCA Alterations and Germline Results Available (combined including co-occurring alterations; N = 112) Population

	Germline		Somatic	
End Point	Olaparib (n = 42)	Control (n = 19)	Olaparib (n = 33)	Control (n = 18)
rPFS, months, median	10.4	1.9	11.1	2.3
HR (95% CI)	0.08 (0.03 to 0.18)		0.16 (0.07 to 0.37)	
OS, months, median	20.8	15.1	18.5	16.6
HR (95% CI)	0.55 (0.27 to 1.16)		0.66 (0.32 to 1.39)	

	Germline		Somatic	
End Point	Olaparib (n = 19)	Control (n = 12)	Olaparib (n = 20)	Control (n = 10)
ORR, % evaluable patients with a response	47.4	0	35.0	0
OR (95% CI)	NC		NC	

Abbreviations: BRCA, *BRCA1* and/or *BRCA2* including co-occurring alterations in other HRR genes; HR, hazard ratio; NC, not calculable; OR, odds ratio; ORR, objective response rate; OS, overall survival; rPFS, radiographic progression-free survival.
Control refers to investigator's choice of next-generation hormonal agent (either abiraterone or enzalutamide).

heterozygous alteration. In the *BRCA2* subgroup (n = 97), 87 patients had a biallelic inactivation and 10 had a heterozygous alteration.

In the biallelic subgroup, confirmed ORR was 60.7% (n = 17/28) in the olaparib arm and 0% in the control arm. Response to olaparib was not restricted to the biallelic subgroup as confirmed ORR among patients in the heterozygous subgroup (no evidence of a second hit loss) of the olaparib arm was 44.4% (n = 4/9; Table 3).

Within the biallelic subgroup, patients with *BRCA2* homozygous deletion (loss of both alleles by structural variants such as deletions rather than by inactivating mutations in the olaparib arm; n = 16) experienced a prolonged median rPFS of 16.6 months (95% CI, 9.3 to NR), with a 12-month progression-free rate of 79%.

DISCUSSION

In this post hoc exploratory analysis of patients with an underlying BRCA alteration in PROfound, treatment with olaparib compared with abiraterone or enzalutamide (control) led to an rPFS and OS benefit for patients with mCRPC and a BRCA alteration whose disease had progressed on previous NHA. Confirmed ORR, PSA, and CTC results were consistent with the rPFS and OS findings. These findings are important as approximately 10% of patients with mCRPC have alterations in *BRCA1* and *BRCA2* genes, which are associated with more aggressive disease and poorer outcomes.[5,24]

For these patients, baseline characteristics were generally balanced between the study arms, although a higher proportion in the control arm had visceral metastases (37.9% *v* 29.4% in the olaparib arm), while more patients in the olaparib arm had received at least one previous taxane (70.6% *v* 60.3% in the control arm).

Our analysis suggests that there is superior clinical benefit with olaparib versus control both in patients who had and had not received previous taxane treatment.

The rate of crossover from control to olaparib at disease progression was 69%, and OS adjustment for crossover suggested that the survival benefit with olaparib could be even greater than was observed in the trial. The results of the crossover analyses, together with the benefit observed for patients who had not received previous taxane, support early treatment with olaparib in patients with BRCA alterations.

Consistent with other genomics studies in mCRPC, most patients with BRCA alterations had *BRCA2* (90.6%; 145/160 patients) rather than *BRCA1* alterations (9.4%; 15/160 patients), which are infrequent in prostate cancer.[5,9,12,24,25] Although *BRCA1* and *BRCA2* alterations are commonly reported together in the literature, we acknowledge most of our data have been generated from patients with *BRCA2* alterations.

The germline versus somatic alteration analysis showed that patients with BRCA alterations had greater rPFS and OS benefit and ORR with olaparib, whether the alteration was of germline or somatic origin. Similar results have been reported in the TOPARP-B study of olaparib 400 mg twice a day (composite response rates of objective response by RECIST v1.1, PSA fall ≥50 and CTC conversion was 77% and 84% for germline and somatic, respectively) and the

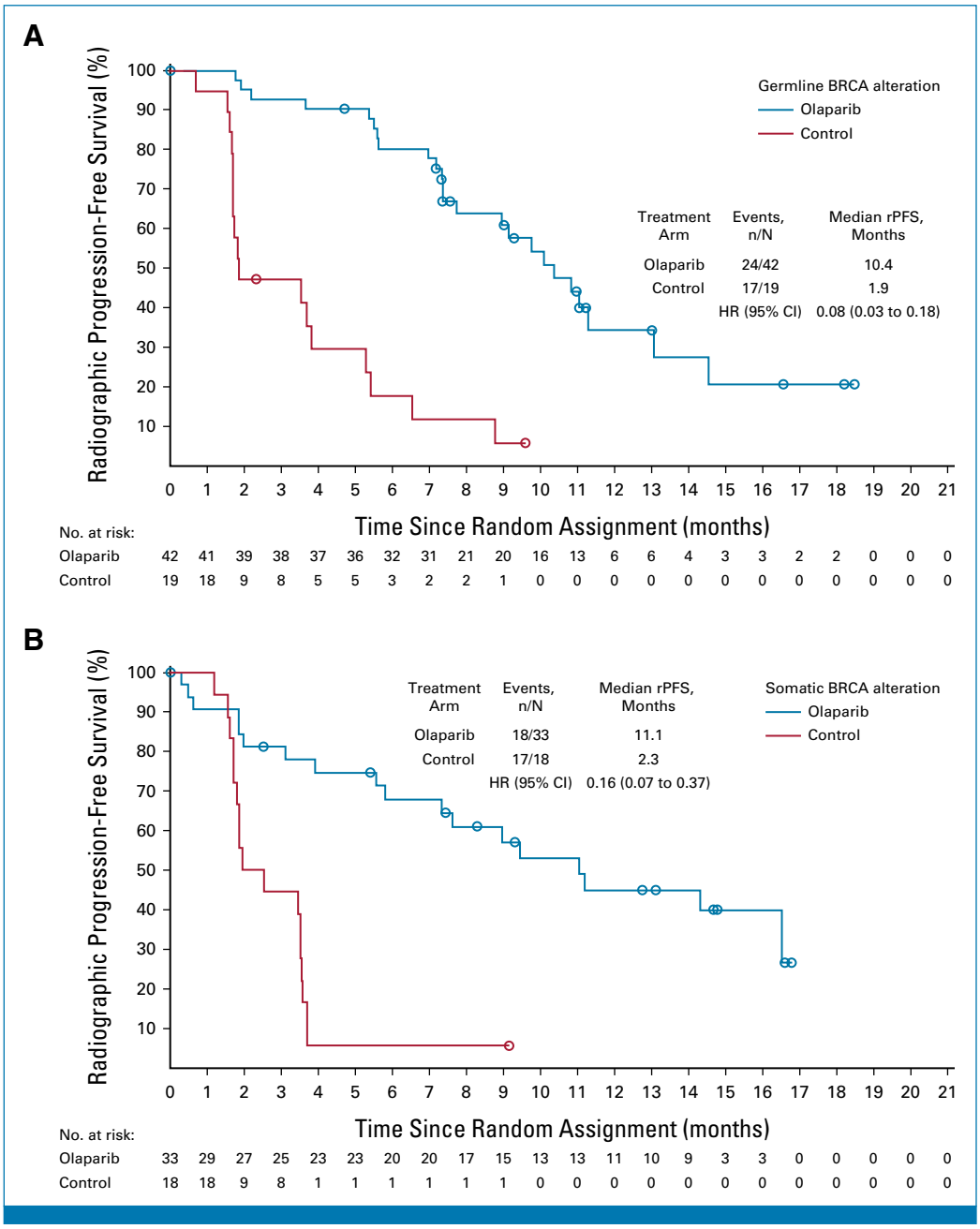

FIG 4. (A) rPFS for patients with a germline BRCA alteration, (B) rPFS for patients with a somatic BRCA alteration, (C) OS for patients with a germline BRCA alteration, and (D) OS for patients with a somatic BRCA alteration. These figures include data from patients with *BRCA1* and/or *BRCA2* including co-occurring alterations in other HRR genes. A circle indicates a censored observation. HR, hazard ratio; HRR, homologous recombination repair; OS, overall survival; rPFS, radiographic progression-free survival. (continued on following page)

rucaparib (PARP inhibitor) studies TRITON2 (ORR of 42.9% and 43.9% for germline and somatic, respectively) and TRITON3 (rPFS for germline HR, 0.52 [95% CI, 0.32 to 0.84] and somatic HR, 0.38 [95% CI, 0.25 to 0.59]).[14,15,18] Safety was similar in the germline and somatic populations. Hence, although germline status identification is relevant for estimating patient and relatives' cancer risk, identification of alterations through tumor testing is sufficient for the treatment indication.

Most (85%) tumors with a BRCA alteration were predicted to harbor biallelic inactivation of the gene, whether the alteration was of germline or somatic origin. Targeted sequencing assays used in clinical practice have limitations to detect certain events, such as copy-neutral loss of heterozygosity, large deletions, or other complex structural variants that may lead to biallelic inactivation, particularly in cases with limited tumor content. In PROfound, tumor responses were observed among the small number of patients

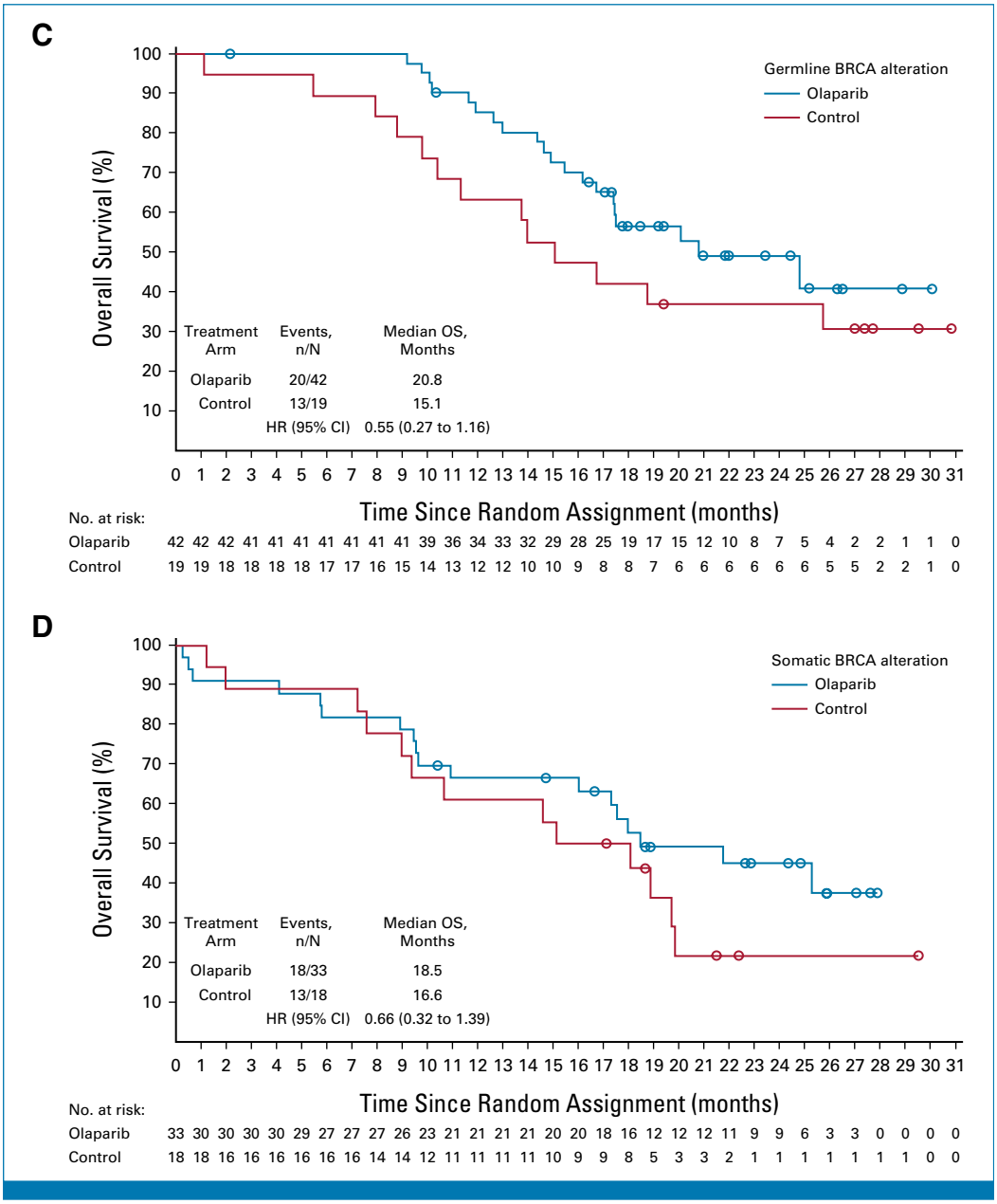

FIG 4. (Continued).

with suspected heterozygous loss, and those where zygosity could not be determined (36% cases). This finding is relevant as it supports that identification of a pathogenic BRCA alteration, particularly in *BRCA2*, is sufficient to identify patients who may benefit from olaparib treatment, even without clear evidence of second events. Although the majority of samples analyzed in PROfound were archival diagnostic specimens, biallelic loss was already present, further endorsing the use of archival samples for BRCA stratification of patients with mCRPC.[26] These results are consistent with previous studies of BRCA alterations in other BRCA-driven tumor types, where patients with BRCA alterations classified as biallelic or heterozygous benefited from treatment with a PARP inhibitor.[15,27,28]

Although the subgroup size is relatively small, the prolonged response among patients with *BRCA2* homozygous deletion in the olaparib arm (n = 16) is consistent with that observed in TOPARP-B,[6] suggesting exceptional responses are common among patients where secondary *BRCA2* reversion mutations cannot emerge because of complete gene absence.[29,30] This is relevant as *BRCA2* homozygous deletions may represent 3% of all patients with metastatic prostate cancer.[31,32]

We acknowledge that these analyses were post hoc and exploratory and PROfound was not powered to detect a treatment effect across these subgroups. Additionally, some subgroups were very small, and they were also not stratified

TABLE 3. Efficacy Results by Zygosity in the Population of Patients With a BRCA Alteration (combined including co-occurring alterations)

	Biallelic/Suspected Biallelic Inactivation		Heterozygous		Unknown	
End Point	Olaparib (n = 53)	Control (n = 35)	Olaparib (n = 12)	Control (n = 3)	Olaparib (n = 37)	Control (n = 20)
rPFS						
Events, No.	28	31	10	3	24	17
Median, months (95% CI)	11.4 (10.12 to 14.55)	3.5 (1.71 to 3.55)	4.7 (1.54 to 7.75)	2.0 (1.87 to NC)	7.4 (5.52 to 10.84)	3.0 (1.68 to 3.75)
HR (95% CI)	0.08 (0.04 to 0.16)		NA		0.30 (0.16 to 0.60)	
OS						
Events, No.	23	24	6	2	24	15
Median, months (95% CI)	26.8 (17.45 to NC)	18.1 (10.41 to 19.75)	16.8 (1.54 to NC)	9.4 (1.97 to NC)	17.6 (10.18 to 20.83)	13.5 (7.23 to 22.97)
HR (95% CI)	0.48 (0.27 to 0.85)		NA		0.77 (0.41 to 1.51)	
ORR						
Patients evaluable for ORR, No.	28	20	9	1	20	12
Patients with a response, No. (%)	17 (60.7)	0	4 (44.4)	0	4 (20.0)	0
OR (95% CI)	NC		NC		NC	

NOTE. Because of the small number of patients in the *BRCA1* subgroup, efficacy by zygosity was only assessed for the overall BRCA population. Only three patients had heterozygous alterations in the control arm; therefore, HRs for rPFS and OS were not calculated.

Abbreviations: BRCA, *BRCA1* and/or *BRCA2* including co-occurring alterations in other HRR genes; HR, hazard ratio; HRR, homologous recombination repair; NA, not applicable; NC, noncalculable; OR, odds ratio; ORR, objective response rate; OS, overall survival; rPFS, radiographic progression-free survival.

or adjusted for differences in baseline characteristics or, in most cases, rate of crossover.

The incidence of BRCA alterations is approximately 10% and these patients typically have poor treatment outcomes. Therefore, treatment guidelines recommend testing patients for underlying genomic alterations.[33-35] These results from the PROfound trial help clinicians interpret the relevance and actionability of BRCA alteration findings.

In conclusion, this exploratory analysis shows that olaparib monotherapy treatment improved outcomes for patients with mCRPC with BRCA alterations whose disease had progressed on previous NHA compared with enzalutamide or abiraterone. The treatment benefit with olaparib was observed in all subgroups assessed, including subgroups on the basis of previous taxane exposure, crossover to olaparib treatment, germline/somatic origin of the BRCA alteration, and zygosity by targeted NGS.

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Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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Olaparib for the Treatment of Patients With Metastatic Castration-Resistant Prostate Cancer and Alterations in *BRCA1* and/or *BRCA2* in the PROfound Trial

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Patents, Royalties, Other Intellectual Property: Title: Systems and methods for tissue imaging, 3676 our file: serial number: UM-14437/US-1/PRO 60/923,385 UM-14437/US-2/ORD 12/101,753 US 8,185,186 (US patent number). Systems and methods for tissue imaging (issued patent) EP 08745653.9 (EP application number). Systems and methods for tissue imaging (pending) CA 2683805 (Canadian application number). Systems and methods for tissue imaging (pending) US 13/362,500 (US application number). Systems and Methods for Tissue Imaging (continuation application of US 8,185,186). Title: Method of treating cancer docket no: serial number: 224990/10-016P2/311733 61/481/671 application filed on: 5/2/2011. Title: Dual inhibition of MET and VEGF for the treatment of castration resistant prostate cancer and osteoblastic bone metastases. Applicant/Proprietor Exelexis, Inc application no/patent no. 11764665.4-1464 application no/patent no. 11764656.2-1464 application filed on: September 26, 2011
Open Payments Link: https://openpaymentsdata.cms.gov/physician/146932/summary

No other potential conflicts of interest were reported.

APPENDIX 1. SUPPLEMENTARY MATERIALS

BRCA Alterations

For each tumor specimen that passed tissue sample and sequencing quality controls, a clinical trial assay report was generated specifying the presence or absence of qualifying gene alterations for the study. A patient had a BRCA alteration if any deleterious or suspected deleterious alteration was found in the *BRCA1* or *BRCA2* genes. An alteration was regarded as deleterious if it results in protein truncation (which includes nonsense, frameshift, or consensus splice site alterations), or select missense alterations well known to be deleterious in ClinVar/BIC databases. Furthermore, larger-scale alterations, such as genomic truncating rearrangements or homozygous deletions, were also classified as qualifying.

Zygosity Subgroup Definitions

The FoundationOne CDx tissue test considers alteration origin, tumor purity, and local allele copy number to predict the zygosity of the alteration. Patients were classified into the subgroups biallelic, heterozygous, or unknown based on the following:

Reasons for Discontinuation of Treatment

In patients with a BRCA alteration, reasons for discontinuation of treatment were objective radiographic progression (43.1% and 63.8%), unequivocal clinical progression (18.6% and 10.3%), adverse events (10.8% and 8.6%), and other reasons including patient decision (14.7% and 17.2%) for patients receiving olaparib and control, respectively.

Symptomatic Skeletal-Related Event

In the subgroup of patients from PROfound with a BRCA alteration, 14 patients (13.7%) in the olaparib arm and 12 patients (20.7%) in the control arm had a symptomatic skeletal-related event (Appendix Fig A1).

TABLE A1. Definitions of Biallelic Inactivation, Suspected Biallelic Inactivation, Heterozygous, and Unknown

Zygosity Subgroup	Definition
Biallelic inactivation	Contains at least one homozygous mutation/alteration or a reported known deletion (deletions are only reported when homozygous); no wild-type allele detected in tumor
Suspected biallelic inactivation	Two or more distinct deleterious mutations/alterations in the same gene—there can be compound heterozygous mutations/alterations or mutations/alterations of unknown zygosity in the same gene. It is not possible to determine whether the mutations/alterations occur in cis or in trans
Heterozygous	A single deleterious mutation/alteration in one allele predicted to be heterozygous; wild-type allele is detected in tumor
Unknown	Zygosity prediction of deleterious alterations cannot be determined—this is usually because of very low tumor purity of the tumor sample[21] or cases with *BRCA1/BRCA2* structural rearrangements

NOTE. For tumors with co-occurring alterations/mutations in BRCA genes, the biallelic inactivation would override any other classification; suspected biallelic inactivation would override heterozygous or unknown classification; unknown classification would override heterozygous if no biallelic inactivation or suspected biallelic inactivation is present in the same tumor. This is because unknown may be biallelic. Zygosity status of any other homologous recombination repair genes co-occurring with BRCA was ignored for this classification.

TABLE A2. Summary of AEs by Category at the Final OS Data Cutoff (March 20, 2020) in Patients With a BRCA Alteration (combined including co-occurring alterations)

Category	Olaparib (n = 102)	Control (n = 58)
Any AE, No. (%)	99 (97.1)	52 (89.7)
Any AE of CTCAE grade ≥3	56 (54.9)	23 (39.7)
Any AE with outcome of death	6 (5.9)	4 (6.9)
Any serious AE (including with outcome of death)	38 (37.3)	14 (24.1)
Any AE leading to discontinuation of treatment	19 (18.6)	6 (10.3)
AE of anemia	52 (51.0)	8 (13.8)

NOTE. *BRCA1* and/or *BRCA2* including co-occurring alterations in other HRR genes. Control refers to investigator's choice of next-generation hormonal agent (either abiraterone or enzalutamide).
Abbreviations: AE, adverse event; BRCA, *BRCA1* and/or *BRCA2* including co-occurring alterations in other HRR genes; CTCAE, Common Terminology Criteria for Adverse Events; HRR, homologous recombination repair; OS, overall survival.

TABLE A3. Subsequent Anticancer Therapies Received by Patients With a BRCA Alteration (combined including co-occurring alterations)

Anticancer Therapy Received After Discontinuation of Study Treatment	Olaparib (n = 102)	Control (n = 58)
Any therapy, No. (%)	43 (42.2)	43 (74.1)
Immune checkpoint inhibitors	2 (2.0)	0
Hormonal therapy	17 (16.7)	5 (8.6)
Taxane-based chemotherapy	21 (20.6)	12 (20.7)
Platinum-based chemotherapy	10 (9.8)	0
PARP inhibitor[a]	2 (2.0)	40 (69.0)
Other	14 (13.7)	1 (1.7)

NOTE. Patients can be counted in more than one anticancer therapy. Control refers to investigator's choice of next-generation hormonal agent (either abiraterone or enzalutamide).
Abbreviations: BRCA, *BRCA1* and/or *BRCA2* including co-occurring alterations in other HRR genes; HRR, homologous recombination repair; PARP, poly(ADP-ribose) polymerase.
[a]PARP inhibitor includes patients who crossed over to olaparib within the trial.

TABLE A4. Germline and Somatic BRCA Alteration Status

Patient	*BRCA1* Only (n = 13)	*BRCA2* Only (n = 128)	BRCA (combined including co-occurring alterations; N = 160)
Evaluable, No.	11	101	112
Germline, No. (%)	7 (63.6)	54 (53.5)	61 (54.5)
Somatic, No. (%)	4 (36.4)	47 (46.5)	51 (45.5)

Abbreviations: BRCA, *BRCA1* and/or *BRCA2* including co-occurring alterations in other HRR genes; *BRCA1* only, alteration in *BRCA1* gene only; *BRCA2* only, alteration in *BRCA2* gene only; HRR, homologous recombination repair.

TABLE A5. Summary of AEs by Category at the Final OS Data Cutoff (March 20, 2020) in Patients With a Germline or Somatic Alteration in BRCA (combined including co-occurring alterations) in the Olaparib Arm[13]

	Olaparib	
Category	Germline BRCA (n = 42)	Somatic BRCA (n = 33)
Any AE, No. (%)	39 (92.9)	33 (100)
Any AE of CTCAE grade ≥3	22 (52.4)	17 (51.5)
Any AE with outcome of death	0	4 (12.1)
Any serious AE (including with outcome of death)	14 (33.3)	13 (39.4)
Any AE leading to discontinuation of treatment	8 (19.0)	7 (21.2)
AE of anemia	24 (57.1)	15 (45.5)

Abbreviations: AE, adverse event; BRCA, *BRCA1* and/or *BRCA2* including co-occurring alterations in other HRR genes; CTCAE, Common Terminology Criteria for Adverse Events; HRR, homologous recombination repair; OS, overall survival.

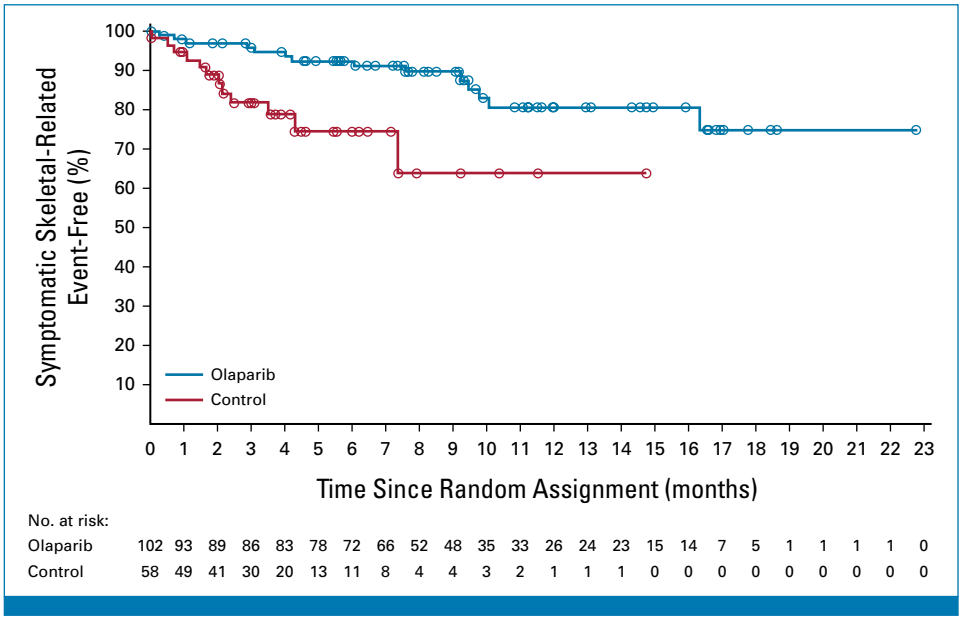

FIG A1. Time to first symptomatic skeletal-related event in patients with a BRCA alteration (combined including co-occurring alterations). A circle indicates a censored observation. BRCA, *BRCA1* and/or *BRCA2* including co-occurring alterations in other HRR genes; HRR, homologous recombination repair.

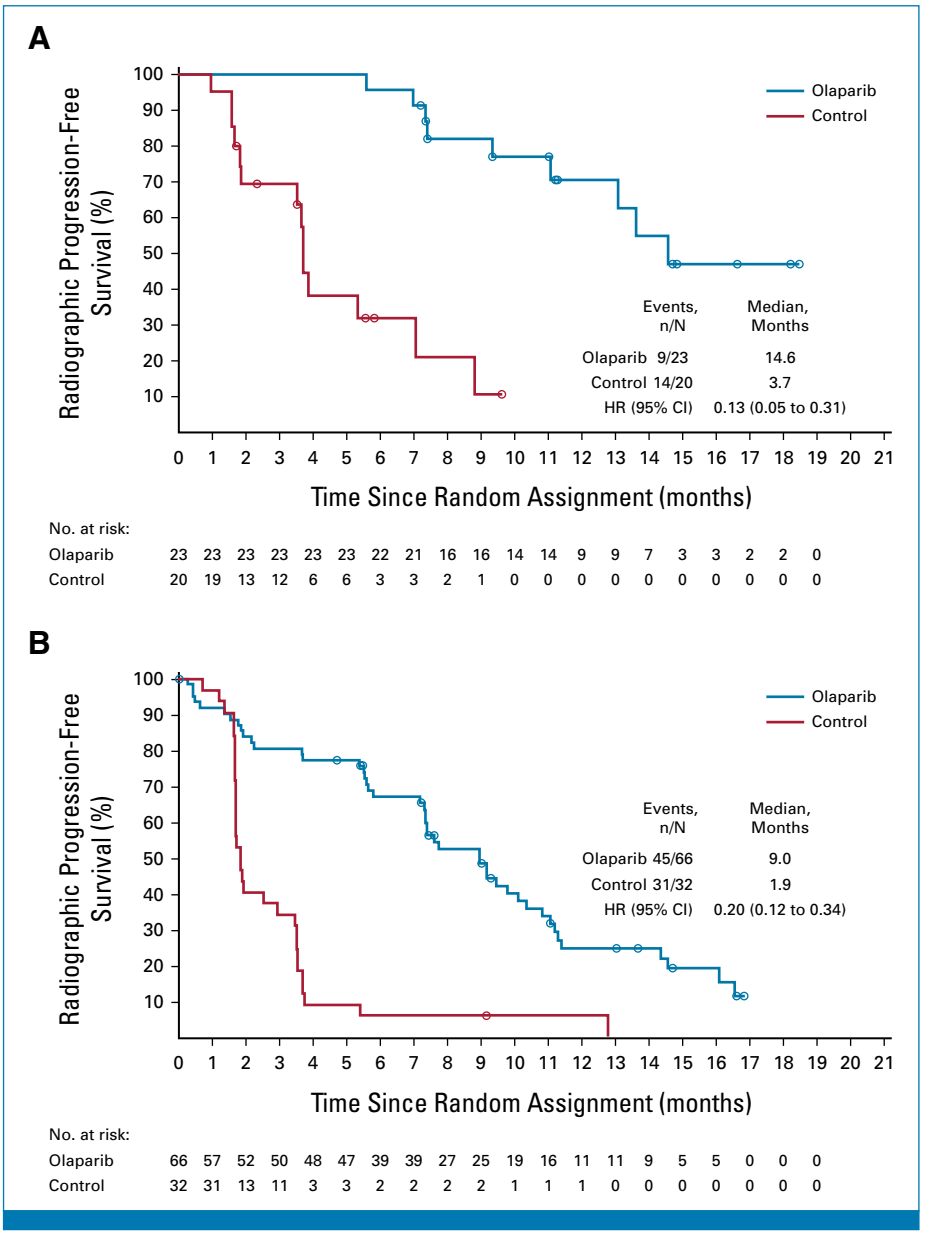

FIG A2. Kaplan-Meier curves of rPFS by (A) no previous taxane and (B) previous taxane in patients with a BRCA alteration. Includes patients with an alteration in *BRCA1* only or *BRCA2* only. A circle indicates a censored observation. HR, hazard ratio; HRR, homologous recombination repair; rPFS, radiographic progression-free survival.

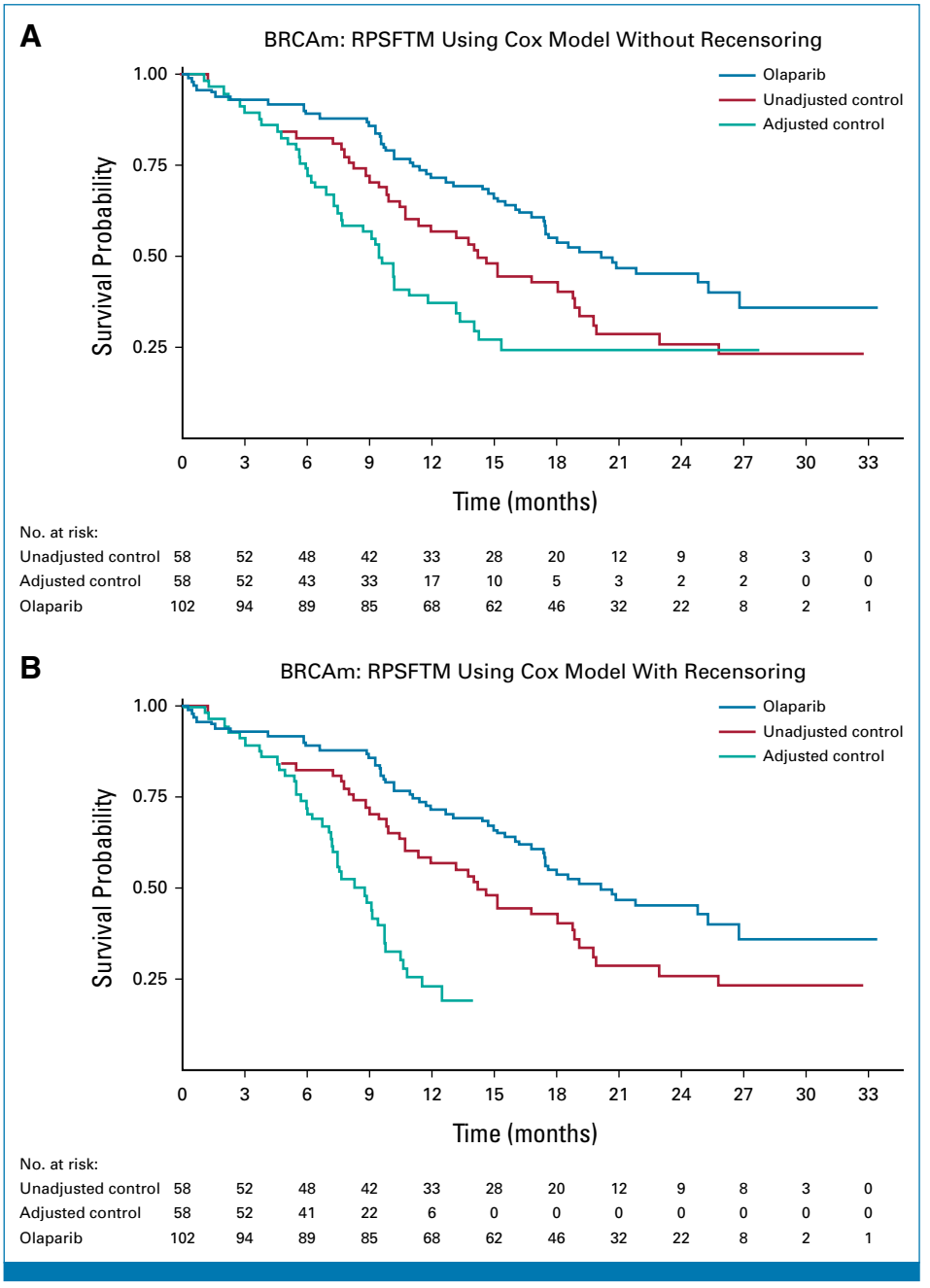

FIG A3. Kaplan-Meier curves for OS in patients with a BRCA alteration, adjusted for treatment switching using RPSFTM (combined including co-occurring alterations).[23] From Evans R et al: Exploring the impact of treatment switching on overall survival from the PROfound study in homologous recombination repair (HRR)-mutated metastatic castration-resistant prostate cancer (mCRPC), *Targeted Oncology* 16:613–23. Copyright © 2021, Springer Nature. Reprinted with permission from Springer Nature. BRCA, *BRCA1* and/or *BRCA2* including co-occurring alterations in other HRR genes; HRR, homologous recombination repair; OS, overall survival; RPSFTM, rank-preserving structural failure time model.

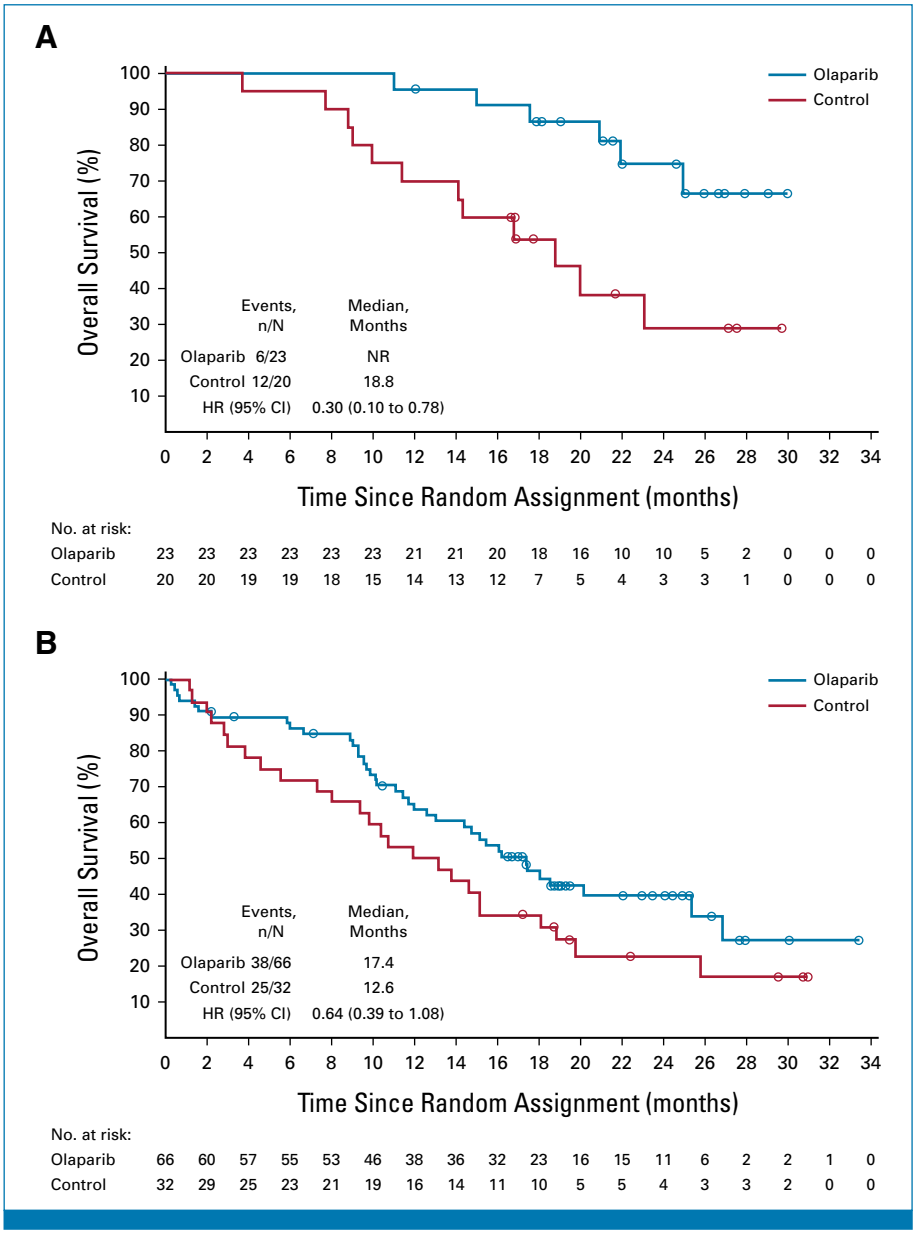

FIG A4. Kaplan-Meier curves of OS by (A) no previous taxane and (B) previous taxane in patients with a BRCA alteration.[13] Includes patients with an alteration in *BRCA1* only or *BRCA2* only. A circle indicates a censored observation. Control refers to investigator's choice of next-generation hormonal agent (either abiraterone or enzalutamide). From Hussain M et al: Survival with olaparib in metastatic castration-resistant prostate cancer, *New England Journal of Medicine* 383:2345–57. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. HR, hazard ratio; HRR, homologous recombination repair; NR, not reached; OS, overall survival.